Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention for Chronic Total Occlusion

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The optimal duration of dual antiplatelet therapy (DAPT) after treatment of chronic total occlusions (CTO) with percutaneous coronary intervention (PCI) is unknown. We aimed to determine if extended (> 12 months) DAPT was associated with a net clinical benefit. The study population included patients who underwent successful CTO PCI within Kaiser Permanente Northern California between 2009 and 2016. Baseline demographic, clinical, and procedural characteristics were compared for patients on DAPT ≤ versus > 12 months. Clinical outcomes (death, myocardial infarction (MI), and ≥ Academic Research Consortium type 3a bleeding) were compared beginning 12 months after PCI using Cox proportional hazards models. We also adjudicated individual causes of death. 1,069 patients were followed for a median of 3.6 years (Interquartile Range = 2.2 to 5.5) following CTO PCI. Patients on DAPT ≤ 12 months (n = 597, 56%) were more likely to have anemia, end stage renal disease, and previous MI. After adjustment for between group differences, > 12 months of DAPT was associated with lower death or MI (hazard ratio [HR]: 0.66; 95% confidence interval [CI]: 0.47 to 0.93) and lower death (HR: 0.54; 95% CI: 0.36 to 0.82). There were no associations with MI (HR: 0.91; 95% CI: 0.55 to 1.5) or bleeding (HR 1.1; 95% CI: 0.50 to 2.4), but a numerically higher proportion of patients on shorter v. longer DAPT died of a cardiovascular cause (37% vs 20%, p = 0.10). In conclusion, > 12 months of DAPT was associated with lower death or MI, without an increase in bleeding. Prospective studies are needed to evaluate the optimal duration of DAPT in this unique subgroup. **(Am J Cardiol 2020;132:44−51)**

The Dual Antiplatelet (DAPT) study, the largest randomized trial to date assessing the effect of prolonged duration (30 months) of aspirin and thienopyridine therapy versus standard duration (12 months) after percutaneous coronary intervention (PCI), did not evaluate chronic total occlusions (CTO).[1] American guidelines recommend 6 months of DAPT after PCI with a drug eluting stent in patients with stable ischemic heart disease, but they also do not address CTOs.[2] The European guidelines, while also recommending 6 months, suggest considering > 6 months of DAPT in patients who are at high thrombotic risk.[3] This was based on data showing improved outcomes with long-term (≥12 months) versus short-term DAPT (3 to 6 months), in patients who underwent complex PCI, which included CTO.[4] In the only previous study to our knowledge that specifically addressed the duration of DAPT in CTO PCI, Lee et al found that DAPT duration ≤ 12 months was associated with similar outcomes compared with > 12 months.[5] However, this study did not include patients with previous coronary artery bypass grafting, or those on oral anticoagulation. Given these remaining knowledge gaps, we aimed to determine if extended (> 12 months) DAPT was associated with a net clinical benefit in patients who underwent CTO PCI.

Methods

The study population included patients who underwent CTO PCI within the regional cardiac catheterization laboratories of Kaiser Permanente Northern California (KPNC) between July 1, 2009 and December 31, 2016. KPNC is an integrated health plan providing comprehensive care to more than 4 million members in Northern California. The health plan owns and operates 21 medical centers, ambulatory care facilities, pharmacies, and laboratories. The KPNC membership is broadly representative of the California population in terms of ethnic and socioeconomic profile.[6]

CTO PCI cases were initially identified using KPNC's cardiac catheterization labs' American College of Cardiology / National Cardiovascular Data Registry data sets with operator-identified CTO as the target lesion. When a guidewire did not cross the lesion, or less than TIMI 2 flow or greater than 50% stenosis was present on the final

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angiogram, the cases were deemed unsuccessful and were excluded. The primary author (A.S.) then did a manual adjudication of every case by chart review and excluded all patients that did not fit the definition of CTO, using clinical presentation, electrocardiogram, and laboratory data (CTOs were defined as lesions with thrombolysis in myocardial infarction 0 flow [i.e., absence of any anterograde flow beyond the occlusion] with an estimated or known occlusion duration of > 3 months).[7] Individual angiograms were not reviewed. Saphenous vein graft CTO PCI and patients treated with bare metal stents were excluded (Figure 1).

Baseline, demographic, and procedural data were extracted from KPNC electronic medical records databases including variables submitted to the American College of Cardiology National Cardiovascular Data Registry Cath PCI Quality Registry in accordance with definitions specified in version 4.4.[8] Laboratory data were obtained at the time of cardiac catheterization or the most recent value before the procedure.

P2Y12 antagonist (clopidogrel, prasugrel, ticagrelor) use was obtained by extracting prescription records through an electronic pharmacy database, using previously validated methods.[9] Subjects in the study obtained medications from health plan pharmacies; those without or with incomplete prescription records were excluded. The number of prescriptions filled, the daily dose, and the number of pills dispensed for each prescription beginning on the day of discharge after the index PCI were used to calculate the duration of P2Y12 antagonist use.

For any two consecutive prescriptions, we examined the time between the projected end date of the first prescription and the date of the next filled prescription. The projected P2Y12 antagonist end date is calculated as the prescription dispensed date plus the days of supply. We allowed a gap

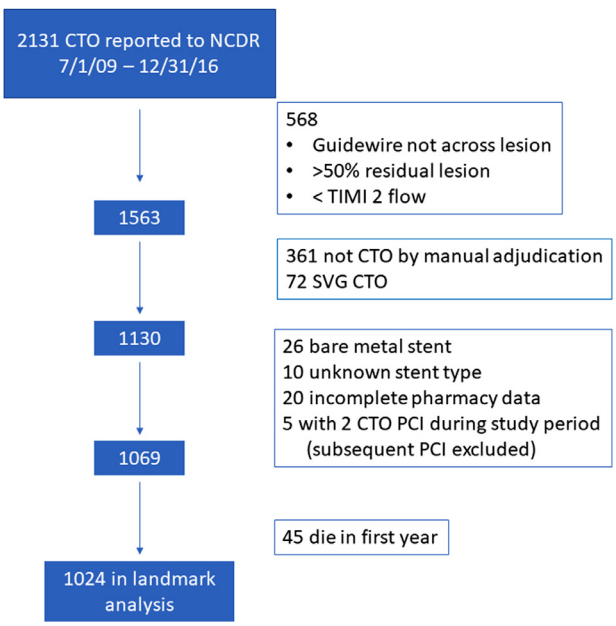

Figure 1. Cohort selection flowchart.
CTO = chronic total occlusion; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention; SVG = saphenous vein graft; TIMI = Thrombolysis in Myocardial Infarction.

of 5 days between dispensed prescriptions. The rationale for this is based on the pharmacokinetics of the drugs[10–12] and has been used before.[13] If the time between the projected end date of the first prescription and the fill date of the next prescription was ≤ 5 days, we considered patients to be continuously receiving the P2Y12 antagonist. If the time interval was >5 days, the patient was considered off the P2Y12 antagonist starting the day after the projected end date. The P2Y12 antagonist duration of therapy was calculated between the start date of the first prescription and projected end date of the last prescription. Additionally, since 28% of patients were already on P2Y12 antagonist therapy before CTO PCI and most prescriptions are dispensed for 90 or 100 days in our system, we included P2Y12 antagonist prescriptions 100 days before CTO PCI. For these patients, the duration is calculated between the CTO PCI date and projected end date of the last prescription.

Aspirin use was not available through the prescription database. Therefore, we performed a chart review of 100 randomly sampled patients not on oral anticoagulants and without documented aspirin allergy to determine the prevalence of concomitant aspirin use. Ninety-nine of 100 (99%) were documented to be taking aspirin at baseline after PCI, and 92% at 1 year.

We also performed a chart review of the 93 patients who were on oral anticoagulant therapy to assess the prevalence of concomitant aspirin therapy given the possibility of lower aspirin use in this population. We found that there was documentation of aspirin use in 96% of the patients. Of the 89 patients that had documentation of aspirin use, 96% were treated with aspirin for at least 1 month. Of those who were treated at least 1 month, 7% were treated for 1 month only, 2% 3 months only, 1% 6 months only, and the remaining 90% were treated with aspirin indefinitely.

Given the very high percentages of patients on concomitant aspirin therapy at one year, we deemed that P2Y12 antagonist therapy was synonymous with “DAPT” for those without a documented aspirin allergy.

The primary end point of the study was a composite of all-cause mortality and MI. Secondary end points included all-cause mortality alone, MI alone, bleeding according Bleeding Academic Research Consortium (BARC) criteria[14] (BARC type 3a or greater), ischemic stroke, and target lesion revascularization (TLR), which was defined as any repeat PCI of the target lesion or coronary artery bypass grafting (CABG) of the target vessel performed for restenosis or other complication of the target lesion. Deaths from any cause were ascertained from the KPNC health plan databases, California state death certificate files, and Social Security Administration Death Master file.[15,16] MI, bleeding, ischemic stroke, and TLR end points were collected by chart review by the primary author (A.S.) by reviewing all subsequent hospital stays after the index PCI hospitalization. Events were counted if coded in the list of discharge summary diagnoses. Individual causes of death (cardiovascular [CV], non-CV, and unclassifiable) were adjudicated using a previously validated method.[17] The follow-up ended on March 31, 2018.

Continuous variables were reported as mean ± standard deviation or median and interquartile range if the

distribution was not normally distributed. The Student *t* test was used for normally distributed variables, and the Wilcoxon rank sum test was used for non-normally distributed variables. Categorical variables were reported as n and percentage and analysis was performed using the chi-square test or Fisher exact test where appropriate.

We used the Kaplan-Meier method and landmark survival analyses to analyze primary and secondary outcomes in subjects who were free of that outcome at 12 months after the index PCI. Patients were followed until they died, had the outcome of interest, their health plan membership ended, or at the study follow-up end date, whichever occurred first. Comparisons between patients with different DAPT durations were conducted using log-rank tests. We calculated the hazard ratio and 95% confidence interval for the association between DAPT use of > 1 year versus ≤ 1 year and outcomes in univariate and multivariate Cox proportional hazards regression models. The multivariate model we developed included adjustments for age, gender, race/ethnicity, hypertension, peripheral arterial disease, previous heart failure, chronic kidney disease stage 3 or greater, diabetes, cerebrovascular disease, CTO PCI for in-stent restenosis, end-stage renal disease, warfarin use, previous MI, stent type (Xience [Abbott Vascular], Promus [Boston Scientific], Resolute [Medtronic], other), and previous anemia. Also, the multivariate models excluded patients with the outcome of interest in the first year and also adjusted for the other major outcomes in the first year (e.g., the hazard ratio [HR] for death or MI excluded patients with death or MI in the first year and adjusted for ischemic stroke, TLR, or > BARC 3a bleeding in the first year). Covariates for the multivariate model were selected a priori based on previously published studies, clinical relevance, or a p-value of < 0.05 in bivariate analysis.

Since the decision to continue DAPT beyond 1 year may correlate with other prognostic factors, we also performed propensity score analyses. The propensity score was constructed for prolonged thienopyridine duration from statistically significant baseline characteristics using multivariate logistic regression. Propensity score matching was conducted using the Statistical Analysis Systems PSMATCH procedure to form a matched set of patients with DAPT ≤ 1 year and DAPT > 1 year who had similar values of the propensity score. Multivariate Cox regression models were then conducted on the matched sets to estimate the hazard ratios for primary and secondary outcomes.

Finally, we performed sensitivity analyses by excluding patients 1) on oral anticoagulants (warfarin, dabigatran, apixaban, and rivaroxaban), and 2) with BARC type 3a or greater bleeding events during the first year.

All analyses were performed using Statistical Analysis Systems 9.4 (SAS institute, Cary, North Carolina). A priori level of statistical significance was set at a 2-sided P of 0.05 for all analyses. KPNC Institutional Review Board approval was received with waiver of the requirement for written informed consent.

Results

After applying eligibility criteria, 1,024 patients were alive 12 months after the index CTO PCI (Table 1). Of the patients on DAPT for more than 1 year, the median duration was 482 days (interquartile range [IQR] 327 to 637). Of those on DAPT ≤ 1 year who survived the first year (n = 552), the median duration was 199 days (IQR 97 to 301). The mean age was 64 ± 11 years, and 19% were female. There was a higher proportion of patients in the ≤ 12 months of DAPT group that had cardiomyopathy, end-stage renal disease, previous PCI, previous MI, and previous anemia. The median follow-up duration after the index PCI was 3.6 years (IQR 2.2 to 5.5).

Events between index PCI and 1 year included a rate of all-cause mortality of 4.2% (n = 45), MI 3.3% (n = 35), ≥BARC type 3a bleeding 3.0% (n = 32), ischemic stroke 0.7% (n = 8), and TLR 4.5% (n = 48). 11.6% (124) of the cohort had at least 1 adverse event in the first year. During the follow-up period (beginning at 12 months after the index PCI), the composite primary end point of all-cause mortality or MI occurred in 15.4% (n = 155) of patients.

In patients free of all-cause mortality or MI at 12 months, those who remained on DAPT for > 1 year had lower rates of the primary outcome than those who took the drug for ≤ 1 year. This finding was driven by all-cause mortality, which was higher in the group that took DAPT for ≤ 1 year, whereas the MI outcome was similar. There was no difference in bleeding rates, ischemic stroke, or TLR (Table 2) (Figure 2).

After multivariate and propensity adjustment, longer DAPT duration was associated with a lower rate of all-cause mortality or MI, driven by a significantly lower rate of all-cause mortality. Rates of MI, major bleeding, ischemic stroke, and TLR remained similar (Table 2).

In sensitivity analyses in which we excluded patients taking oral anticoagulants, we continued to show the same pattern, that is, patients taking longer DAPT also had lower rates of all-cause mortality or MI (HR 0.64; 95% confidence interval [CI]: 0.44 to 0.93), and all-cause mortality alone (HR 0.51; 95% CI: 0.33 to 0.81), and similar rates of MI (HR 0.89; 95% CI: 0.51 to 1.54), bleeding (HR 0.94; 95% CI: 0.41 to 2.18), ischemic stroke (HR 1.0; 95% CI: 0.40 to 2.51), and TLR (HR 1.31; 95% CI: 0.79 to 2.18). Findings were similar when we excluded patients with ≥ BARC 3a bleeding during the first year of follow-up [All-cause mortality or MI (HR 0.71; 95% CI: 0.49 to 1.02), all-cause mortality (HR 0.60; 95% CI: 0.39 to 0.92), MI (HR 0.92; 95% CI: 0.53 to 1.57), ischemic stroke (HR 0.83; 95% CI: 0.30 to 2.29), and TLR (HR 1.33; 95% CI: 0.80 to 2.19)].

We also performed an adjudication of causes of death in the cohort, classifying patients as CV death, non-CV death, and unclassifiable, using a validated methodology (Table 3). In this adjudication, there were a higher proportion of deaths that were related to cardiovascular causes in the group that received shorter DAPT duration, although not statistically significant. There was a similar percentage of patients in each group who died of non-CV causes, numerically higher in the longer DAPT duration group. When reviewing cases of definite or possible fatal sudden cardiac death, fatal coronary heart disease, and fatal MI, we found that 90% (18/20) of these deaths occurred suddenly out of hospital, at an emergency room out of network, or in a network hospital but suddenly.

Table 1
Study population

Characteristics	ThienopyridineDuration of therapy >12 months (n = 472)	≤12 months (n = 597)	p-value
Age (years)	64 ± 11	64 ± 11	0.438
Women	93 (20%)	107 (18%)	0.459
Race/ethnicity			0.057
White	291 (62%)	318 (53%)	
Hispanic	49 (10%)	83 (14%)	
Asian	91 (19%)	131 (22%)	
Black	19 (4%)	37 (6%)	
Other	22 (5%)	28 (5%)	
Weight (kilograms)	88 ± 21	86 ± 20	0.104
Body-mass index (kilograms/meters squared)	30 ± 6	29 ± 6	0.325
Thienopyridine*			
Clopidogrel	449 (95%)	554 (93%)	0.116
Prasugrel	35 (7%)	47 (8%)	0.780
Ticagrelor	4 (1%)	5 (1%)	1.000
Ticlopidine	1 (0%)	2 (0%)	1.000
Diabetes mellitus	193 (41%)	262 (44%)	0.325
Hypertension	381 (81%)	478 (81%)	0.790
Hyperlipidemia	402 (85%)	519 (87%)	0.407
Current cigarette smoker or within past year	50 (11%)	84 (14%)	0.088
Cerebrovascular disease	39 (8%)	62 (10%)	0.239
Previous heart failure	90 (19%)	143 (24%)	0.055
Cardiomyopathy	64 (14%)	122 (20%)	0.003
Pre-percutaneous coronary intervention left ventricular ejection fraction	50 ± 12	50 ± 13	0.804
Peripheral arterial disease	49 (10%)	68 (11%)	0.60
Chronic lung disease	47 (10%)	57 (10%)	0.822
Chronic kidney disease, stage 3 or greater	53 (11%)	72 (12%)	0.674
End stage renal disease	15 (3%)	36 (6%)	0.030
Previous percutaneous coronary intervention	164 (35%)	249 (42%)	0.020
Previous coronary artery bypass grafting	71 (15%)	91 (15%)	0.928
Previous myocardial infarction	149 (32%)	240 (40%)	0.004
Previous Anemia†	141 (30%)	242 (41%)	0.0003
Canadian Cardiovascular Society anginal class within last 2 weeks			0.865
I	19 (4%)	26 (4%)	
II	95 (20%)	114 (19%)	
III	169 (36%)	232 (39%)	
IV	143 (30%)	172 (29%)	
No symptoms, no angina	46 (10%)	53 (9%)	
Other medications			
Statins	454 (96%)	565 (95%)	0.234
Beta-blockers	445 (94%)	554 (93%)	0.331
Calcium-channel blocker	101 (21%)	93 (16%)	0.014
Ranolazine	5 (1%)	10 (2%)	0.395
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	367 (78%)	441 (74%)	0.142
Warfarin	35 (7%)	58 (10%)	0.185
Dabigatran	2 (0.4%)	3 (0.5%)	1.0
Apixaban	0 (0%)	1 (0.2%)	1.0
Rivaroxaban	0 (0%)	0 (0%)	n/a
Type of drug eluting stent at index procedure			
Everolimus-eluting, Xience	68 (14%)	86 (14%)	0.214
Everolimus-eluting, Promus	169 (36%)	215 (36%)	
Everolimus-eluting, Synergy	45 (10%)	40 (7%)	
Zotarolimus-eluting, Resolute	159 (34%)	196 (33%)	
Zotarolimus-eluting, Endeavor	5 (1%)	8 (1%)	
Sirolimus-eluting, Cypher	14 (3%)	19 (3%)	
Paclitaxel-eluting, Taxus	5 (1%)	13 (2%)	
Paclitaxel-eluting, Taxus Ion	6 (1%)	20 (3%)	
Vessel treated			0.399
Left main	5 (1%)	2 (0.3%)	
Left anterior descending / diagonal	159 (34%)	221 (37%)	

(*continued*)

Table 1 (***Continued***)

Characteristics	ThienopyridineDuration of therapy >12 months (n = 472)	≤12 months (n = 597)	p-value
Circumflex / obtuse marginal	105 (22%)	116 (19%)	
Right coronary artery / posterior descending artery / posterior left ventricular artery	200 (42%)	254 (43%)	
Ramus	3 (0.6%)	3 (0.5%)	
In-stent restenosis	30 (6%)	57 (10%)	0.058
Number of stents placed in target vessel	1.8 ± 1	1.7 ± 1	0.764
Multivessel percutaneous coronary intervention	132 (28%)	152 (28%)	0.878
Maximum stent diameter			0.743
< 3 millimeters	189 (40%)	246 (41%)	
≥ 3 millimeters	281 (60%)	351 (59%)	
Lesion length	25 ± 15	27 ± 16	0.052
Bifurcation lesion	73 (15%)	113 (19%)	0.138
Thrombolysis in Myocardial Infarction flow post procedure			0.554
2	10 (2%)	16 (3%)	
3	462 (98%)	581 (97%)	
Fluoroscopy time (minutes)	34 ± 21	34 ± 20	0.531
Contrast volume (milliliters)	260 ± 118	259 ± 119	0.937

Due to rounding, percentages may not add up to 100%.

Values are expressed as count (percentage) or mean ± standard deviation.

* Percent > 100 because a few patients were transitioned to a different thienopyridine during their treatment period. Of the > 12 months thienopyridine arm, 17 patients were on more than one thienopyridine during their treatment. Of the ≤ 12 months arm, there were 11.

† Previous anemia defined, on lab closest to the procedure date, as hemoglobin value < 11.5 g/dL for women and < 13 g/dL for men.

Table 2
Landmark analysis of risk of clinical end points for patients treated with > 12 months versus 12 months of Thienopyridine after index percutaneous coronary intervention

	Events		Univariate		MultivariateAdjusted		PropensityAdjusted	
	≤12 months	>12 months	HR	95% CI	HR	95% CI	HR	95% CI
Death or myocardial infarction	100 (18%)	55 (12%)	0.60	0.43−0.83	0.66	0.47−0.93	0.69	0.49−0.99
Death	81 (15%)	35 (7%)	0.46	0.31−0.69	0.54	0.36−0.82	0.58	0.38−0.89
Myocardial infarction	35 (6%)	28 (6%)	0.87	0.53−1.43	0.91	0.55−1.53	0.94	0.55−1.59
≥Bleeding academic research consortium 3a bleeding	15 (3%)	13 (3%)	0.92	0.44−1.93	1.10	0.50−2.35	1.0	0.47−2.26
Ischemic Stroke	13 (2.4%)	10 (2.1%)	0.83	0.36−1.88	0.99	0.42−2.38	0.95	0.39−2.35
Target lesion revascularization	34 (6%)	35 (8%)	1.10	0.69−1.77	1.29	0.78−2.11	1.23	0.73−2.06

Patients free of event at 12 months assessed for event after 12 months to end of follow-up

Values n (%)

Multivariable adjusted for: age, gender, race/ethnicity, hypertension, peripheral arterial disease, previous heart failure, chronic kidney disease stage 3 or greater, diabetes mellitus, cerebrovascular disease, in-stent restenosis treated, end-stage renal disease, warfarin use, myocardial infarction/ischemic stroke/target lesion revascularization/> Bleeding Academic Research Consortium 3a bleeding in the first 12 months after percutaneous coronary intervention, previous myocardial infarction, stent type (Xience, Promus, Resolute, other), and previous anemia.

Propensity adjusted for propensity to use thienopyridine for > 12 months.

Discussion

We observed that a longer duration of DAPT therapy after CTO PCI (> 1 year vs ≤ 1 year) was associated with a lower rate of the composite outcome of all-cause mortality or MI, a finding which was driven by a reduction in all-cause mortality. MI events alone were similar. Also, there appears to be no trade-off of increased bleeding with longer DAPT duration. The benefit of longer DAPT persisted after both multivariate and propensity adjustment, and sensitivity analyses. In addition, on review of causes of death, we demonstrated that a greater proportion of patients in the shorter DAPT duration group died of cardiovascular causes.

Our study adds to the limited data regarding duration of DAPT after CTO PCI. The largest randomized trial to evaluate duration of DAPT after PCI did not evaluate CTOs.[1] Two other studies included CTO PCI as one of several elements to define complex PCI,[4,18] but neither evaluated the relation of DAPT duration to outcomes in the CTO subgroup alone. To the best of our knowledge, this is only the second dedicated study of the association between DAPT duration and outcomes after CTO PCI.

Our study differs from the first[5] in a few ways. First, it has a larger sample size and therefore more statistical power. Second, it includes patients with previous CABG as well as those on oral anticoagulation, both of which are groups

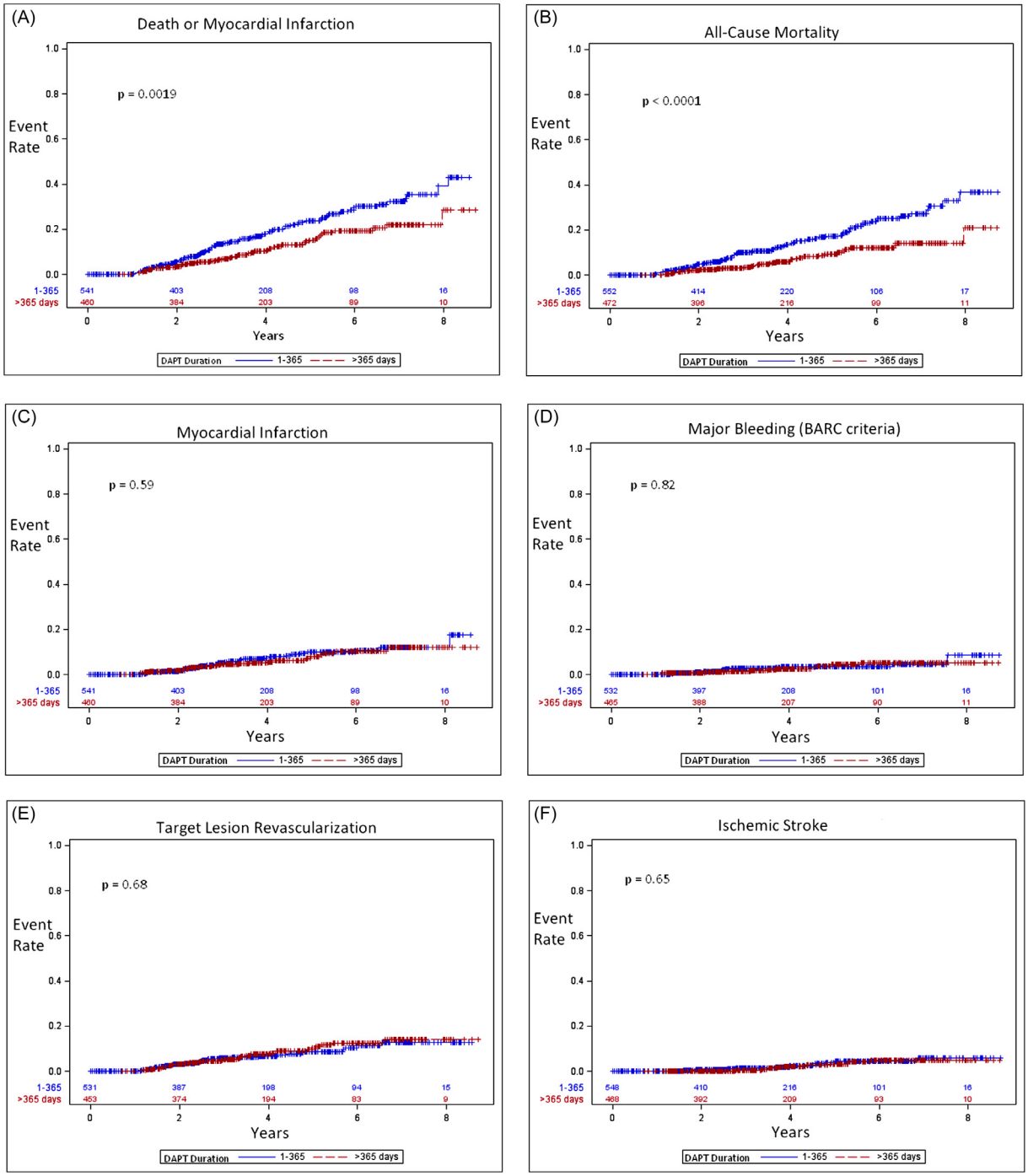

Figure 2. (*A-F*). Clinical outcomes after chronic total occlusion percutaneous coronary intervention by DAPT duration.
Kaplan-Meier failure plots for outcomes of (*A*) death or myocardial infarction, (*B*) all-cause death, (*C*) myocardial infarction, (*D*) ≥ Bleeding Academic Research Consortium 3a bleeding, (*E*) target lesion revascularization, and (*F*) ischemic stroke.
CTO = chronic total occlusion. PCI = percutaneous coronary intervention.

commonly seen in CTO PCI practice, especially patients with previous CABG.[19] Although we similarly showed no difference in rates of bleeding, MI, or stroke, we found a lower rate of all-cause mortality in the group exposed to longer DAPT, whereas the previous study did not show a difference between longer or shorter duration of DAPT.

One may hypothesize that the lower death rate associated with longer durations of DAPT was due to a lower rate of ischemic events. However we found similar rates of MI and ischemic stroke in groups with short and longer DAPT durations. When we adjudicated causes of death, we found that a higher proportion of patients in the shorter duration group died of CV causes. And when we further reviewed cases of definite or possible fatal sudden cardiac death, fatal coronary heart disease, and fatal MI, we found that the majority occurred suddenly out of hospital, at an

Table 3
Cause of death adjudication

	Deathsn = 116 DAPT duration, deaths	
All	1−365 days n = 81	>365 days n = 35
Cardiovascular death, individual causes	n = 30 (37%)	n = 7 (20%)
Definite fatal coronary heart disease (CHD)	6	1
Possible fatal CHD	2	0
Definite fatal CHF	3	2
Possible fatal CHF	5	0
Definite fatal hemorrhagic stroke	3	1
Definite fatal MI	3	1
Possible fatal MI	2	0
Definite sudden cardiac death	3	1
Possible sudden cardiac death	1	0
Definite fatal ischemic stroke	1	1
Possible fatal ischemic stroke	1	0
Non cardiovascular death, individual causes	n = 40 (49%)	n = 19 (54%)
Ambiguous	2	1
Aspiration event	0	1
C difficile colitis	2	0
Cancer	10	5
Dementia	6	2
Exposure to uncontrolled fire	2	0
Gastrointestinal bleeding	1	0
Liver disease	1	0
Lung disease	3	2
Neurologic disease	1	0
Pneumonia	3	0
Renal failure	2	2
Septic shock	4	6
Suicide	1	0
Traumatic intracranial hemorrhage	2	0
Unclassifiable	n =11 (14%)	n = 9 (26%)

emergency room out of network, or in a network hospital but suddenly—these deaths were not coded as MI as a discharge diagnosis. This suggests that there may be a possible ischemic mechanism underlying the lower death rate seen in the longer DAPT duration group that was not captured by chart review for MI.

This study has several limitations. This was an observational study, and DAPT duration was not randomly assigned. Although we observed an association between lower all-cause mortality and longer DAPT duration, even after adjustment for possible confounders and sensitivity analyses, there still may remain unmeasured confounders that account for the observed differences in outcomes. Specifically, possible unmeasured confounders revealed by cause of death adjudication include dementia, malignancy, as well as underlying frailty, which is an emerging health status measure that may be relevant in patients who undergo PCI.[20]

Ascertainment of the exposure, namely P2Y12 antagonist, was based on pharmacy prescription records. Pill counts may have provided a more precise estimate of thienopyridine use, but the use of filled prescriptions has been shown to reflect actual medication use by patients with a high degree of accuracy.[21]

Aspirin use was not available through the pharmacy prescription database. However, our analyses of patients both on and off oral anticoagulants show high rates of concomitant aspirin use for those taking P2Y12 antagonists. Although this does not necessarily prove adherence, it supports that patients were likely taking aspirin. Finally, CTO PCI cases were operator identified, which is a potential source of bias. To account for this the primary author manually adjudicated every case, using the standard clinical definition of CTO.

Disclosures

None

Author contributions

Amit Sachdeva: Conceptualization, Methodology, Validation, Investigation, Writing - original draft, Visualization, Funding acquisition. Yun-Yi Hung: Formal analysis, Investigation, Resources, Data curation, Writing - review & editing. Matthew D. Solomon: Conceptualization, Writing - review & editing. Edward J. McNulty: Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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