



ORIGINAL RESEARCH

Premature Discontinuation of Dual Antiplatelet Therapy After Coronary Stenting in Veterans: Characteristics and Long-Term Outcomes

Scott Kinlay , MBBS, PhD; Lien Quach, MD, PhD; Jean Cormack, PhD; Natalie Morgenstern, MPH; Ying Hou, MD, BSc; Melissa Young, MPH; Rebecca Sherrod, MPH, MA; Kelly Cho, PhD; David P. Faxon, MD; Ronnie Ramadan, MD; Michael Gaziano, MD, PhD; David Gagnon , MD, MPH, PhD

BACKGROUND: Premature discontinuation of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention is related to higher short-term risks of adverse outcomes. Whether these risks persist in the long-term is uncertain.

METHODS AND RESULTS: We assessed all patients having percutaneous coronary intervention with coronary second- or first-generation drug-eluting stents in the Veterans Affairs healthcare system between 2006 and 2012 who were free of major ischemic or bleeding events in the first 12 months. The characteristics of patients who stopped DAPT prematurely (1–9 months duration), compared with >9 to 12 months, or extended duration (>12 months) were assessed by odds ratios (ORs) from multivariable logistic models. The risk of adverse clinical outcomes over a mean 5.1 years in patients who stopped DAPT prematurely was assessed by hazard ratios (HRs) and 95% CIs from Cox regression models. A total of 14 239 had second-generation drug-eluting stents, and 8583 had first-generation drug-eluting stents. Premature discontinuation of DAPT was more likely in Black patients (OR, 1.54; 95% CI, 1.40–1.68), patients with greater frailty (OR, 1.04; 95% CI, 1.03–1.05), and patients with higher low-density lipoprotein cholesterol, and less likely in patients on statins (OR, 0.87; 95% CI, 0.80–0.95). Patients who stopped DAPT prematurely had higher long-term risks of death (second-generation drug-eluting stents: HR, 1.35; 95% CI, 1.19–1.56), myocardial infarction (second-generation drug-eluting stents: HR, 1.46; 95% CI, 1.22–1.74), and repeated coronary revascularization (second-generation drug-eluting stents: HR, 1.24; 95% CI, 1.08–1.41).

CONCLUSIONS: Patients who stop DAPT prematurely have features that reflect greater frailty, poorer medication use, and other social factors. They continue to have higher risks of major adverse outcomes over the long-term and may require more intensive surveillance many years after percutaneous coronary intervention.

Key Words: compliance/adherence ■ drug-eluting stent ■ dual antiplatelet therapy ■ percutaneous coronary intervention

Dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with drug-eluting stents prevents myocardial infarction (MI) and death attributable to stent thrombosis and new plaque disruption in coronary artery segments remote from the PCI. Current guidelines recommend DAPT for 6 to 12 months after PCI for stable angina and for at least

12 months for acute coronary syndromes or complex disease.^{1,2} Premature cessation of DAPT after PCI because of poor medical adherence, comorbidities, or major bleeding in the first 12 months after PCI is associated with increased risks of death or MI in the first 1 to 2 years after PCI.^{3–7} This increased risk could be attributable to the loss of antithrombotic effects from

Correspondence to: Scott Kinlay, MBBS, PhD, Cardiovascular Division, Veterans Affairs Boston Healthcare System, 1400 VFW Pkwy, West Roxbury, MA 02132. E-mail: scott.kinlay@va.gov

Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018481>

For Sources of Funding and Disclosures, see page 11.

© 2021 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Patients who prematurely discontinue dual antiplatelet therapy after percutaneous coronary intervention are not only at higher short-term risk of adverse events, but have a high risk long-term of these complications for many years.
- This elevated risk relates to frailty and several other social factors.

What Are the Clinical Implications?

- Patients who prematurely discontinue dual antiplatelet therapy after percutaneous coronary intervention may warrant more intensive long-term follow-up to prevent long-term adverse events.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
VA	Veterans Affairs

DAPT cessation or other patient characteristics that impact poor health outcomes. Over the long-term, the anti-ischemic benefits of DAPT decline, as supported by several recent trials supporting a shift to shorter durations of DAPT therapy, as outlined in the recent guidelines.^{1,2} The long-term risks of premature discontinuation of DAPT, among patients who are free of major adverse events in the first year, may relate to comorbidities and socioeconomic factors impacting health behaviors and are not well described. We sought to describe the characteristics of patients who discontinue DAPT prematurely, and who were free of major adverse events in the first year after PCI, on the long-term outcomes >1 year and up to a median of 5 years after PCI.

METHODS

The authors declare that all supporting data are available within the article. We identified all patients having PCI with drug-eluting stents between October 2006 and September 2012 in all Veterans Affairs (VA) facilities across the United States from the VA Clinical Assessment Reporting and Tracking program.⁸ The Clinical Assessment Reporting and Tracking program records all PCIs in the VA Healthcare System and includes procedural data, such as the dimensions and the name of the stent implanted. We used this database to assess 2 groups of stents:

first-generation drug-eluting stents (sirolimus or paclitaxel) and second-generation drug-eluting stents (everolimus or zotarolimus). These data were imported into the secure VA Informatics and Computing Infrastructure server, and patient data were linked to the VA Corporate Data Warehouse, which provided baseline demographic data, clinical history information, duration of medication prescriptions, and the diagnoses for readmissions. In addition, we linked data on non-VA hospital admission diagnoses using the Centers for Medicare and Medicaid Services database (Medicaid inpatient, and Medicare Provider Analysis and Review (MedPAR), files). The study was approved by the VA Boston Institutional Review Board, which waived the requirement for informed consent.

Subjects were excluded if they had missing or incongruent data (no records or unable to link to outcome data files after PCI, no record of DAPT use after PCI, or missing data on race, cholesterol levels, or stent dimensions), a life expectancy <3 years (cancer diagnosis and chemotherapy, length of stay after index PCI >15 days), patients were receiving different types of stents at the index PCI, or patients were undergoing long-term anticoagulation (the last 3 exclusions are similar to the DAPT trial). By design, we excluded patients who died or had MI, stroke, repeated coronary revascularization, or a major bleed in the first 12 months after their index PCI, as these short-term events likely increase the long-term risk of these events (Figure 1).

Demographic Data

Data from the index PCI included patient age, sex, and race. We defined comorbidities based on *International Classification of Diseases, Ninth Revision (ICD-9)*, codes in the 5 years before 12 months after the index PCI (ie, up to the start of the landmark analysis: Table S1, Supplementary Appendix). Smoking was defined as “never smoked” or “current or former smoking” using a probabilistic algorithm validated in the Million Veterans Program.⁹

We used the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) bleeding score to identify patients at high risk of bleeding. This score was originally developed for patients with atrial fibrillation on anticoagulation, but the factors in the score (aged ≥75 years, estimated glomerular filtration rate <30 mL/min, hemoglobin <13 g/L for men and <12 g/L for women, any prior hemorrhage, or hypertension) include many of the criteria in other high-risk bleeding scores.¹⁰ We defined high bleeding risk as an ATRIA score of ≥4.¹¹

As frailty may relate to DAPT duration, we used a previously validated frailty score based on 1 point for each of 31 comorbidities defined from ICD-9 codes

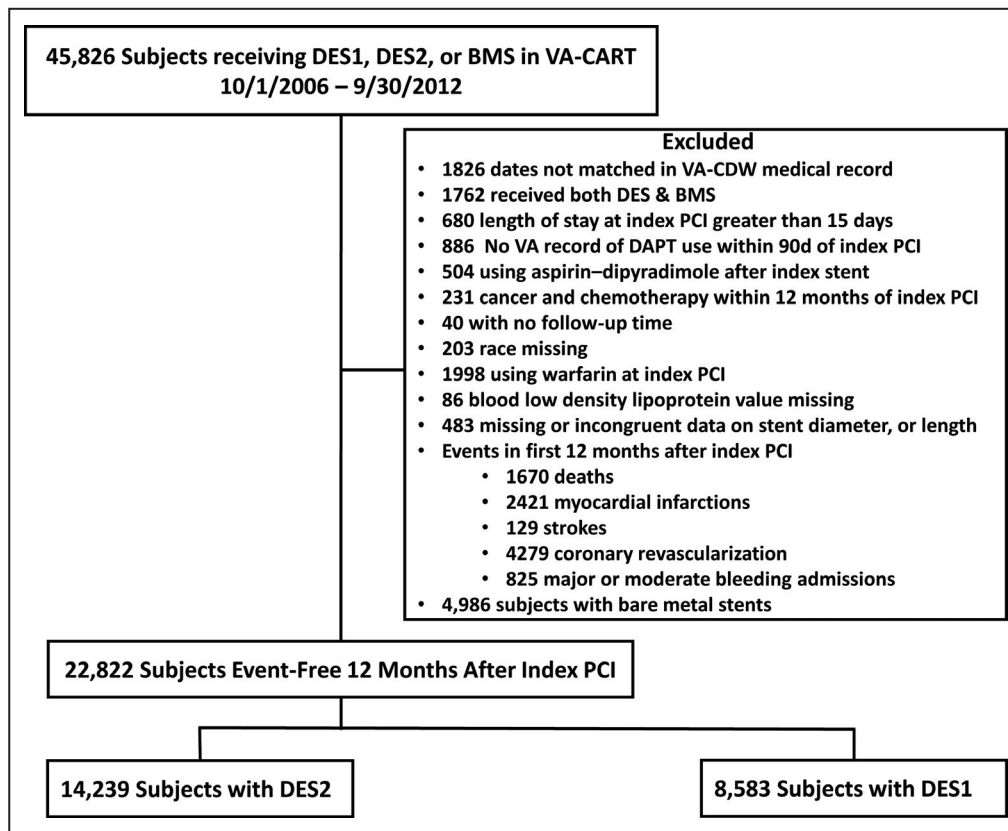


Figure 1. Flow diagram of exclusions and final cohort for analysis.

BMS indicates bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DES1, first-generation DES; DES2, second-generation DES; PCI, percutaneous coronary intervention; VA, Veterans Affairs; VA-CART, VA Clinical Assessment Reporting and Tracking; and VA-CDW, VA Corporate Data Warehouse.

in the patient health records, including anemia, atrial fibrillation, cancer, cerebrovascular disease, coronary artery disease, type 2 diabetes mellitus, heart failure, hypertension, chronic kidney disease, chronic obstructive pulmonary disease or asthma, falls or fall-related diagnosis, failure to thrive, and weight loss in the past year (see Data S1 for details).¹²

DAPT Use and Procedural Data

We tracked the use of thienopyridines over the duration of follow-up. Because 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 PCI. Aspirin use is a VA quality assessment measure, and other studies show high use of aspirin in VA patients with coronary artery disease.¹³

If a thienopyridine prescription lapsed >30 days from the last day of supply, the patient was considered not on DAPT. We defined premature discontinuation of DAPT as a DAPT duration of 1 to 9 months after PCI, based on guidelines at the time of PCI (2006–2012)

recommending at least 12 months of DAPT^{14–16} and continuous models of risk of death using restricted cubic spline hazard curves, which identified an increase in risk in patients with drug-eluting stents with DAPT duration <9 months duration of DAPT (Figure 2). We divided DAPT use into 3 groups: DAPT 1 to 9 months after PCI (premature discontinuation), DAPT >9 to 12 months, and DAPT >12 months.

We used the Clinical Assessment Reporting and Tracking database to extract the minimum and maximum stent diameters, number of stents implanted, the total length of all stents implanted, and the location or territory of the native artery or graft.

Outcomes

We determined late adverse clinical outcomes >12 months after PCI in all patients who were free of death and of these events in the first 12 months. Clinical outcomes after the index PCI were identified using ICD-9 codes until September 30, 2015 (Table S1). These included all-cause death, any MI, admissions with a new discharge diagnosis of any revascularization by PCI or

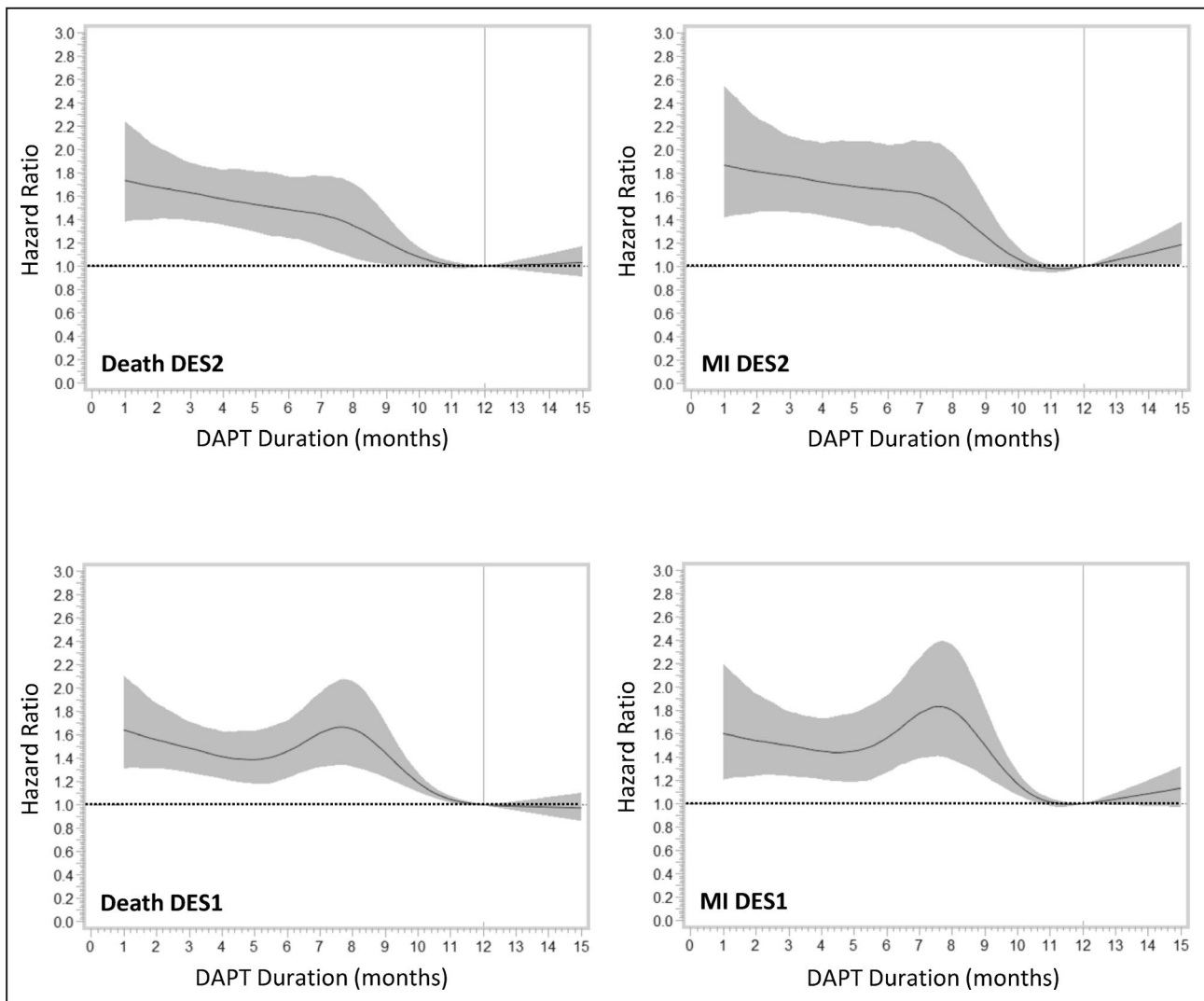


Figure 2. Cubic spline curves showing the relationship of events to dual antiplatelet therapy (DAPT) duration as a continuous variable for different events and stent types.

DES1 indicates first-generation drug-eluting stent; DES2, second-generation drug-eluting stent; and MI, myocardial infarction.

coronary artery bypass grafting, ischemic stroke, and hospitalization for major bleeding. Major bleeding was developed from a report by Jasuja et al, which was validated in a VA population.¹⁷ Our definition included bleeding into critical and noncritical anatomical sites, as defined by Jasuja et al,¹⁷ including intracranial and gastrointestinal bleeding.¹⁸

Statistical Analysis

We stratified the analysis by stent type a priori. Comorbidities and procedural characteristics were compared across the 3 DAPT durations using χ^2 , ANOVA, or Kruskal-Wallis tests, where appropriate. We identified baseline characteristics related to premature discontinuation of DAPT using odds ratios and 95% CIs from forward stepwise

logistic regression, with a *P* value to enter of <0.1 . Multivariable models assessing characteristics related to premature discontinuation of DAPT included the frailty score or comorbidities, but not both together because of collinearity between ATRIA score, frailty score, and comorbidities. The relationships of premature discontinuation of DAPT and long-term outcomes (starting 1 year after the index PCI) were estimated using hazard ratios (HRs) and 95% CIs from Cox proportional hazards regression models. Patient follow-up was censored after September 30, 2015, the last recorded VA visit, or 9 years after the index procedure. Multivariable models were developed from >50 variables and included if they were related to death (Data S1). A second method of adjustment used propensity

models to adjust for the propensity for DAPT duration >12 months, as this was the recommended duration of DAPT after PCI by national guidelines during this time period.^{14–16} We developed propensity models based on baseline variables significantly related to DAPT duration on multivariable logistic regression (Data S1). We used stabilized inverse probability weighting of the propensity score in the Cox proportional hazards models to assess the HRs for ischemic and bleeding events.¹⁹ Similarly, models assessed the relationship of DAPT duration with risk of MI, repeated revascularization, stroke, or major bleeding. In a sensitivity analysis, we restricted the cohort to patients who had no prior PCI or coronary artery bypass grafting before the index PCI in this study. All programming used SAS statistical software. Because of the multiple comparisons in this study, statistical significance was defined as a probability of <0.01.

RESULTS

From 2006 to 2012, 45 826 unique patients had PCI in the VA Healthcare System. After exclusions, 22 822 patients had complete data, including 14 239 subjects having PCI with a second-generation drug-eluting stent and 8583 subjects having PCI with a first-generation drug-eluting stent. For this analysis, we excluded 4986 patients having PCI with a bare-metal stent (Figure 1). The median duration of follow-up was 5.1 (interquartile range, 3.8–6.5) years.

The proportion of patients with an acute coronary syndrome at the index PCI was similar for second-generation drug-eluting stents (n=6581 [46%]) and first-generation drug-eluting stents (n=3920 [46%]). Acute coronary syndromes were less commonly associated with standard duration (9–12 months) DAPT (Table 1).

DAPT duration was similar for second-generation (median, 12.5 months; interquartile range, 8.8–20.4 months) and first-generation drug-eluting stents (median, 12.4 months; interquartile range, 8.3–20.5 months). During the time frame of PCI (2006–2012), clopidogrel was used in 98% of PCIs, with prasugrel used in 1.8% and ticagrelor used in 0.1% of PCIs.

Characteristics of Premature Discontinuation of DAPT

Table 1 shows the baseline characteristics of patients having PCI with second- or first-generation drug-eluting stents by the 3 periods of DAPT duration. Premature discontinuation of DAPT (<9 months) occurred in 3468 (24%) of patients with second-generation drug-eluting stents and in 2234 (26%) of

patients with first-generation drug-eluting stents. On univariate analysis, patients with premature discontinuation of DAPT were slightly younger, were more likely to be Black than White patients, were more likely to have diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, prior stroke, PCI or MI, a higher ATRIA score, and higher low-density lipoprotein cholesterol, and were more frail. They were also less likely to be taking statin medications and β -blockers.

Table 2 shows the stent number and dimensions at the index PCI. The numerical differences in stent diameters were small between DAPT duration groups (even though some reached statistical significance). Compared with standard DAPT duration (9–12 months), patients with premature discontinuation of DAPT (<9 months) and patients with >12 months DAPT more often had multiple stents or longer stent lengths.

Multivariable Models of Premature DAPT

We evaluated 2 multivariable models of associations with premature discontinuation of DAPT, one with the frailty score without comorbidities, and the other with comorbidities but not the frailty score (Table 3). Variables significantly associated with a higher risk of premature discontinuation of DAPT in multivariable models were patients who were Black individuals, those who had higher low-density lipoprotein cholesterol, or a higher frailty score, and those less frequently taking statins and antihypertensive medications. In the model without the frailty score, the comorbidities of diabetes mellitus requiring insulin, congestive heart failure, and prior stroke, PCI, or MI were associated with a higher risk of premature discontinuation of DAPT. The ATRIA score was not included in these models because of collinearity between frailty score and comorbidities.

DAPT Duration and Long-Term Outcomes

Table 4 shows the relationship of DAPT duration to death, MI, repeated coronary revascularization, stroke, and major bleeding starting from 12 months after the index PCI by the 2 stent types. These were patients who had no ischemic or bleeding events in the first year after PCI. The table shows univariate, multivariable-adjusted models, and propensity score adjusted risk of events related to DAPT duration. The multivariable and propensity score models included frailty, comorbidities, and medications (see Appendix), and were adjusted for the ATRIA score as a measure of bleeding risk. Compared with standard duration DAPT (9–12 months post-PCI), premature discontinuation of DAPT (1–9 months) associated with increased risks of late death, MI, and repeated

Table 1. Baseline Characteristics of Patients Having PCI With a Second- or First-Generation Drug-Eluting Stent by Duration of DAPT

Descriptive Variable	Second-Generation Drug-Eluting Stents				First-Generation Drug-Eluting Stents			
	DAPT Duration, mo				DAPT Duration, mo			
	≤9	9–12	>12	P Value	≤9	9–12	>12	P Value
	(n=3468)	(n=2767)	(n=8004)		(n=2234)	(n=1563)	(n=4786)	
Age, mean (SD), y	63.91 (9.12)	64.27 (8.37)	64.5 (8.22)	<0.0001	62.93 (9.63)	63.61 (8.9)	63.68 (8.55)	<0.001
Men, n (%)	3408 (98.3)	2709 (97.9)	7888 (98.6)	0.06	2191 (98.1)	1539 (98.5)	4718 (98.6)	0.28
Race, n (%)								
White	2829 (81.6)	2410 (87.1)	6998 (87.4)	<0.0001	1819 (81.4)	1364 (87.3)	4195 (87.7)	<0.0001
Black	547 (15.8)	280 (10.1)	817 (10.2)		348 (15.6)	164 (10.5)	472 (9.9)	
Other*	92 (2.7)	77 (2.8)	189 (2.4)		67 (3)	35 (2.2)	119 (2.5)	
Acute coronary syndrome at index PCI, n (%)	1721 (49.6)	1212 (43.8)	3648 (45.6)	<0.0001	1079 (48.3)	670 (42.9)	2171 (45.4)	0.003
Comorbidities 5 y before index PCI, n (%)								
Hypertension	3083 (88.9)	2395 (86.6)	7094 (88.6)	0.006	1983 (88.8)	1383 (88.5)	4294 (89.7)	0.27
Diabetes mellitus	1603 (46.2)	1189 (43)	3755 (46.9)	0.002	1085 (48.6)	700 (44.8)	2223 (46.4)	0.06
On oral hypoglycemic	1247 (36)	929 (33.6)	2965 (37)	0.005	874 (39.1)	535 (34.2)	1772 (37)	0.009
Diabetes mellitus on insulin	674 (19.4)	445 (16.1)	1437 (18)	0.0005	422 (18.9)	251 (16.1)	814 (17)	0.05
Chronic obstructive pulmonary disease	1123 (32.4)	781 (28.2)	2455 (30.7)	0.002	679 (30.4)	487 (31.2)	1489 (31.1)	0.81
Chronic kidney disease	477 (13.8)	307 (11.1)	952 (11.9)	0.003	287 (12.8)	165 (10.6)	546 (11.4)	0.07
Peripheral artery disease	225 (6.5)	132 (4.8)	517 (6.5)	0.004	146 (6.5)	83 (5.3)	287 (6)	0.29
Smoker	2857 (82.4)	2290 (82.8)	6643 (83)	0.72	1827 (81.8)	1294 (82.8)	3929 (82.1)	0.72
Congestive heart failure	691 (19.9)	421 (15.2)	1327 (16.6)	<0.0001	482 (21.6)	269 (17.2)	831 (17.4)	<0.0001
Angina	1176 (33.9)	815 (29.5)	2552 (31.9)	0.009	854 (38.2)	487 (31.2)	1740 (36.4)	<0.0001
Anemia	547 (15.8)	400 (14.5)	1194 (14.9)	0.31	366 (16.4)	222 (14.2)	703 (14.7)	0.11
Prior stroke	260 (7.5)	143 (5.2)	473 (5.9)	0.0003	180 (8.1)	84 (5.4)	293 (6.1)	0.001
Prior CABG	105 (3)	67 (2.4)	254 (3.2)	0.13	63 (2.8)	32 (2)	132 (2.8)	0.26
Prior PCI	1536 (44.3)	1036 (37.4)	3165 (39.5)	<0.0001	1095 (49)	615 (39.3)	2049 (42.8)	<0.0001
Prior AMI	1351 (39)	828 (29.9)	2717 (33.9)	<0.0001	846 (37.9)	490 (31.3)	1679 (35.1)	0.0002
Medication use, n (%)								
Statins	2941 (84.8)	2410 (87.1)	7054 (88.1)	<0.0001	1892 (84.7)	1373 (87.8)	4199 (87.7)	0.001
β-Blockers	2477 (71.4)	2066 (74.7)	6061 (75.7)	<0.0001	1735 (77.7)	1225 (78.4)	3841 (80.3)	0.03
Calcium channel blocker	903 (26)	749 (27.1)	2151 (26.9)	0.57	551 (24.7)	414 (26.5)	1309 (27.4)	0.06
ACE inhibitor	2067 (59.6)	1670 (60.4)	4926 (61.5)	0.12	1438 (64.4)	1005 (64.3)	3095 (64.7)	0.95
Angiotensin receptor blocker	318 (9.2)	282 (10.2)	952 (11.9)	<0.001	180 (8.1)	140 (9)	511 (10.7)	0.001
Diuretics	169 (4.9)	150 (5.4)	461 (5.8)	0.16	97 (4.3)	101 (6.5)	265 (5.5)	0.01
Atria score ≥4, n (%)	865 (24.9)	613 (22.2)	1855 (23.2)	0.03	572 (25.6)	374 (23.9)	1111 (23.2)	0.09
Laboratory values, median (IQR)								
LDL cholesterol, mg/dL	84 (65–109)	80 (64–99)	76 (61–94)	<0.001	86 (67–110)	80 (64–99)	78.5 (63–96)	<0.04
Creatinine, mg/dL	1.02 (0.9–1.2)	1.01 (0.9–1.2)	1.04 (0.9–1.2)	0.008	1.07 (0.9–1.29)	1.03 (0.9–1.2)	1.08 (0.9–1.23)	0.21
eGFR, mL/min	77 (62–91)	78 (63–91)	76 (62–90)	0.002	76 (60–92)	77 (62–90)	74 (60–90)	0.06
Frailty score, median (IQR)	6 (4–8)	5 (3–7)	5.5 (4–8)	<0.0001	6 (4–8)	5 (4–7)	5 (4–8)	<0.0001

ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LDL, low-density lipoprotein; and PCI, percutaneous coronary intervention.

*Other includes non-White/non-Black

Table 2. Stent Dimensions and Number of Stents at Index PCI by Type of DES

Variable	Duration of Dual Antiplatelet Therapy, mo			P Value
	≤9	9–12	>12	
Second-generation DES (N=14 239)	3468	2767	8004	
Minimum diameter, mean (SD), mm	2.86 (0.42)	2.87 (0.42)	2.88 (0.42)	0.02
Maximum diameter, mean (SD), mm	3.00 (0.44)	3.00 (0.44)	3.02 (0.44)	0.001
No. of stents, n (%)				
1	2156 (62.2)	1835 (66.3)	5010 (62.6)	<0.0001
2	899 (25.9)	661 (23.9)	1959 (24.5)	
≥3	413 (11.9)	271 (9.8)	1035 (12.9)	
Length of stents, mean (SD), mm	29.0 (19.7)	27.8 (18.5)	29.8 (21.1)	0.003
First-generation DES (N=8583)	2234	1563	4786	
Minimum diameter, mean (SD), mm	2.85 (0.42)	2.85 (0.40)	2.84 (0.40)	0.61
Maximum diameter, mean (SD), mm	2.98 (0.43)	2.95 (0.41)	2.98 (0.42)	0.06
No. of stents, n (%)				
1	1456 (65.2)	1064 (68.1)	2958 (61.8)	<0.0001
2	541 (24.2)	348 (22.3)	1228 (25.7)	
≥3	237 (10.6)	151 (9.7)	600 (12.5)	
Length of stents, mean (SD), mm	28.6 (19.3)	27.6 (19.1)	30.2 (20.8)	<0.0001

DES indicates drug-eluting stent; SD, standard deviation; and PCI, percutaneous coronary intervention.

revascularization, and remained significant in multivariable and propensity score models and after adjusting for the ATRIA score. Shorter DAPT also associated with stroke for second-generation drug-eluting stents.

Figure 3 shows event curves for death, MI, and repeated revascularization by stent type and DAPT duration. These show the differences in absolute risk for the models in Table 4 and the higher absolute long-term risk of major ischemic events in patients who discontinued DAPT prematurely.

Sensitivity Analyses

Separate models that combined both stent types showed no significant interactions with stent type and the risk of poorer ischemic outcomes with premature discontinuation of DAPT. We also restricted the cohort to the 12 979 patients without PCI or coronary artery bypass grafting before their index PCI in this study, and the results from multivariable models were similar for premature discontinuation of DAPT. For patients having second-generation drug-eluting stents in this restricted analysis, premature discontinuation of DAPT was significantly ($P<0.01$) associated with death (HR, 1.34; 95% CI, 1.09–1.63) and MI (HR, 1.55; 95% CI, 1.19–2.02). Similarly, among patients having first-generation drug-eluting stents, premature discontinuation of DAPT was significantly associated with death (HR, 1.37; 95% CI, 1.13–1.67), MI (HR, 1.60; 95% CI, 1.23–2.08), and repeated coronary revascularization (HR, 1.46; 95% CI, 1.21–1.76).

DISCUSSION

Our rates of premature discontinuation of DAPT of 23% to 24% are similar to other PCI registries of 23% to 29%,^{4–6,20} but larger than the DAPT randomized trial of 5%.⁷ Other observational studies reported higher short-term risks of death and ischemic events in the first 1 to 2 years after PCI among patients who discontinued DAPT prematurely.^{3–7} Our study shows that these risks persist, so that *even in patients who were free of adverse events in the first year*, premature discontinuation of DAPT continued to have a high late risk of death and ischemic events over an average 5 years after PCI.

In our study, Black race was associated with higher rates of premature discontinuation of DAPT. Other studies have found more premature discontinuation of DAPT in Black versus White patients²¹ and higher long-term risks of ischemic events after PCI in Black patients that are attenuated when adjusted for differences in comorbidities and socioeconomic status.^{21–24} This is consistent with our multivariable models, where use of statins and anti-hypertensive medications was less common and a higher frailty score more common in patients with premature discontinuation of DAPT. However, in our study, there was a residual elevated risk of premature discontinuation of DAPT in Black patients that may reflect other differences in social conditions or opportunities.

In the multivariable model without the frailty score, several comorbidities, such as diabetes mellitus, prior

stroke, PCI, or MI, were associated with premature discontinuation of DAPT. This seems paradoxical as these are high-risk factors for future cardiovascular disease and may benefit from longer DAPT therapy. However, these comorbidities increase the frailty score and are related to increased risk of bleeding, as evidenced by their higher ATRIA score (Table 1).

Our study assessed the long-term risk of DAPT duration over an average 5 years after PCI. The exclusion of events in the first year of our study attempted to remove the impact these short-term risks would have on long-term risk, which was our primary objective. The strong relationships between premature discontinuation of DAPT and long-term outcomes in our study reflect the impact of factors that likely relate to premature discontinuation of DAPT and adverse outcomes. The variables related to premature discontinuation of DAPT in our study were similar to those found in other studies examining the risk of adverse events within 2 years of PCI, such as medication nonadherence,⁷ patient location,⁴ less education,⁶ avoidance of health care because of cost,⁶ and other preexisting cardiovascular disease or anemia.⁶

The ATRIA score, which is a measure of bleeding risk, includes variables that are included in the frailty score, such as age and comorbidities. Thus, premature discontinuation of DAPT could also be attributable to prescriber concerns of increased bleeding risk as well as frailty. Although premature discontinuation of DAPT was not significantly associated with an increased risk of long-term major bleeding, the HRs all trend to an increased risk of bleeding in this group and support a higher risk, as indicated by the higher ATRIA score and other risk factors for bleeding. Our study shows that the risk of adverse events related to premature discontinuation of DAPT persists over a longer time frame than previously described.

The implication of our study is that patients who prematurely discontinue DAPT are a high-risk group many years after their PCI. This increased risk likely relates to comorbidities that increase frailty, bleeding risk, and other social factors, which may warrant more intensive follow-up after PCI to prevent long-term adverse events.

The limitations of this study relate to its observational nature and the potential for unknown confounders to

Table 3. ORs and 95% CIs From Multivariable Models of Variables Related to Premature Discontinuation of DAPT

Variable	Model 1		Model 2	
	OR	95% CI	OR	95% CI
Age	0.992	0.989–0.996	0.994	0.990–0.997
Men vs women	1.033	0.813–1.314	0.986	0.775–1.253
Race				
Black vs White	1.535	1.401–1.683	1.499	1.367–1.644
Other race vs White	1.131	0.931–1.374	1.133	0.932–1.377
Second- vs first-generation drug-eluting stent	0.922	0.864–0.983	0.932	0.874–0.994
Frailty score	1.043	1.032–1.053		
Diabetes mellitus requiring insulin			1.103	1.034–1.177
Congestive heart failure history			1.185	1.091–1.288
Prior stroke			1.294	1.145–1.463
Prior PCI			1.212	1.132–1.298
Prior myocardial infarction			1.130	1.053–1.212
Medication use				
Statins	0.870	0.795–0.952	0.850	0.776–0.930
β-Blockers	0.888	0.825–0.955	0.881	0.819–0.949
Calcium channel blockers	0.911	0.847–0.980	0.929	0.863–0.999
Angiotensin receptor blocker	0.774	0.694–0.864	0.768	0.688–0.857
Diuretic	0.837	0.725–0.967	0.862	0.745–0.996
Low-density lipoprotein	1.007	1.006–1.008	1.007	1.007–1.008

The 2 models had either the frailty score or comorbidities attributable to collinearity between these variables. DAPT indicates dual antiplatelet therapy; OR, odds ratio; and PCI, percutaneous coronary intervention.

Table 4. Duration of DAPT by Each Stent Type and Risk of End Points >1 Year After the Index PCI

DAPT Duration	Model	Death HR (95% CI) P Value	Myocardial Infarction HR (95% CI) P Value	Coronary Revascularization HR (95% CI) P Value	Stroke HR (95% CI) P Value	Major Bleed HR (95% CI) P Value
Second-generation drug-eluting stents						
≤9 mo	No. of events	556	380	560	102	138
	Unadjusted	1.51 (1.32–1.74) <0.0001*	1.68 (1.41–2.00) <0.0001*	1.32 (1.16–1.51) <0.0001*	1.86 (1.31–2.64) 0.0005†	1.34 (0.93–1.93) 0.12
	Multivariable	1.35 (1.185–1.56) <0.0001*	1.46 (1.22–1.74) <0.0001*	1.24 (1.08–1.41) 0.002‡	1.66 (1.17–2.36) 0.005‡	1.35 (0.93–1.96) 0.11
	Propensity	1.24 (1.08–1.44) 0.0033‡	1.38 (1.15–1.65) 0.0006†	1.22 (1.06–1.40) 0.005‡	1.49 (1.03–2.16) 0.0355	1.19 (0.81–1.73) 0.38
>9–12 mo	No. of events	299	188	351	45	106
	All	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>12 mo	No. of events	904	659	1153	167	296
	Unadjusted	1.02 (0.89–1.16) 0.82	1.20 (1.02–1.41) 0.0305	1.13 (1.00–1.27) 0.0495	1.26 (0.91–1.75) 0.17	1.18 (0.79–1.76) 0.41
	Multivariable	0.96 (0.84–1.09) 0.52	1.14 (0.97–1.34) 0.12	1.11 (0.99–1.25) 0.08	1.20 (0.86–1.66) 0.29	1.19 (0.80–1.78) 0.39
	Propensity	0.92 (0.80–1.05) 0.20	1.11 (0.94–1.31) 0.24	1.11 (0.98–1.25) 0.10	1.15 (0.82–1.61) 0.43	1.08 (0.72–1.63) 0.70
First-generation drug-eluting stents						
≤9 mo	No. of events	605	379	596	81	143
	Unadjusted	1.42 (1.23–1.62) <0.0001*	1.42 (1.19–1.68) 0.0001†	1.34 (1.18–1.54) <0.0001*	1.15 (0.81–1.64) 0.43	1.25 (0.95–1.64) 0.11
	Multivariable	1.30 (1.13–1.49) 0.0002†	1.28 (1.08–1.53) 0.005‡	1.28 (1.12–1.47) 0.0003‡	1.08 (0.76–1.54) 0.68	1.20 (0.91–1.57) 0.20
	Propensity	1.37 (1.19–1.58) <0.0001*	1.26 (1.06–1.50) 0.0101	1.27 (1.11–1.46) 0.0006†	1.11 (0.78–1.59) 0.56	1.16 (0.88–1.53) 0.30
>9–12 mo	No. of events	310	197	334	51	83
	All	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>12 mo	No. of events	869	639	1036	115	241
	Unadjusted	0.90 (0.79–1.03) 0.13	1.05 (0.89–1.23) 0.58	1.00 (0.89–1.14) 0.95	0.72 (0.52–1.00) 0.053	0.94 (0.73–1.20) 0.60
	Multivariable	0.87 (0.77–0.99) 0.038	1.00 (0.85–1.17) 0.98	0.99 (0.87–1.12) 0.83	0.71 (0.51–0.98) 0.038	0.91 (0.71–1.17) 0.48
	Propensity	0.92 (0.81–1.06) 0.24	0.97 (0.83–1.15) 0.75	0.96 (0.85–1.09) 0.53	0.73 (0.53–1.02) 0.068	0.91 (0.71–1.17) 0.46

HRs are for unadjusted, adjusted, and propensity score inverse probability weighted models. DAPT indicates dual antiplatelet therapy; HR, hazard ratio; and PCI, percutaneous coronary intervention.

* $P < 0.0001$.

† $P < 0.001$.

‡ $P < 0.01$.

influence the results. Our methods of assessing medication used pharmacy records of dispensing and renewing drug prescriptions and may not reflect methods used in clinical trials, such as pill counting of returned medications. Although aspirin use is high in patients with coronary artery disease in the VA Health System,¹³ aspirin use was not recorded and some patients may have stopped aspirin, remained on a thienopyridine as monotherapy, and been considered in the DAPT group.

In conclusion, in patients who are free of ischemic and bleeding events in the 12 months after PCI,

premature discontinuation of DAPT in the first year after PCI was more common in Black patients and patients with higher rates of comorbidities and lower rates of other guideline-based medical therapies for cardiovascular disease. Patients who discontinue DAPT prematurely have a persistently high long-term risk of ischemic events over an average of 5 years. They may benefit from efforts to promote the use of guideline-based medical therapies and more intensive surveillance to prevent long-term cardiovascular events.

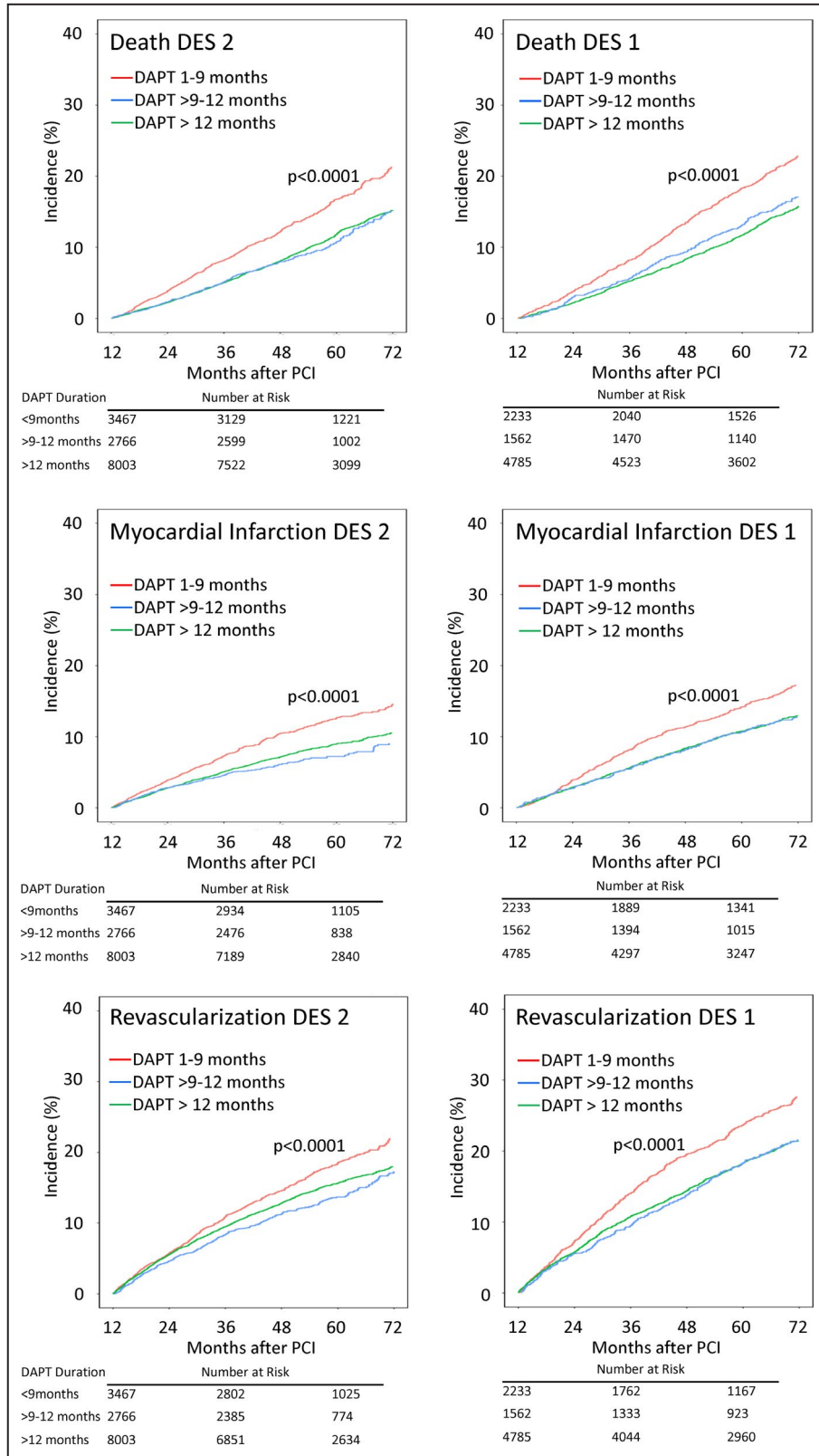


Figure 3. Event curves for death, myocardial infarction, and coronary revascularization events occurring >12 months after percutaneous coronary intervention (PCI) for second-generation drug-eluting stents (DES2s) and first-generation drug-eluting stents (DES1s) by dual antiplatelet therapy (DAPT) duration.

ARTICLE INFORMATION

Received October 20, 2020; accepted February 4, 2021.

Affiliations

Veterans Affairs Boston Healthcare System, West Roxbury, MA (S.K., L.Q., J.C., N.M., Y.H., M.Y., R.S., K.C., R.R., M.G., D.G.); Brigham and Women's Hospital, Boston, MA (S.K., D.P.F., R.R., M.G.); Harvard Medical School, Boston, MA (S.K., D.P.F., R.R., M.G.); Department of Biostatistics, Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) VA Boston Healthcare System, Boston, MA (S.K., L.Q., J.C., N.M., Y.H., M.Y., K.C., M.G., D.G.); and Boston University School of Public Health, Boston, MA (D.G.).

Sources of Funding

This research was supported by the Veterans Affairs Clinical Science Research and Development Awards 1/01CX000440 and 1/01CX001549.

Disclosures

Dr Kinlay consulted for the Colorado Prevention Center (Data Safety Monitoring Board [DSMB]). The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Table S1

REFERENCES

- Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;134:e123–e155. DOI: 10.1161/CIR.0000000000000404.
- Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39:213–260. DOI: 10.1093/eurheartj/ehx419.
- Cutlip DE, Kereiakes DJ, Mauri L, Stoler R, Dauerman HL; EDUCATE Investigators. Thrombotic complications associated with early and late nonadherence to dual antiplatelet therapy. *JACC Cardiovasc Interv*. 2015;8:404–410. DOI: 10.1016/j.jcin.2014.10.017.
- Mathews R, Wang W, Kaltenbach LA, Thomas L, Shah RU, Ali M, Peterson ED, Wang TY. Hospital variation in adherence rates to secondary prevention medications and the implications on quality. *Circulation*. 2018;137:2128–2138. DOI: 10.1161/CIRCULATIONAHA.117.029160.
- Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet*. 2013;382:1714–1722. DOI: 10.1016/S0140-6736(13)61720-1.
- Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, Messenger JC, Khanal S, Peterson ED, Bach RG, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113:2803–2809. DOI: 10.1161/CIRCULATIONAHA.106.618066.
- Stefanescu Schmidt AC, Steg PG, Yeh RW, Kereiakes DJ, Tanguay JF, Hsieh WH, Massaro JM, Mauri L, Cutlip DE; DAPT Investigators. Interruption of dual antiplatelet therapy within six months after coronary stents (from the Dual Antiplatelet Therapy Study). *Am J Cardiol*. 2019;124:1813–1820. DOI: 10.1016/j.amjcard.2019.09.006.
- Maddox TM, Plomondon ME, Petrich M, Tsai TT, Gethoffer H, Noonan G, Gillespie B, Box T, Fihn SD, Jesse RL, et al. A national clinical quality program for Veterans Affairs catheterization laboratories (from the Veterans Affairs clinical assessment, reporting, and tracking program). *Am J Cardiol*. 2014;114:1750–1757. DOI: 10.1016/j.amjcard.2014.08.045.
- Song RJ, Ho Y-L, Nguyen X-MT, Honerlaw J, Quaden R, Gaziano JM, Concato J, Cho K, Gagnon DR; Group MVP. Development of an electronic health record-based algorithm for smoking status using the Million Veteran Program (MVP) cohort survey response. *Circulation*. 2016;134(suppl 1):A18809.
- Urban P, Mehran R, Collieran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. *Circulation*. 2019;140:240–261.
- Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study. *J Am Coll Cardiol*. 2011;58:395–401. DOI: 10.1016/j.jacc.2011.03.031.
- Orkaby AR, Nussbaum L, Ho YL, Gagnon D, Quach L, Ward R, Quaden R, Yaksic E, Harrington K, Paik JM, et al. The burden of frailty among U.S. veterans and its association with mortality, 2002–2012. *J Gerontol A Biol Sci Med Sci*. 2019;74:1257–1264. DOI: 10.1093/geronol/gly232.
- Jha AK, Perlin JB, Steinman MA, Peabody JW, Ayanian JZ. Quality of ambulatory care for women and men in the Veterans Affairs Health Care System. *J Gen Intern Med*. 2005;20:762–765.
- Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574–e651. DOI: 10.1161/CIR.0b013e31823ba622.
- Smith SC, Feldman TE, Hirshfeld JW, Jacobs AK, Kern MJ, King SB III, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (ACC/AHA/SCAI writing committee to update the 2001 guidelines for percutaneous coronary intervention). *Circulation*. 2006;113:156–175. DOI: 10.1161/CIRCULATIONAHA.105.170815.
- Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI); Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliquet T, Garg S, Huber K, James S, Knuuti J, et al. Guidelines on myocardial revascularization. *Eur Heart J*. 2010;31:2501–2555.
- Jasuja GK, Reisman JI, Miller DR, Berlowitz DR, Hylek EM, Ash AS, Ozonoff A, Zhao S, Rose AJ. Identifying major hemorrhage with automated data: results of the Veterans Affairs study to improve anticoagulation (VARIA). *Thromb Res*. 2013;131:31–36. DOI: 10.1016/j.thromres.2012.10.010.
- Wimmer NJ, Dufour AB, Cho K, Gagnon DR, Quach L, Ly S, Do J-M, Ostrowski S, Michael Gaziano J, Faxon DP, et al. Long-term outcomes in patients with acute coronary syndromes related to prolonging dual antiplatelet therapy more than 12 months after coronary stenting. *Catheter Cardiovasc Interv*. 2017;89:1176–1184. DOI: 10.1002/ccd.26831.
- Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*. 2000;11:561–570. DOI: 10.1097/00001648-200009000-00012.
- Smolderen KG, Spertus JA, Tang F, Oetgen W, Borden WB, Ting HH, Chan PS. Treatment differences by health insurance among outpatients with coronary artery disease: insights from the National Cardiovascular Data Registry. *J Am Coll Cardiol*. 2013;61:1069–1075. DOI: 10.1016/j.jacc.2012.11.058.
- Sullivan LT II, Mulder H, Chiswell K, Shaw LK, Wang TY, Jackson LR II, Thomas KL. Racial differences in long-term outcomes among black and white patients with drug-eluting stents. *Am Heart J*. 2019;214:46–53. DOI: 10.1016/j.ahj.2019.04.005.

-
22. Ellis SG, Cho L, Raymond R, Nair R, Simpfendorfer C, Tuzcu M, Bajzer C, Lincoff AM, Kapadia S. Comparison of long-term clinical outcomes after drug-eluting stenting in blacks-vs-whites. *Am J Cardiol.* 2019;124:1179–1185. DOI: 10.1016/j.amjcard.2019.07.020.
 23. Kobayashi T, Glorioso TJ, Armstrong EJ, Maddox TM, Plomondon ME, Grunwald GK, Bradley SM, Tsai TT, Waldo SW, Rao SV, et al. Comparative outcomes after percutaneous coronary intervention among black and white patients treated at US Veterans Affairs Hospitals. *JAMA Cardiol.* 2017;2:967–975. DOI: 10.1001/jamacardio.2017.2180.
 24. Pradhan J, Schreiber TL, Niraj A, Veeranna V, Ramesh K, Saigh L, Afonso L. Comparison of five-year outcome in African Americans versus Caucasians following percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2008;72:36–44. DOI: 10.1002/ccd.21556.

Supplemental Material

Data S1.

Supplemental Methods

Covariates in the Multivariable Model

The HRs from final multivariable models for each outcome were adjusted for the baseline characteristics of smoking, acute coronary syndrome on admission, comorbidities of diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, congestive heart failure, prior stroke, prior PCI, prior myocardial infarction, use of statins, beta-blockers, calcium-channel blockers, angiotensin receptor blockers or converting enzyme inhibitors, diuretics, warfarin use within 7 days of the index procedure, year of stent placement, and total stent length.

Frailty Score

The frailty score was developed from the following 31 variables defined from ICD9 codes in the patient health records: anemia, atrial fibrillation, cancer, cerebrovascular disease, coronary artery disease, type 2 diabetes mellitus, heart failure, hypertension, chronic kidney disease without dialysis, chronic kidney disease with dialysis, liver disease or cirrhosis, lung disease (COPD or asthma), thyroid disease, osteoporosis, incontinence, arthritis, use of durable medical equipment, falls or fall related diagnosis, fatigue, gait abnormality, Parkinson's disease and tremors, peripheral vascular disease or intermittent claudication, muscular wasting (including cachexia or debility), hearing impairment or aid, peripheral neuropathy, vision impairment (macular degeneration, glaucoma, blindness), dementia, anxiety, depression or bipolar disease, chronic pain, failure to thrive, weight loss in the past year.

Propensity Score

Forward multiple logistic regression (p-value to enter < 0.1) was used to select baseline variables associated with the propensity for DAPT duration more than 12 months duration. These were selected from demographic variables, comorbidities, medications, and procedural characteristics at the index PCI. Variables selected for the score were: sex, race, diabetes, chronic obstructive pulmonary disease, peripheral artery disease, smoking status, history of congestive heart failure, history of angina, anemia, prior stroke, prior CABG, prior PCI, prior myocardial infarction, use of statins, beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, diuretics, total stent length, LDL cholesterol.

Table S1. ICD9 codes used to define comorbidities and major ischemic and bleeding events.

Event	ICD9 Codes
Myocardial Infarction	410.x
Coronary Revascularization	ICD9: 36.10-36.19, 36.06, 35.07, 00.66, or CPT codes: 92980, 92981, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944
Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436
Major Bleeding	379.23, 423.0, 430-432, 568.81, 719.1x, 456.0, 459.0, 530.21, 530.7, 530.82, 531.x0, 531.x0, 533.x0, 534.x0, 535.01, 535.x1, 535.71, 537.83, 562.12, 562.13, 569.3, 569.85, 578.0, 578.1, 578.9, 784.8, 786.30, 786.31, 786.39
Acute coronary syndrome	VA CART indication of ST-elevation MI, Non-ST-elevation MI, unstable angina, or if no indication in CART, a CDW ICD9 code of 410.x, 411.1, 411.8
Angina	413.x
Hypertension	401.x
Congestive Heart Failure	428
Diabetes Mellitus	250.x
Anemia	281, 283-5
Cancer	140-208, 209.0-209.3x, 209.7x
Chronic Obstructive Airways Disease	490-493, 494, 496
Peripheral Artery Disease	440.2x
Chronic Kidney Disease	585