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Dual Antiplatelet Therapy Is Associated with Increased Risk of Bleeding and Decreased Risk of Stroke Following Carotid Endarterectomy

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Abstract

Objectives: Despite many patients undergoing carotid endarterectomy (CEA) being on dual antiplatelet therapy (DAPT) for cardiac or neurologic indications, the impact of such therapy on perioperative outcomes remains unclear. We aim to compare rates of postoperative bleeding, stroke and major adverse events (stroke, death or MI) among patients on Aspirin alone (ASAA) versus DAPT (Clopidogrel and Aspirin).

Methods: Patients undergoing CEA for carotid artery stenosis between 2010-2021 in the Vascular Quality Initiative (VQI) were included. We excluded patients undergoing concomitant or re-do operations or patients with missing antiplatelet information. Propensity score matching was performed between the two groups ASAA and DAPT based on age, sex, race, presenting symptoms, major comorbidities [hypertension, diabetes and coronary artery disease (CAD)], degree of ipsilateral stenosis, presence of contralateral occlusion, as well as preoperative medications. Intergroup differences between the treatment groups and differences in perioperative outcomes were tested with the McNemar's test for categorical variables and paired t-test or Wilcoxon matched-pairs signed-rank test for continuous variables where appropriate. Relative risk with 95% confidence intervals were estimated as the ratio of the probability of the outcome event in the patients treated within each treatment group.

Results: A total of 125,469 patients were included [ASAA n= 82,920(66%) and DAPT n= 42,549(34%)]. Patients on DAPT were more likely to be symptomatic, had higher rates of CAD,

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prior percutaneous coronary intervention or coronary artery bypass grafting, and higher rates of diabetes. After propensity score matching, the DAPT group had an increased rate of bleeding complications (RR: 1.6: 1.4-1.8, P<0.001) as compared with those on ASAA despite being more likely to receive both drains and protamine. Additionally, patients on DAPT had a slight decrease in the risk of in-hospital stroke as compared with patients on ASAA (RR: 0.80: 0.7-0.9, p=.001).

Conclusions: This large multi-institutional study demonstrates a modest decrease in the risk of in-hospital stroke for patients on DAPT undergoing CEA as compared with those on ASAA. This small benefit is at the expense of a significant increase in the risk of perioperative bleeding events incurred by those on DAPT at the time of CEA. This analysis suggests avoiding DAPT when possible, during CEA.

Keywords

Carotid Endarterectomy; Dual antiplatelet therapy; Aspirin; Stroke; Bleeding; Outcomes

INTRODUCTION

Dual antiplatelet therapy (DAPT) is becoming an increasingly common strategy in the management of carotid artery stenosis, coronary artery disease (CAD), and peripheral arterial disease. Thus, vascular surgeons planning to perform CEA are commonly faced with the decision of whether or not to continue DAPT during the perioperative period and/or delay CEA until a patient may be taken off their second antiplatelet agent safely. Currently there are no guidelines regarding the continuation of DAPT during the perioperative period for patients undergoing CEA. The Society for Vascular Surgery recommends that the use of DAPT should be decided on a “case by case” basis and an individualized decision between surgeon and patient.[1]

The impact of DAPT on post-operative bleeding events following CEA remains controversial. Most studies suggest that DAPT conveys an increased risk of postoperative bleeding. Jones et al. demonstrated that DAPT was associated with an increased risk of reoperation for bleeding.[2] This was similar to findings of Zimmermann et al. who found that DAPT was associated with a higher risk of bleeding following CEA.[3] However, a prospective trial which compared patients undergoing CEA on DAPT with those on Aspirin alone (ASAA) demonstrated no difference in hemorrhagic complications.[4] Similarly, a large retrospective study which included CEA patients found no difference in transfusion rates and reoperation for bleeding between patients on ASAA and those on DAPT.[5] A small study out of the U.K. looking at 100 symptomatic patients undergoing expedited CEA on DAPT identified only three hemorrhagic complications.[6]

The impact of DAPT on major adverse cardiac events (MACE) after CEA is even less well described. Jones et al. demonstrated that DAPT was associated with a 40% risk reduction of neurologic events[2] whereas Zimmermann et al. did not find a significant difference in perioperative stroke rate.[3] Similarly, Alcocer et al. did not find any difference in the rates of perioperative stroke in patients on DAPT compare to those on ASAA.[7] However, an increase in all-cause mortality among patients older than 75 receiving DAPT was noted for asymptomatic carotid artery disease.[5]

Given these conflicting findings regarding the increased risk of bleeding conveyed by DAPT and the benefit it might convey in decreasing MACE, it is not surprising that antiplatelet management practices vary widely among surgeons performing CEA. Huibers et al. surveyed surgeons participating in the Asymptomatic Carotid Surgery Trial-2 (ACST-2) and demonstrated that only 31% of surgeons continued DAPT preoperatively.[8]

The lack of a general consensus regarding optimal management strategies for antiplatelet agents in the perioperative period warrants further research to better understand the association between DAPT and adverse events following CEA. In this study, we describe the use of DAPT in a multi-institutional national cohort and evaluate its association with post-operative bleeding, MACE and survival after CEA.

METHODS

Database:

We retrospectively identified all patients who underwent CEA in the VQI database between September 2016 and July 2021. The VQI is a prospectively maintained database collecting around 200 patient- and procedure-related variables as well as postoperative outcomes for up to one year of follow up. The VQI currently includes 700 centers with over 3500 participating physicians of different specialties, including vascular surgeons, cardiologists, radiologists, cardiac surgeons, general surgeons, among others. [9] The VQI Research Advisory Committee approved the release of VQI data for this study. The need for individual informed consent and Institutional Review Board approval is waived for this study due to the retrospective, deidentified nature of the data.

Patient Population:

All patients who underwent CEA for carotid artery stenosis from September 2016 to July 2021 in the VQI database were included. Our cohort was divided into two groups based on their consumption of preoperative antiplatelet therapy. First group included patients who were on aspirin alone (ASAA) and second group included patients on aspirin plus a P2Y12 inhibitor (DAPT).

Variables Definition:

Baseline patients' characteristic included demographics [age, sex, race, ethnicity], preoperative symptomatic status [amaurosis fugax, TIA, or stroke], medical comorbidities [diabetes, hypertension, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), coronary artery disease (CAD), chronic kidney disease (CKD), or hemodialysis], preoperative medications (beta blockers, anticoagulants, statins, and ACE inhibitors), smoking history (never, prior, or current), degree of ipsilateral carotid artery stenosis, American Society of Anesthesiologists (ASA) physical status classification, and prior cardiovascular procedures [coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), prior CEA or CAS, and major amputations]. Operative factors included drain placement, heparin reversal, and anesthesia type (general or local/regional). Symptomatic status was defined as the presence of any ipsilateral neurologic event (amaurosis fugax, transient ischemic attack (TIA), or stroke) within the last 6 months prior

to the procedure. We excluded patients who underwent any concomitant procedures with CEA.

Outcomes:

The primary endpoints were postoperative bleeding and in-hospital MACE, including stroke, death, or myocardial infarction (MI). Secondary endpoints were in-hospital all-cause mortality and stroke rates. Postoperative bleeding was defined as access site bleeding resulting in reoperation or needing any surgical or interventional treatment. In-hospital stroke was defined as any ipsilateral or contralateral vertebra-basilar, retinal, or cortical stroke. MI included cases with elevated troponin only or EKG/clinically diagnosed MI.

Statistical Analysis:

The study included 2 groups: dual antiplatelet (ASA and P2Y12 antagonist - DAPT) and aspirin alone (ASAA). Descriptive statistics was reported as mean ± standard error of the mean (SEM) or count with percent, as appropriate. Baseline characteristics and comorbidities were compared between the two groups. Intergroup differences between the two treatment groups and differences in in-hospital outcomes were tested with the McNemar's test for categorical variables and paired t-test or Wilcoxon matched-pairs signed-rank test for continuous variables where appropriate.

Given the significant differences in distribution of key variables between study groups, we employed propensity score matching (PSM) to ensure balance of these covariates. One-to-One PSM without replacement and with a caliper size of 0.10 was performed. Matching was based on age, sex, race, presenting symptoms, HTN, diabetes, CAD, CHF, prior CABG/PCI, COPD, CKD, dialysis, preoperative smoking status, ipsilateral stenosis more than 80%, prior contralateral CEA/CAS, preoperative medications (statins, anticoagulants, ACE inhibitors), presence of contralateral occlusion, drain placement, heparin reversal, procedure urgency, and center identifier. Patients' characteristics were compared before and after propensity score matching. We evaluated balance of covariate between study groups before and after matching using standardized differences. In line with convention, an absolute standardized difference of 0.10 or more was used to indicate imbalance of variables between groups. [10] Univariable logistic regression analysis was used to assess the relationship between in-hospital outcomes and preoperative antiplatelet consumption (DAPT vs ASAA) before and after matching. Analyses were performed using Stata version 17 statistical software (StataCorp LP, College Station, Texas). P-value of <0.05 was considered statistically significant and all tests were two sided.

RESULTS

A total of 125,469 patients underwent CEA in the study period. Among these patients, 82,920(66%) were taking ASAA and 42,549(34%) were on DAPT. Patients on DAPT were more likely to be symptomatic (35% vs 26.3%), had higher rates of CAD (35.8 % vs 24.4%), prior PCI or CABG (45.9% vs 29.7%), and higher rates of diabetes (39.7% vs 34.4%). No significant variations were noticed between the two groups in other

comorbidities such as smoking history, COPD, CKD, CHF, dialysis, prior contralateral CEA/CAS, contralateral occlusion, and ipsilateral stenosis ≥ 80%.

Preoperative anticoagulation was used more commonly in the ASAA group vs DAPT group (11.8% vs 4.1%). However, statins (89.4% vs 84.1%) and beta blockers (60.8% vs 54.8%) were used more often in the DAPT group vs ASAA group. Patients on DAPT were more likely to have a drain placed than patients on ASAA (42.8% vs 36.7%) and they were more likely to receive protamine (75% vs 68.4%). We found no difference between the groups in terms of intraoperative heparin use with 99.1% of patients in both the ASAA and DAPT groups receiving heparin during the case (mean standardized difference = 0.003). In terms of EEG monitoring and shunt placement, we found no difference between our groups – EEG monitoring occurred in 29.4% of the ASAA group and 27.8% of the DAPT group (mean standardized difference = 0.04) while shunting occurred in 49.4% of the ASAA group and 51.8% of the DAPT group (mean standardized difference = 0.05). A standardized difference > 0.10 indicated significant imbalance between the two groups (Table I). After propensity score matching, we had 34,939 well-balanced pairs (Table I).

On univariate analysis, there was more bleeding in the DAPT group (1.4% vs 0.8%, p<0.001), increased MI in the DAPT group (0.9% vs 0.7%, p<0.001, and decreased stroke in the DAPT group (1.1% vs 1.3%, p<0.04) however, there was no significant difference between the two groups in terms of MACE (OR=1.1, 95%CI 0.99-1.2) and in-hospital death (OR=1.05, 95%CI 0.86-1.3) (Table II). After propensity score matching, patients on DAPT had 60% increased rate of bleeding complications requiring reoperation (RR 1.6, 95%CI 1.4-1.8, p<0.001) as compared with those on ASAA, despite being more likely to receive protamine and have a drain in place (Table III). Additionally, patients on DAPT had a 20% decreased risk of in-hospital stroke (RR 0.80, 95%CI 0.7-0.9, p=.001) and 30% increased risk of MI (RR 1.3, 95%CI 1.1-1.5, p=0.007) as compared with patients on ASAA (Table III, Figure 1).

DISCUSSION

This large nationally representative retrospective study of 34,939 well-matched pairs of patients, demonstrates that the use of DAPT may be associated with a 20% reduction in risk of postoperative stroke compared with patients on ASAA among patients undergoing CEA. This is supported in the literature with the use of transcranial doppler in symptomatic carotid artery disease patients in two randomized trials showing efficacy in stroke prevention with a DAPT regimen and a randomized trial of 15,000 patients with reduced symptomatic embolic events after DAPT.[11-13] However, patients on DAPT had an increased risk of bleeding compared with patients on ASAA in our study as well as in one randomized trial.[13] The significant increased risk of postoperative bleeding and subsequently increased rate of re-operation in patients who utilize DAPT might offset the small benefit of perioperative stroke reduction in the same group of patients. These findings are important as some patients undergoing CEA might have significant cardiac comorbidities, or have recently received coronary drug eluting stents where the use of DAPT is supported. For these patients especially if asymptomatic from their carotid artery stenosis, it might be better to delay the CEA until they can be safely taken off the second antiplatelet agent. While in patients with

symptomatic carotid artery stenosis, where the use of DAPT is not strongly indicated, it may be better to stop clopidogrel prior to performing CEA to decrease the risk of bleeding. It is interesting that despite being on DAPT in our study these patients had 30% increased risk of MI. Residual confounders despite matching could be the cause of increased MI because DAPT is likely a marker for severe CAD and prior coronary intervention. Database studies have inherent limitations given that not all confounders can be accounted for and therefore in order to suggest any change to current guidelines or protocols, a prospective or randomized trial would be needed.

The decreased risk of stroke and increased risk of perioperative bleeding observed with DAPT in our study may have some explanatory pathways. Hayes et al. reported that platelets in patients with a high number of postoperative embolic signals detected by transcranial doppler following CEA demonstrated high sensitivity to adenosine diphosphate (ADP).[14] ADP is a platelet agonist that causes platelet shape change and aggregation as well as generation of thromboxane A2, another platelet agonist. There are two receptors for ADP on the platelets, $P2Y_1$ and $P2Y_{12}$. $P2Y_{12}$ receptor inhibitors, such as clopidogrel, may play a role in prevention of postoperative carotid thrombosis thus, decreasing perioperative stroke incidence.[14] On the other hand, aspirin inhibits only the cyclo-oxygenase pathway in platelets which will block the release of thromboxane A2. Thromboxane A2 is produced by activated platelets and stimulates activation of new platelets as well as platelet aggregation. Whereas, in patients with high embolic signals, platelets will remain activated through alternative pathways, DAPT may increase the risk of bleeding via the synergistic antiplatelet action by the two medications.[15] Similarly, in a study by Payne et al, the addition of low dose clopidogrel to aspirin resulted in a significant increase in bleeding time and a decrease in platelet aggregation.[16]

Currently, there are no guidelines regarding the use of DAPT in the preoperative and perioperative periods of CEA. A European questionnaire study was conducted in 2008 to assess perioperative use of antiplatelet medications amongst vascular surgeons and found that over 40% of surgeons wound stop clopidogrel versus approximately 10% who would stop aspirin.[15] Given the lack of guidelines, it is often left to surgeon preference on how to proceed.

Our study builds upon the findings of multiple previous studies. Although prior work nearly uniformly describes an increased risk of bleeding associated with the use of DAPT at the time of CEA, findings regarding the association of DAPT and perioperative MACE vary. A prior VQI study by Jones et al. found an almost 2-fold increased risk of bleeding events and a 40% decrease in neurological events in patients on DAPT at the time of CEA.[2] In a large systematic review and meta-analysis of 36,000 cases, Barkat et al. demonstrated that there was no difference between DAPT and ASAA in regards to risk of stroke, TIA, and death; however, DAPT was associated with increased risk of perioperative bleeding in patients undergoing CEA.[17] This is in contrast to our study, where DAPT after CEA was associated with a 20% decreased risk of postoperative stroke. As our study captures the largest number of patients (125,469) with 34,939 well-balanced pairs, it is likely that we are able to better ascertain the association between DAPT and risk of perioperative bleeding and MACE.

There are several limitations to this retrospective study such as confounding by indication. While unmeasured confounders may still exist, we believe that using a large sample of patients, controlling for patient level details and applying propensity score risk-adjustment can achieve national representation of outcomes and a valid comparison between ASAA and DAPT undergoing CEA. Additionally, any registry is subject to under-reporting and data entry inaccuracy. However, VQI performs claims validation (hospitals and physician billing) routinely to ensure complete entry of eligible cases. Another important limitation to this study is that VQI does not allow us to account for clopidogrel and aspirin sensitivity and resistance among the patients. Prior work has demonstrated that approximately 20% of patients may exhibit clopidogrel resistance.[18] Thus, it is possible that we are over-estimating the association of DAPT and our outcomes of bleeding and MACE. Given we are unable to account for antiplatelet resistance, we urge providers to perform testing when prescribing these medications. Finally, this study does not include the long-term outcomes between these two groups of patients.

CONCLUSION

This is a large nationally representative study confirming a decreased risk of stroke for patients on DAPT undergoing CEA as compared with those on ASAA. This small benefit is countered by a significant increase in the risk of perioperative bleeding requiring reoperation in patients on DAPT at the time of CEA. Based on these finding, we recommend avoiding DAPT, if possible, during CEA.

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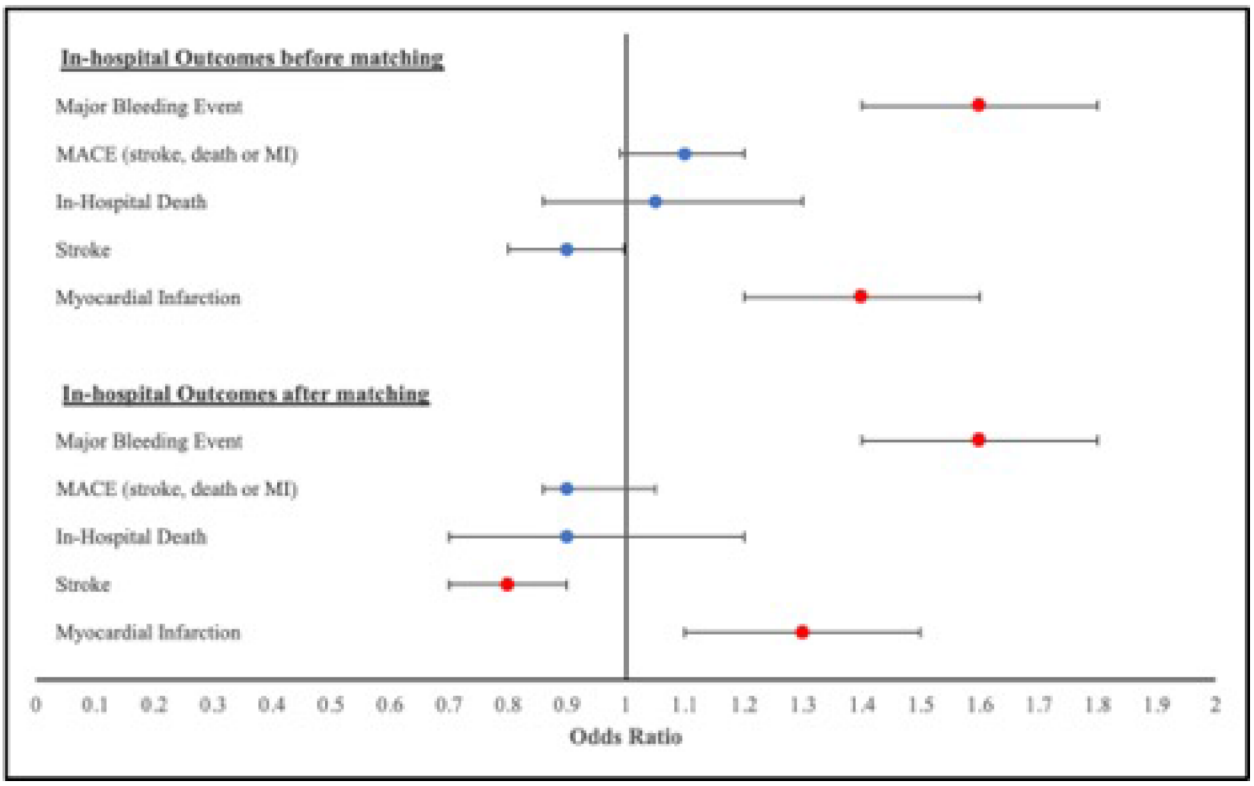

Figure 1:
Forest plot demonstrating odds ratios before and after propensity-score matching.

Table I:

Baseline Characteristics before and after Propensity Score Matching

	Unmatched			Matched		
	ASAA (N=82,920)	**DAPT (N=42,549)**	**Mean Standardized Difference****	**ASAA (N=34,939)**	**DAPT (N=34,939)**	**Mean Standardized Difference***
Mean Age in years (±SD)	70.84±9	70.02±9	0.09	70.3±9	70.2±9	0.003
Ethnicity	2351 (2.8)	1424 (3.4)	0.03	1073 (3.1)	1150 (3.3)	0.01
Female Gender	32560 (39.3)	15813 (37.2)	0.04	13013 (37.2)	13107 (37.5)	0.006
Race						
White	75591 (91.2)	38062 (89.5)	0.06	31367 (89.8)	31414 (89.9)	0.004
Black	3562 (4.3)	2255 (5.3)	0.05	1790 (5.1)	1750 (5)	0.005
Others	3730 (4.5)	2214 (5.2)	0.03	1782 (5.1)	1775 (5.1)	0.001
Symptomatic Status	21233 (25.6)	14876 (35)	0.2	11785 (33.7)	11427 (32.7)	0.02
Hypertension	73499 (88.7)	38695 (91.1)	0.08	31752 (90.9)	31684 (90.7)	0.007
Diabetes	28526 (34.4)	16867 (39.7)	0.1	13546 (38.8)	13408 (38.4)	0.01
CAD	20174 (24.4)	15217 (35.8)	0.2	11549 (33.1)	11408 (32.7)	0.01
Prior CABG/PCI	24591 (29.7)	19511 (45.9)	0.3	15011 (43)	14840 (42.5)	0.01
Congestive heart failure	8541 (10.3)	5374 (12.6)	0.07	4046 (11.6)	4069 (11.6)	0.002
COPD	17868 (21.6)	10207 (24)	0.06	8264 (23.7)	8166 (23.4)	0.01
CKD	27295 (33.5)	14248 (34.1)	0.01	11777 (33.7)	11775 (33.7)	0.0001
Smoking						
Prior Smoker	40332 (48.7)	20726 (48.8)	0.002	17082 (48.9)	17086 (48.9)	0.0003
Current Smoker	21145 (25.5)	11358 (26.7)	0.03	9124 (26.1)	9229 (26.4)	0.007
Prior ipsilateral CEA	1235 (1.5)	962 (2.3)	0.06	519 (1.5)	726 (2.1)	0.04
Prior ipsilateral CAS	114 (0.1)	226 (0.6)	0.07	55 (0.2)	168 (0.5)	0.06
Prior Contralateral CEA/CAS	10872 (13.1)	6536 (15.4)	0.06	4718 (13.5)	4708 (13.5)	0.001
Contralateral Occlusion	3010 (4.2)	1975 (5.2)	0.05	1726 (4.9)	1715 (4.9)	0.001
Ipsilateral Stenosis ≥ 80%	40234 (49.4)	19509 (46.8)	0.05	16132 (46.2)	16143 (46.2)	0.001
Preoperative Medications						
Statin	69734 (84.1)	38039 (89.4)	0.16	31224 (89.4)	31165 (89.2)	0.005
Beta Blockers	45459 (54.8)	25852 (60.8)	0.1	20747 (59.4)	20620 (59)	0.007
Anticoagulation	9100 (11.8)	1675 (4.1)	0.3	1529 (4.4)	1504 (4.3)	0.003
ACE Inhibitors	40667 (52.6)	22485 (55.2)	0.05	19059 (54.5)	19140 (54.8)	0.005
Elective procedures	72585 (87.6)	36335 (85.5)	0.06	29709 (85)	30011 (85.9)	0.02
Drain Placed	30105 (36.7)	18108 (42.8)	0.1	14460 (41.4)	14337 (41)	0.007
Protamine Given	56660 (68.4)	31845 (75)	0.1	26130 (74.8)	26088 (74.7)	0.003
General anesthesia	76557 (92.4)	39003 (91.8)	0.02	32481 (93)	32019 (91.7)	0.05

Abbreviations: N, frequency (count); CEA, carotid endarterectomy; CAS, carotid artery stenting; IQR, interquartile range; CAD, coronary artery disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease

[*] Propensity score matching was performed based on age, sex, race, presenting symptoms, HTN, diabetes, CAD, CHF, prior CABG/PCI, COPD, CKD, dialysis, preoperative smoking status, prior CEA/CAS, ipsilateral stenosis more than 80%, prior contralateral CEA/CAS, preoperative medications (aspirin, P2Y12 antagonists, statins, anticoagulants, ACE inhibitors,), presence of contralateral occlusion, and elective status.

[**] An absolute standardized difference of .10 or more indicates that covariates are imbalanced between groups

Table II:

In-Hospital Outcomes before Matching

In-Hospital Outcomes	**ASAA (N=82,920)**	**DAPT (N=42,549)**	**P value**	**DAPT vs. ASAA**	
	N (%)	**N (%)**		***OR (95% CI)***	***P-value***
Major bleeding event	699 (0.8)	576 (1.35)	<0.001	1.6 (1.4-1.8)	<0.001
MACE (stroke, death, or MI)	1,606 (1.9)	886 (2.1)	0.08	1.1 (0.99-1.2)	0.08
In-Hospital Death	273 (0.33)	147 (0.35)	0.637	1.05 (0.86-1.3)	0.637
Stroke	974 (1.3)	459 (1.1)	0.04	0.9 (0.8-0.997)	0.04
Myocardial Infarction	536 (0.65)	375 (0.88)	<0.001	1.4 (1.2-1.6)	<0.001

Table III:

In-Hospital Outcomes after Matching

In-Hospital Outcomes	**ASAA (N= 34,939)**	**DAPT (N= 34,939)**	**P value**	**DAPT vs. ASAA**	
	N (%)	**N (%)**		***RR (95% CI)***	***P-value***
Major bleeding event	298 (0.8)	468 (1.3)	<0.001	1.6 (1.4-1.8)	<0.001
MACE (stroke, death, or MI)	753 (2.2)	716 (2.05)	0.329	0.9 (0.86-1.05)	0.329
In-Hospital Death	120 (0.34)	110 (0.31)	0.509	0.9 (0.7-1.2)	0.509
Stroke	486 (1.4)	388 (1.1)	0.001	0.8 (0.7-0.9)	0.001
Myocardial Infarction	233 (0.7)	295 (0.8)	0.007	1.3 (1.1-1.5)	0.007