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Thrombotic Complications Associated With Early and Late Nonadherence to Dual Antiplatelet Therapy

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ABSTRACT

OBJECTIVES This study sought to assess the frequency and clinical impact of dual antiplatelet therapy (DAPT) nonadherence.

BACKGROUND There are limited data on the impact of DAPT nonadherence during the first year after a second-generation drug-eluting stent placement.

METHODS After successful Endeavor zotarolimus-eluting stent implantation, 2,265 patients were enrolled in a registry with limited exclusions and monitored during 12 months of prescribed DAPT. Predictors of any nonadherence (ANA) at 6 months were analyzed by multivariable analysis, and the association between ANA at 6 or 12 months with the endpoints of death, myocardial infarction, and stent thrombosis was assessed.

RESULTS The study population included 30% female patients, 34% with diabetes and 36% with acute coronary syndromes. ANA occurred in 208 patients (9.6%) before 6 months and 378 patients (18.5%) before 1 year. Major bleeding (odds ratio [OR]: 12.83, 95% confidence interval [CI]: 7.55 to 21.80, $p < 0.001$) was the only predictor of ANA at 6 months. In time-dependent analyses, ANA before 6 months was associated with an increased risk of death or myocardial infarction (7.6% vs. 3.0%, $p < 0.001$) and a numerical increase in stent thrombosis (2.0% vs. 0.9%, $p = 0.12$). After adjustment for baseline differences, ANA within 6 months remained associated with death or MI (OR: 1.95, 95% CI: 1.02 to 3.75). ANA occurring after 6 months did not increase the risk of subsequent ischemic events.

CONCLUSIONS DAPT ANA occurs frequently and is associated with increased risk for thrombotic complications if it occurs within the first 6 months. Major bleeding was a significant correlate of DAPT ANA within 6 months. (EDUCATE: The MEDTRONIC Endeavor Drug Eluting Stenting: Understanding Care, Antiplatelet Agents and Thrombotic Events; NCT01069003) (J Am Coll Cardiol Intv 2015;8:404–10) © 2015 by the American College of Cardiology Foundation.

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When used in routine practice, first-generation drug-eluting stents (DES) increased the risk for stent thrombosis beyond the traditional subacute (30-day) period as compared with the risk associated with bare-metal stents (1,2). In 2007, the consensus recommendation from cardiology societies and the U.S. Food and Drug Administration was for 12 months of continuous dual antiplatelet therapy (DAPT) (3,4). Despite earlier concerns that 12 months of continuous DAPT might be too short, several randomized trials have not confirmed a benefit for therapy beyond 12 months (5–7). Due to low event rates and issues of trial design, a more definitive assessment of the prolonged DAPT controversy awaits completion of the larger DAPT randomized trial (8). Meanwhile, based on lower rates of late stent thrombosis with newer generation DES, other studies have tested even shorter DAPT durations of 3 or 6 months in low-risk populations and shown no statistical difference compared with the standard 12-month duration (9–11).

SEE PAGE 411

Similarly, the significance of interruptions or any nonadherence (ANA) to DAPT during the prescribed 12 months is unclear. Indeed, recent observational studies have suggested that interruptions as early as 31 days are not associated with increased risk for stent thrombosis (12–15), but these studies have either not addressed the specific impact of ANA at intervals between 31 days and 6 months, had infrequent ANA during this interval, or had low overall event rates.

Given this ongoing controversy, we explored the issue of early (within 6 months) or late (6 to 12 months) DAPT ANA after second-generation DES placement in the context of a large prospective multicenter registry. We hypothesized that ANA to prescribed DAPT within 6 months is associated with increased risk of thrombotic events; additionally, we sought to assess the frequency and predictors of nonadherence within 6 months.

METHODS

PATIENT POPULATION. The EDUCATE (Endeavor Drug-Eluting Stenting: Understanding Care, Antiplatelet Agents and Thrombotic Events) registry is a prospective registry designed to assess practice patterns and patient adherence to DAPT and the risk of subsequent thrombotic events. All patients >18 years of age undergoing coronary stenting with an Endeavor zotarolimus-eluting stent (E-ZES) (Medtronic, Minneapolis, Minnesota) of diameter 2.5 to 3.5 mm at a participating institution and with life expectancy >3 years were eligible for participation. After 12 months of follow-up, patients who were free of ischemic or bleeding events and who met appropriate inclusion and exclusion criteria were to be randomized to continue aspirin plus clopidogrel (or prasugrel) or aspirin plus placebo for an additional 18 months as part of the larger DAPT trial (8). This report is limited to events in the first 12 months prior to randomization and includes all subjects enrolled. The study was approved by the appropriate ethics review committee for each participating institution.

ABBREVIATIONS AND ACRONYMS

ANA = any nonadherence

DAPT = dual antiplatelet therapy

DES = drug-eluting stent

E-ZES = Endeavor zotarolimus-eluting stent

MI = myocardial infarction

DUAL ANTIPLATELET THERAPY AND MEDICATION ADHERENCE. All patients were prescribed open-label aspirin plus either clopidogrel or prasugrel for a recommended duration of 12 months. Adherence to study medication was assessed during follow-up visits at 30 days, 6 months, and 12 months. The duration of all interruptions was recorded. ANA was defined as missing 1 or more days of either medication. Severe nonadherence was defined as missing 14 or more consecutive days of either study medication.

STUDY ENDPOINTS. Endpoints included all-cause mortality, cardiac death, myocardial infarction (MI), stent thrombosis, and major bleeding. A composite endpoint of death or MI was also analyzed. Cardiac death included all deaths for which a cardiac cause could not be excluded. MI was defined during the periprocedural period (48 h) as creatine kinase-myocardial band or troponin >3× the individual clinical center upper reference limit and during follow-up based on evidence of ischemic signs or symptoms and any elevation of troponin or creatine kinase-myocardial band. Stent thrombosis was defined according to the Academic Research Consortium classification and reported as definite or probable (16). Major bleeding events were classified according to the GUSTO (Global Use of Strategies to Open Coronary Arteries) trial as moderate or severe (17). All endpoints were adjudicated by an independent clinical events committee.

STATISTICAL ANALYSIS. Primary comparisons for this analysis are between subjects with ANA and those with full adherence to prescribed DAPT during the first 6 months after stent implantation. Categorical data are reported as percentages and compared using chi square. Continuous variables are reported as mean ± SD and compared using a Student *t* test. The cumulative incidence of ANA, severe nonadherence, and clinical endpoints were calculated using the Kaplan-Meier method, and differences in clinical outcomes between groups were compared

using the log rank test. Because periprocedural events are unrelated to DAPT adherence, the time-dependent analysis began after 48 h. Patients were analyzed according to the timing of ANA, such that events occurring in patients with eventual ANA but in the interval prior to ANA are analyzed as full adherence. The predictors of ANA and independent correlates of the composite of death or MI were assessed using logistic regression. All statistical analyses were performed using SAS (version 9.1 or higher, SAS Institute, Cary, North Carolina).

RESULTS

STUDY POPULATION. Of 2,265 consecutive patients enrolled, 10 subjects were withdrawn due to administrative reasons at 1 site and data for DAPT adherence were missing for 96 subjects. Thus, 2,159 patients were included in the final analysis (Figure 1). Approximately one-third of patients had diabetes mellitus and one-third were enrolled after presentation with an acute coronary syndrome (Table 1). Compared with patients with full adherence to DAPT, patients with ANA were slightly older and had higher frequency of diabetes, heart failure, previous stroke or transient ischemic attack, peripheral vascular disease, and warfarin use.

FREQUENCY AND PREDICTORS OF DAPT NONADHERENCE. The cumulative incidence of DAPT nonadherence is shown in Figure 2. By 6 months, 208 patients (9.6%) reported ANA, including severe nonadherence in 112 (5.2%). The only significant independent correlate with ANA during the first 6 months was the development of a major bleeding event (odds ratio: 12.83, 95% confidence interval: 7.55 to 21.80, $p < 0.001$). Requirement for noncardiac surgery was not a significant predictor of ANA. Of note, however, only 23 patients underwent noncardiac surgery or an invasive procedure within 6 months.

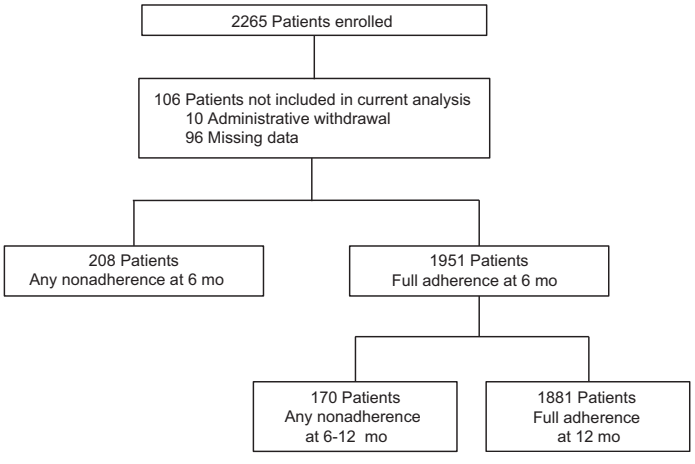
TABLE 1 Baseline Clinical Characteristics According to 6-Month DAPT Adherence

	Any Nonadherence (n = 208)	Full Adherence (n = 1,951)	p Value
Age, yrs, mean	65.6	63.8	0.02
Female	34.6	29.8	0.15
Diabetes mellitus	41.3	33.2	0.02
Hypertension	83.2	81.9	0.71
History of smoking	59.6	56.7	0.46
Hyperlipidemia	83.2	83.0	1.00
Previous MI	27.4	23.8	0.27
Previous PCI	38.9	35.7	0.36
Previous heart failure	15.4	8.0	<0.01
PCI for acute coronary syndrome	52.9	46.5	0.08
Renal insufficiency	8.5	6.4	0.28
Previous stroke or TIA	11.1	5.6	<0.01
History of GI bleeding	2.4	0.9	0.06
Previous CABG	16.3	14.9	0.54
Warfarin	5.3	2.4	0.02
Clopidogrel	75.0	76.7	0.60
Prasugrel	18.3	16.9	0.63
Multiple stents	36.5	35.2	0.70

Values are percentages unless otherwise indicated.

CABG = coronary artery bypass graft; GI = gastrointestinal; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

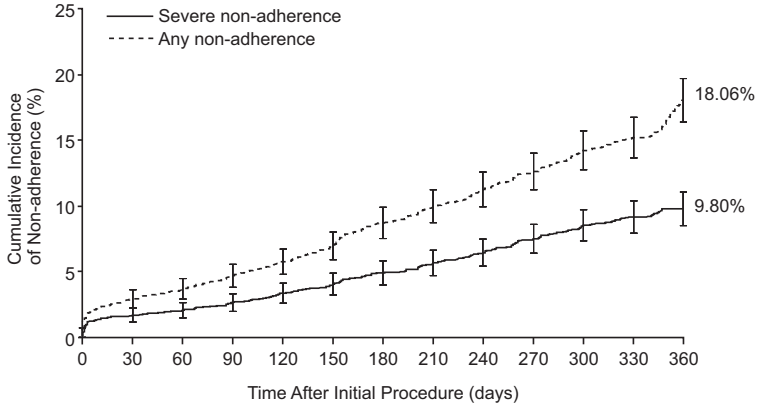
FIGURE 1 Patient Enrollment



Patient enrollment flow chart depicting frequency of any nonadherence at 6 months and subsequent any nonadherence after 6 months.

CLINICAL OUTCOMES AND DAPT NONADHERENCE. One-year unadjusted clinical outcomes based on 6-month DAPT adherence are shown in Table 2 and Figure 3. Individual endpoints of all-cause mortality, cardiac death, MI, and stent thrombosis as well as the composite endpoint of death or MI were all more frequent for ANA within 6 months of DES implantation. After adjustment for differences in baseline characteristics, ANA within 6 months remained a significant correlate of death or MI (Table 3). The risk for the composite endpoint of death or MI was similar for ANA between 0 to 90 days and 91 to 180 days (8.9% vs. 7.0%). In contrast, for patients who were fully adherent to DAPT during the first 6 months, subsequent nonadherence after 6 months compared with continued full adherence was not associated with increased subsequent risk for the composite endpoint of death or MI (1.1% vs 1.3%).

FIGURE 2 Cumulative Incidence of Nonadherence to Prescribed DAPT



No. at risk													
Severe nonadherence	2265	2253	2170	2141	2099	2067	2043	2010	1968	1941	1869	1799	1772
Any nonadherence	2265	2253	2143	2105	2057	2019	1986	1934	1882	1845	1767	1685	1652
No. of events													
Severe nonadherence	10	28	8	13	15	15	18	16	16	22	20	13	12
Any nonadherence	10	56	17	21	23	26	37	27	27	28	32	19	55

Cumulative incidence of any nonadherence and severe nonadherence during the 12 months of prescribed therapy. DAPT = dual antiplatelet therapy.

Major bleeding was more frequent in the early ANA group (Figure 3C), with most bleeding occurring within the first 6 months and preceding nonadherence in all cases. The risk for death or MI was significantly higher among the 22 patients with ANA that was associated with major bleeding than for other ANA (35.0% vs. 7.0%, $p < 0.001$).

DISCUSSION

In this broadly inclusive multicenter international registry of patients undergoing stenting with the E-ZES, nonadherence with the prescribed 12 months of DAPT was frequent, including prolonged (>14 days) nonadherence in over 5% of patients within 6 months of DES implantation. ANA in the first 6 months correlated strongly with the occurrence of major bleeding. ANA within the first 6 months was independently associated with adverse thrombotic outcomes at 1 year. For patients fully compliant with DAPT during the first 6 months after E-ZES implantation, subsequent ANA between 6 and 12 months did not confer increased ischemic risk.

Our findings contribute significantly to the ongoing debate regarding the timing and risk of DAPT interruption after second-generation DES implantation. Although the concept of DAPT duration as short as 3 months after E-ZES as suggested by Kim et al. (10) is attractive, our findings raise concern about broad application of this practice. Similarly other studies assessing DAPT durations shorter than 12 months may have limited statistical power to assess differences in stent thrombosis and may not be generalizable to higher-risk routine practice populations (6,9,11).

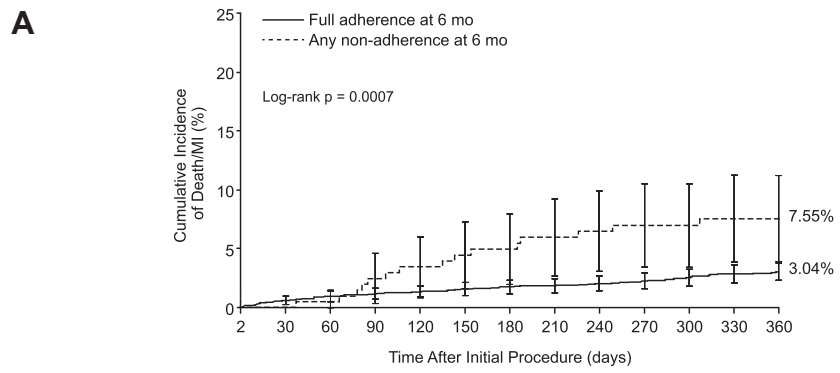
Moreover, our findings suggest that clinical attention to the problem of DAPT nonadherence remains important for the first 6 months after second-generation DES implantation. There is general agreement with this concern within the first 30 days after DES implantation (13,15,18,19), but our data are in contrast to several studies reporting no adverse impact of DAPT interruptions after 30 days (13,15,20).

TABLE 2 1-Year Clinical Outcomes According to 6-Month DAPT Adherence

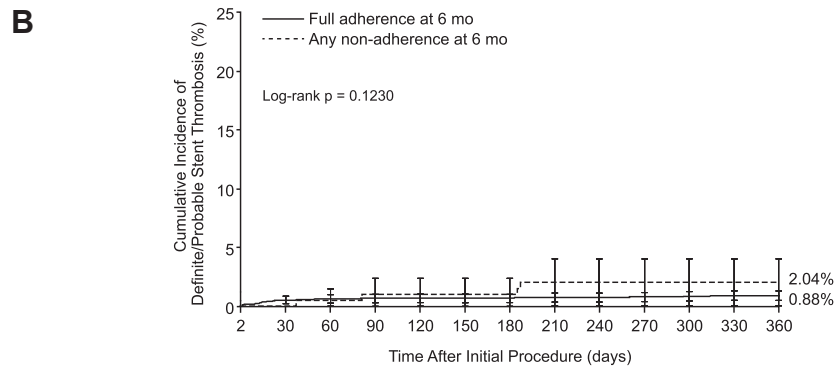
	Any Nonadherence (n = 208)	Full Adherence (n = 1,951)	p Value
All-cause mortality	5.0	1.7	0.001
Cardiac death	2.5	0.9	0.028
MI	4.7	1.5	0.002
Death or MI	7.6	3.0	<0.001
Definite or probable ST	2.0	0.9	0.123
Major bleeding	16.2	2.7	<0.001
Stroke	3.5	0.6	<0.001

Values are percentages.
DAPT = dual antiplatelet therapy; MI = myocardial infarction; ST = stent thrombosis.

FIGURE 3 Cumulative Incidences of Clinical Outcomes



No. at risk													
Full adherence at 6 mo	1956	1951	1939	1930	1922	1916	1910	1904	1880	1869	1825	1779	1762
Any non-adherence at 6 mo	203	203	203	202	197	194	192	191	184	182	174	167	166
No. of events													
Full adherence at 6 mo	1	11	7	4	3	5	3	2	4	4	5	6	3
Any non-adherence at 6 mo	0	0	1	4	2	2	1	2	1	1	0	1	0



No. at risk													
Full adherence at 6 mo	1956	1952	1939	1932	1924	1919	1915	1910	1887	1877	1833	1786	1771
Any non-adherence at 6 mo	203	203	203	202	198	195	193	192	185	183	176	169	169
No. of events													
Full adherence at 6 mo	0	10	2	1	0	0	0	1	0	1	1	1	0
Any non-adherence at 6 mo	0	0	1	1	0	0	0	2	0	0	0	0	0

(A) Cumulative incidence of death or myocardial infarction for any nonadherence within 6 months compared with full adherence for 6 months.
(B) Cumulative incidence of stent thrombosis for any nonadherence within 6 months compared with full adherence for 6 months.
(C) Cumulative incidence of major bleeding for any nonadherence within 6 months compared with full adherence for 6 months.

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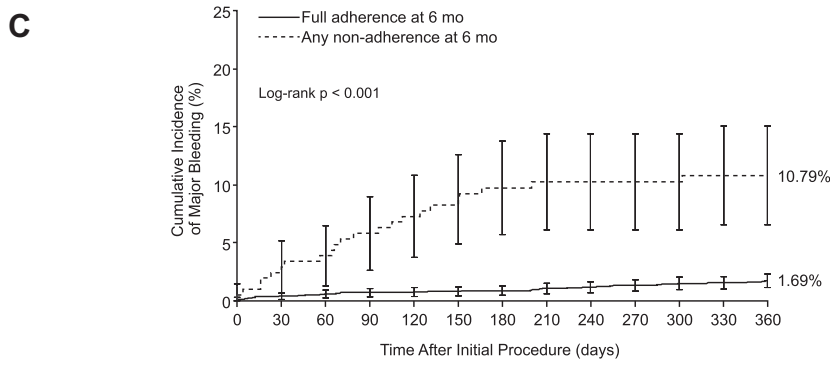
Ferreira-Gonzalez et al. (20) reported on 172 patients with DAPT interruptions between 30 days and 1 year and, compared with patients without interruptions, noted no increase in major adverse cardiac events. These investigators grouped all interruptions between 30 days and 1 year, however, and interruptions in the first 6 months were infrequent. Similarly, Silber et al. (15) reported that ANA between 30 days and 1 year after implantation of the Resolute ZES was not associated with an increased risk for cardiac death or MI, but also did not distinguish nonadherence before or after 6 months. Naidu et al. (13) also did not note an increased risk for 1-year stent thrombosis with interruptions after 30 days in the XIENCE V USA (XIENCE V Everolimus Eluting Coronary Stent System USA post-approval study), but the rate of stent thrombosis was very low (0.8%) and the effect of interruptions before 6 months was not reported.

Previous studies have suggested that re-endothelialization after first- or second-generation DES may continue well beyond 30 days, especially

FIGURE 3 Continued



No. at risk													
Full adherence at 6 mo	1951	1949	1935	1928	1920	1915	1910	1904	1878	1866	1822	1774	1759
Any non-adherence at 6 mo	208	207	201	199	194	189	185	182	176	174	166	160	159
No. of events													
Full adherence at 6 mo	2	5	4	2	1	1	1	4	2	3	3	1	3
Any non-adherence at 6 mo	1	5	2	4	3	3	2	1	0	0	0	1	0

when used for longer and more complex lesions (21–24). Thus we hypothesized that DAPT interruptions were more likely to be associated with thrombotic events during the entire period of early healing. Our findings that full adherence to DAPT is most important in the first 6 months are consistent with those of a large Japanese registry by Kimura et al. (12), which demonstrated no clinical benefit for continued thienopyridine in addition to aspirin beyond 6 months after sirolimus-eluting stent placement. Our results extend these findings to the second-generation E-ZES stent used in patients seen during routine practice in the United States.

Recently, Mehran et al. (14) reported that DAPT interruptions during the first 2 years after DES implantation had a variable effect on clinical outcome depending on the reason for interruption. They noted that therapy "disruptions" due to major bleeding, but not physician-directed interruptions due to a need for noncardiac surgery, were associated with an increased risk for major adverse cardiac events. In their study, DAPT disruption occurred at a mean of 230 days after stenting and frequently involved stopping both aspirin and a thienopyridine, whereas other interruptions occurred at mean 357 days and aspirin was usually continued. Our multicenter registry amplifies these findings by identifying an independent association of major bleeding with ANA within 6 months, and consistent with Mehran et al. (14), confirming these clinically triggered interruptions were associated with a significant risk of ischemic events. Our findings emphasize that this association is only true if the interruption occurred within 6 months of DES implantation. The failure to reliably predict nonadherence in most cases points to the difficulty in preventing these events.

TABLE 3 Predictors of 1-Year Death or MI

	Odds Ratio (95% CI)	p Value
Any nonadherence at 6 months	1.95 (1.02–3.75)	0.045
Diabetes	3.16 (1.89–5.27)	<0.001
Age, per year	1.06 (1.03–1.09)	<0.001
Current smoking	2.83 (1.57–5.08)	<0.001
Nonelective procedure	2.04 (1.22–3.45)	0.006

Other variables that were included in the multivariable regression model and were not significant included: previous MI, previous CABG, previous PCI, previous stroke or TIA, history of heart failure, and history of peripheral vascular disease.

CI = confidence interval; other abbreviations as in Table 1.

STUDY LIMITATIONS. Our study is a multicenter prospective registry and not a randomized clinical trial. Patients with ANA are different than those without ANA. We used multivariable analysis to control for differences between ANA and fully adherent patients, but it is possible that unknown confounders may lead to increased risk of ischemic events associated with DAPT nonadherence. Our study identified major bleeding as the sole independent predictor of ANA. It is possible that other lower frequency events (i.e., noncardiac surgery after DES implantation) might be associated with ANA and a larger registry would be required to determine this definitively. Finally, our study analyzed the impact of early ANA versus late ANA with respect to 1 second-generation DES (E-ZES), which is no longer in general use. Although this DES has been associated with low risk of late stent thrombosis, the applicability of our findings to other DES with possible lower risk for stent thrombosis warrants further study.

The impact of these results on DAPT strategy for newer generation DES is uncertain. Given reports of lower late stent thrombosis for both the cobalt chromium everolimus-eluting stent and the Resolute ZES, there has been increased interest in even shorter durations of prescribed DAPT (25). Importantly, the E-ZES used in our study has also been associated with lower risk for very late stent thrombosis (26).

CONCLUSIONS

Any nonadherence to DAPT occurred frequently and was associated with increased risk for death or myocardial infarction if within the first 6 months. Our results suggest that larger randomized clinical trials including higher-risk patients treated in routine practice are required to determine the safety of durations of uninterrupted DAPT therapy <6 months.

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