Comparison of Aspirin Monotherapy versus Dual Antiplatelet Therapy Following Coronary Artery Bypass Grafting

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Aspirin remains the gold standard antiplatelet regimen following coronary artery bypass grafting (CABG), however, there is growing support for dual antiplatelet therapy (DAPT). This study compares outcomes of aspirin monotherapy versus DAPT following CABG. This was a propensity-matched retrospective study from a large, multi-hospital healthcare system. It included patients who received either aspirin monotherapy or DAPT following isolated CABG between 2011 and 2018. Patients prescribed aspirin monotherapy were started on 81 mg aspirin daily, and patients on DAPT were prescribed 81 mg aspirin daily and 75 mg clopidogrel daily. Patients received alternative drug dosing or antiplatelet agents other than clopidogrel only if this was prescribed for another diagnosis or they had a preexisting contraindication. Primary outcomes included overall survival and major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of death, myocardial infarction, stroke, or repeat revascularization. Kaplan-Meier analysis and the log-rank test were used to compare survival and cumulative incidence curves and Gray's test were used to compare MACCE. A total of 3,562 propensity-matched patients were included, 1,242 (34.9%) receiving aspirin monotherapy and 2,320 (65.1%) receiving DAPT. Groups were well-matched with respect to age, baseline comorbidity, indication for CABG, and completeness of revascularization. Median follow-up was 4.90 years (IQR 3.30 to 6.90 years). DAPT was associated with higher rate of postoperative transfusion (30.7% vs 25.4%, p = 0.001). Overall survival was comparable between groups (1-year aspirin 95.9% versus DAPT 97.2% and 5-years aspirin 86.3% versus DAPT 87.8%; log-rank p = 0.194). Rates of MACCE were also similar (1-year aspirin 9.4% versus DAPT 8.7% and 5-years aspirin 26.7% versus DAPT 24.7%; p = 0.798). In this propensity-matched analysis, DAPT did not confer any advantage in terms of improved survival or freedom from MACCE compared to aspirin monotherapy following isolated CABG, and was associated with a higher postoperative transfusion rate. **(Am J Cardiol 2021;148:44−52)**

Aspirin has been the first line antiplatelet therapy for patients following coronary artery bypass grafting (CABG) to prevent graft occlusion and adverse cardiac events.[1,2] However, prior studies have suggested that clopidogrel as a monotherapy may be superior to aspirin alone in prevention of major adverse cardiac and cerebrovascular events (MACCE).[3] Furthermore, treatment with dual antiplatelet therapy (DAPT) with aspirin and another antiplatelet agent has continued to gain popularity. Several studies have supported the use of DAPT post-CABG due to reduced incidence of MACCE and/or decreased native disease formation or graft occlusion.[4−8] Conversely, other trials have reported no differences in these outcomes with DAPT over aspirin monotherapy in terms of MACCE or graft patency.[9−11] Because the literature remains conflicted, postoperative antiplatelet therapy often remains at the discretion of the individual surgeon or practice. These practices can vary considerably, even within individual health institutions. This study compared outcomes of postoperative DAPT versus aspirin monotherapy in isolated CABG.

Methods

This study was a propensity-matched retrospective analysis from a single academic institution comprised of multiple hospitals in a regional healthcare system. It included adults (18 years or older) that underwent primary isolated CABG between January 2011 and June 2018. Patients that underwent redo cardiac surgery or concomitant procedures were excluded. Patients were then stratified based on antiplatelet regimen at time of discharge: aspirin monotherapy versus DAPT consisting of aspirin in addition to another antiplatelet agent. Patients that received other forms of systemic anticoagulation or had a contraindication to anticoagulation and/or antiplatelet therapy were excluded. Patients not surviving to discharge from the index hospitalization were also excluded from long-term analysis. This study was approved by the Institutional Review Board at the University of Pittsburgh.

In our institution, patients on aspirin monotherapy are started on 81 mg of aspirin daily. If a DAPT regimen is used, this consists of 81 mg daily and 75 mg clopidogrel

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daily. Patients only receive alternative dosages of medications or alternative antiplatelet agents in lieu of clopidogrel if they were previously prescribed prior to CABG, or have a contraindication. Antiplatelet agents are started on the first postoperative day unless concern for postoperative bleeding or thrombocytopenia exist. Actual chest tube drainage or platelet count cutoffs for withholding antiplatelet therapy in the immediate postoperative setting were surgeon dependent. Long-term post-CABG antiplatelet and/or anticoagulation regimens were analyzed by compiling active medication lists for each patient at the 3 months, 6 months, 1 year, and 5 years timepoints from the time of surgical revascularization.

Primary outcomes included overall survival and rates of MACCE. MACCE was defined as a composite endpoint of death, myocardial infarction, stroke, or need for repeat revascularization. Secondary outcomes included freedom from hospital readmission, postoperative blood transfusion requirements, and postoperative complications. Exploratory analysis was performed to investigate location of post-CABG myocardial infarction and associated bypass grafting to the affected region. For these events, location of infarction was determined by presenting electrocardiogram pattern, new wall motion abnormality on echocardiography, and/or intervenable lesion on coronary catheterization. Additionally, all available post-CABG computed tomography angiography studies were assessed to assess bypass graft patency.

Continuous data are presented as mean ± standard deviation for Gaussian variables or median [interquartile range (IQR)] for non-gaussian variables and all categorical data as number (percentage). Normality was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous data and categorical data were compared with Pearson's Chi-squared test or Fisher's exact test when 25% of available data points had expected values <5. Non-Gaussian distributions were evaluated using Mann-Whitney U test.

Propensity score matching on a 1:2 basis was performed using nearest neighbor matching without replacement and caliper setting of 0.2 of the standard deviation of the logit propensity score. Patients were matched base on all preoperative demographics, comorbidities, cardiac presentation, operation status, as well as preoperative usage of antiplatelets, anticoagulation, and/or intravenous inotropes. Additionally, patients were matched based on number of diseased coronary vessels, usage of bilateral internal mammary artery harvest, usage of cardiopulmonary bypass, and completeness of revascularization following CABG. A standardized mean differences <10% between cohorts was considered adequately matched for each characteristic. This resulted in 3,562 cases, 1,242 receiving aspirin monotherapy and 2,320 receiving DAPT. Kaplan-Meier curves were created and compared using the log-rank test for overall survival. Cumulative incidence function curves were generated for MACCE and the Gray's test was used to compare these curves.

Results

A total of 5,482 patients were included in this study, 1,246 (22.7%) who received aspirin monotherapy and 4,236 (77.3%) who received DAPT following CABG. In the non-matched cohorts, median age was 66 years, and patients had similar mean body mass index, body surface area, and had similar distributions of gender and race. The DAPT cohort had a higher prevalence of diabetes mellitus and chronic obstructive pulmonary disease. The most common presentation for CABG in both groups was NSTEMI, and number of diseased coronary vessels was similar. Median Society of Thoracic Surgeons risk for mortality was higher in the DAPT cohort. There was a higher utilization of cardiopulmonary bypass in the aspirin monotherapy group (89.1% vs 65.9%; p <0.001), with shorter median perfusion (89 minutes [IQR 73-111] versus 99 minutes [IQR 78 to 120], p <0.001) shorter cross-clamp times (59 minutes [IQR 46 to 75] versus 71 minutes [IQR 55 to 90], p <0.001), and with less frequent usage of bilateral internal mammary artery (IMA) grafting (20.0% vs 30.7%, p <0.001). Completeness of revascularization was higher in the DAPT group (83.6% vs 80.1%, p = 0.004). 61.2% of patients receiving aspirin monotherapy underwent CABG at Hospital 3 while 58.6% of patients receiving DAPT underwent CABG at Hospital 5 (Table 1). Long-term post-discharge antiplatelet and anticoagulation regimens are presented in Table 2.

Propensity score matching resulted in a total of 3,562 patients, 1,242 (34.9%) receiving aspirin monotherapy and 2,320 (65.1%) receiving DAPT following CABG. Distributions of propensity scores before and after matching are shown in Supplementary Figure 1. Patients were well-matched with regard to all baseline variables, with a standardized mean difference <10% for each variable after propensity-matching (Table 3).

In the unmatched analysis, rates of reoperation and 30-day mortality were equivalent between patients receiving aspirin monotherapy versus DAPT. Patients receiving DAPT were more likely to receive blood product transfusion (30.1 vs 25.4%, p = 0.001) and have a postoperative transient ischemic attack event (0.50% vs 0.08%, p = 0.041). Patients receiving aspirin alone had higher rate of postoperative sepsis (1.04% vs 0.14%, p <0.001) and superficial wound infection (1.69% vs 0.76%, p = 0.003) (Table 4).

After propensity matching, 30-day mortality and reoperation remained similar between cohorts. Rate of blood transfusion remained higher in the DAPT cohort (30.7% vs 25.4%, p = 0.001), as well as transient ischemic attack events (0.56% vs 0.08%, p = 0.029). Rates of postoperative sepsis and superficial wound infection remained higher in the aspirin monotherapy group (Table 5).

Median follow-up in the unmatched analysis was 4.94 years (IQR 3.25 to 7.03). One- and 5-year survival were comparable in the un-matched cohorts (Figure 1). In the propensity-matched analysis, median follow-up was 4.90 years (IQR 3.30 to 6.90). Overall survival to 5 years remained comparable between cohorts after propensity-matching (Figure 1). Rates of MACCE between aspirin monotherapy and DAPT were similar both in the unmatched and propensity-matched analyses (Figure 2).

In the unmatched analysis, rates of 1-year stroke, myocardial infarction, and MACCE were equivalent. Five-year all-cause readmission (45.6% vs 41.7%, p = 0.014) and cardiac readmission (39.4% vs 35.1%, p = 0.005) were higher

Table 1
Unmatched comparison of baseline demographics and operative characteristics between patients receiving either aspirin monotherapy versus dual antiplatelet therapy following CABG

Variable	Aspirin (n = 1246)	DAPT (n = 4236)	p	Standardized mean difference
Age (years)	66.00 (59.00-73.00)	65.00 (58.00-73.00)	0.103	0.06
Body mass index (kg/m^2)	29.33 (25.93-33.40)	29.38 (25.97-33.30)	0.728	0.01
Body surface area (m^2)	2.06 ± 0.27	2.05 ± 0.25	0.680	0.01
Women	300 (24.08%)	1077 (25.42%)	0.335	0.03
White	1179 (94.62%)	3887 (91.76%)	0.001	0.12
Black	38 (3.05%)	234 (5.52%)		
Other	29 (2.33%)	115 (2.71%)		
Diabetes mellitus	524 (42.05%)	1952 (46.08%)	0.012	0.08
Dialysis dependency	24 (1.93%)	93 (2.20%)	0.563	0.02
Chronic obstructive pulmonary disease	197 (15.81%)	907 (21.41%)	0.000	0.14
Hypertension	1096 (87.96%)	3718 (87.77%)	0.857	0.01
Immunosuppression	54 (4.33%)	176 (4.15%)	0.782	0.01
Family history of CAD	300 (24.08%)	1172 (27.67%)	0.012	0.08
Cerebrovascular disease	241 (19.34%)	886 (20.92%)	0.227	0.04
Peripheral vascular disease	176 (14.13%)	881 (20.80%)	0.000	0.18
Prior cerebrovascular accident	75 (6.02%)	302 (7.13%)	0.174	0.04
Previous myocardial infarction	766 (61.48%)	2678 (63.22%)	0.263	0.04
Cardiac presentation				
Asymptomatic	123 (9.87%)	395 (9.32%)	0.007	0.02
Symptoms unlikely to be ischemia	1 (0.08%)	32 (0.76%)		
Stable angina pectoris	121 (9.71%)	490 (11.57%)		
Unstable angina pectoris	489 (39.25%)	1768 (41.74%)		
NSTEMI	393 (31.54%)	1150 (27.15%)		
STEMI	78 (6.26%)	278 (6.56%)		
Symptoms equivalent to angina pectoris	15 (1.20%)	44 (1.04%)		
Other	26 (2.09%)	79 (1.86%)		
Congestive heart failure	137 (11.00%)	542 (12.80%)	0.090	0.06
NYHA symptoms				
1	1115 (89.49%)	3695 (87.23%)	0.140	0.07
2	32 (2.57%)	113 (2.67%)		
3	53 (4.25%)	241 (5.69%)		
4	46 (3.69%)	187 (4.41%)		
Cardiac arrhythmia	134 (10.75%)	422 (9.96%)	0.416	0.03
Number of coronary coronary arteries				
0	2 (0.16%)	14 (0.33%)	0.212	0.06
1	43 (3.45%)	198 (4.67%)		
2	261 (20.95%)	859 (20.28%)		
3	940 (75.44%)	3165 (74.72%)		
Intravenous inotropes	17 (1.36%)	53 (1.25%)	0.754	0.01
Cardiopulmonary bypass utilization	1110 (89.09%)	2793 (65.93%)	<0.001	0.58
Perfusion time (minutes)	89.00 (73.00-111.0)	99.00 (78.00-120.0)	<0.001	0.21
Cross-clamp time (minutes)	59.00 (46.00-75.00)	71.00 (55.00-90.00)	<0.001	0.47
Intra-aortic balloon pump				
None	1118 (89.73%)	3930 (92.78%)	0.001	0.13
Preoperative	112 (8.99%)	246 (5.81%)		
Intraoperative	15 (1.20%)	53 (1.25%)		
Postoperative	1 (0.08%)	7 (0.17%)		
Bilateral IMA harvest	249 (19.98%)	1300 (30.69%)	<0.001	0.25
Serum creatinine (mg/dL)	0.94 (0.79- 1.12)	1.00 (0.80- 1.20)	<0.001	0.04
Serum total albumin (g/dL)	3.60 (3.30- 3.80)	3.60 (3.40- 3.90)	<0.001	0.19
Total bilirubin (mg/dL)	0.50 (0.40- 0.70)	0.60 (0.40- 0.80)	<0.001	0.21
Left ventricular EF (%)	55.00 (43.00-60.00)	55.00 (45.00-58.00)	0.066	0.04
Operative status				
Elective	458 (36.76%)	1413 (33.36%)	0.018	0.07
Urgent	743 (59.63%)	2609 (61.59%)		
Emergent	45 (3.61%)	214 (5.05%)		
STS Mortality Risk	0.99 (0.55- 2.06)	1.08 (0.58- 2.22)	0.021	0.04
International normalized ratio (INR)	1.00 (1.00- 1.10)	1.10 (1.00- 1.10)	<0.001	0.09
Complete revascularization	998 (80.10%)	3541 (83.59%)	0.004	0.09

(*continued*)

Table 1 (***Continued***)

Variable	Aspirin (n = 1246)	DAPT (n = 4236)	p	Standardized mean difference
Hospital number				
1	144 (11.56%)	846 (19.97%)	<0.001	0.23
2	65 (5.22%)	176 (4.12%)		
3	762 (61.16%)	278 (6.56%)		
4	63 (5.06%)	456 (10.76%)		
5	212 (17.01%)	2480 (58.55%)		

CAD = coronary artery disease; EF = ejection fraction; IMA = internal mammary artery; NSTEMI = non-ST elevation myocardial infarction; NYHA = New York Heart Association; STEMI = ST elevation myocardial infarction; STS = Society of Thoracic Surgeons.

Table 2
Antiplatelet and anticoagulation medications after discharge

Variable Aspirin only cohort	3 months (n = 1,188)	6 months (n = 1,182)	1 year (n = 1,168)	5 years (n = 616)
Aspirin only	719 (60.52%)	738 (62.44%)	779 (66.70%)	411 (66.72%)
Single antiplatelet (other than aspirin)	8 (0.67%)	9 (0.76%)	13 (1.11%)	10 (1.62%)
Aspirin + additional antiplatelet	97 (8.16%)	94 (7.95%)	106 (9.08%)	95 (15.42%)
Aspirin + *anticoagulation	40 (3.37%)	39 (3.30%)	34 (2.91%)	22 (3.57%)
†DAPT + *anticoagulation	1 (0.08%)	1 (0.08%)	1 (0.09%)	3 (0.49%)
*Anticoagulation only	10 (0.84%)	14 (1.18%)	13 (1.11%)	12 (1.95%)
No antiplatelet or *anticoagulation	313 (26.35%)	287 (24.28%)	223 (19.09%)	63 (10.23%)
Other	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
DAPT cohort	(n = 4,094)	(n = 4,074)	(n = 4,030)	(n = 2,436)
Aspirin + additional antiplatelet	3,107 (75.89%)	2,857 (70.13%)	2,534 (62.88%)	976 (40.07%)
Aspirin + anticoagulation*	73 (1.78%)	78 (1.91%)	89 (2.21%)	120 (4.93%)
DAPT† + anticoagulation*	52 (1.27%)	43 (1.06%)	47 (1.17%)	26 (1.07%)
Aspirin only	332 (8.11%)	603 (14.80%)	942 (23.37%)	1,092 (44.83%)
Single antiplatelet agent (other than aspirin)	144 (3.52%)	136 (3.34%)	139 (3.45%)	84 (3.45%)
Anticoagulation* only	14 (0.34%)	12 (0.29%)	16 (0.40%)	39 (1.60%)
No antiplatelet or anticoagulation*	372 (9.09%)	332 (8.15%)	246 (6.10%)	83 (3.41%)
Other	0 (0.00%)	13 (0.32%)	17 (0.42%)	16 (0.66%)

DAPT = dual antiplatelet therapy.
Antiplatelet regiments including two agents other than aspirin were not included.
* Anticoagulation includes any of the following: warfarin, dabigatran, rivaroxaban, edoxaban, or apixaban.
† dual antiplatelet regiment including aspirin.

in the DAPT group. Rates of 5-year myocardial infarction, stroke and MACCE were equivalent.

After propensity matching, 5-year rates of all-cause readmission (45.0% vs 41.6%, p = 0.052) were not significantly different, but 5-year cardiac-specific readmission (38.8% vs 35.0%, p = 0.028) was higher in the DAPT cohort. Individual rates of myocardial infarction, stroke, or repeat revascularization at 1-year and 5-years were comparable between groups as well (Table 6).

Exploratory analysis was performed on the propensity-matched cohorts who experienced myocardial infarction within the 5-year post-CABG period. Of available data, the highest proportion of infarction occurred in the lateral territory for the aspirin only cohort, and the anterior territory for the DAPT cohort (Table 6). In both cohorts, the territory of infarction was most commonly supplied by a vein graft. Of post-CABG myocardial infarctions, 30.4% of patients in the aspirin cohort and 45.6% of patients in the DAPT cohort, the patient experienced troponinemia and diagnosis of myocardial infarction without discernable electrocardiogram, echocardiogram, or angiographic findings to suggest location.

In this study, a total of 18 (1 aspirin only, 17 DAPT) patients underwent dedicated cardiac computed tomography angiography adequate to assess coronary bypass graft patency after CABG procedure. In the aspirin monotherapy cohort, this patient had a 3-vessel CABG performed, and at 69.6 months post-CABG, was found to have one patent arterial graft (left internal mammary artery) and one patent saphenous vein graft, with one occluded vein graft. In the DAPT cohort, median time of cardiac angiography was 24.8 months (IQR 14.0 to 44.5 months) post-CABG. Patients had a median of 3 grafts performed (IQR 2 to 4) at time of revascularization, and were found to have a median of 0 occluded arterial grafts (IQR 0 to 0) and 0 vein grafts (IQR-1).

Discussion

The importance of dual antiplatelet therapy in preventing stent thrombosis after percutaneous coronary intervention is well established and the practice is widely utilized. The utility of DAPT after CABG is less known, and antiplatelet management varies substantially between centers and

Table 3
Propensity-matched comparison of baseline demographics and operative characteristics between patients receiving either aspirin monotherapy versus DAPT following CABG

Variable	Aspirin (n = 1242)	DAPT (n = 2320)	p	Standardized mean difference
Age (years)	66.00 (59.00-73.00)	66.00 (59.00-73.00)	0.708	0.01
Body mass index (kg/m^2)	29.31 (25.93-33.36)	29.38 (26.02-33.22)	0.697	0.00
Women	298 (23.99%)	565 (24.35%)	0.811	0.01
White	1175 (94.61%)	2180 (93.97%)	0.670	0.03
Black	38 (3.06%)	84 (3.62%)		
Other	29 (2.33%)	56 (2.41%)		
Diabetes mellitus	523 (42.11%)	1025 (44.18%)	0.235	0.04
Dialysis dependency	24 (1.93%)	43 (1.85%)	0.869	0.01
Chronic obstructive pulmonary disease	197 (15.86%)	409 (17.63%)	0.181	0.05
Hypertension	1092 (87.92%)	2041 (87.97%)	0.964	0.00
Immunosuppression	54 (4.35%)	98 (4.22%)	0.862	0.01
Family history of CAD	300 (24.15%)	584 (25.17%)	0.503	0.02
Cerebrovascular disease	240 (19.32%)	461 (19.87%)	0.696	0.01
Peripheral vascular disease	176 (14.17%)	384 (16.55%)	0.063	0.06
Previous myocardial infarction	762 (61.35%)	1436 (61.90%)	0.750	0.01
Cardiac presentation				
Asymptomatic	123 (9.90%)	252 (10.86%)	0.972	0.03
Symptoms unlikely to be ischemia	1 (0.08%)	1 (0.04%)		
Stable angina pectoris	121 (9.74%)	226 (9.74%)		
Unstable angina pectoris	489 (39.37%)	922 (39.74%)		
NSTEMI	390 (31.40%)	714 (30.78%)		
STEMI	77 (6.20%)	140 (6.03%)		
Symptoms equivalent to angina pectoris	15 (1.21%)	24 (1.03%)		
Other	26 (2.09%)	41 (1.77%)		
Congestive heart failure	136 (10.95%)	257 (11.08%)	0.908	0.00
NYHA symptoms				
1	1112 (89.53%)	2067 (89.09%)	0.652	0.01
2	32 (2.58%)	50 (2.16%)		
3	53 (4.27%)	103 (4.44%)		
4	45 (3.62%)	100 (4.31%)		
Cardiac arrhythmia	133 (10.71%)	239 (10.30%)	0.705	0.01
Number of narrowed coronary arteries				
0	2 (0.16%)	5 (0.22%)	0.950	0.01
1	43 (3.46%)	84 (3.62%)		
2	261 (21.01%)	473 (20.39%)		
3	936 (75.36%)	1758 (75.78%)		
Preoperative antiplatelet therapy	1168 (94.04%)	2180 (93.97%)	0.927	0.00
Preoperative anticoagulation	550 (44.28%)	989 (42.63%)	0.342	0.03
Intravenous inotropes	16 (1.29%)	22 (0.95%)	0.347	0.03
Cardiopulmonary bypass utilization	1106 (89.05%)	2029 (87.46%)	0.163	0.05
Intra-aortic balloon pump				
None	1118 (90.02%)	2119 (91.34%)	0.461	0.05
Preoperative	108 (8.70%)	168 (7.24%)		
Intraoperative	15 (1.21%)	30 (1.29%)		
Postoperative	1 (0.08%)	3 (0.13%)		
Bilateral IMA harvest	249 (20.05%)	491 (21.16%)	0.434	0.03
Serum creatinine (mg/dL)	0.94 (0.79- 1.12)	1.00 (0.80- 1.19)	<0.001	0.00
Serum total albumin (g/dL)	3.60 (3.30- 3.80)	3.60 (3.40- 3.80)	0.060	0.06
Left ventricular EF (%)	55.00 (43.00-60.00)	55.00 (45.00-58.00)	0.155	0.01
Operative status				
Elective	458 (36.88%)	846 (36.47%)	0.970	0.01
Urgent	739 (59.50%)	1390 (59.91%)		
Emergent	45 (3.62%)	84 (3.62%)		
STS Mortality Risk (%)*	0.98 (0.55- 2.04)	1.05 (0.59- 2.08)	0.111	0.02
International normalized ratio (INR)	1.00 (1.00- 1.10)	1.10 (1.00- 1.10)	0.002	0.03
Complete revascularization	998 (80.35%)	1901 (81.94%)	0.247	0.04

CAD = coronary artery disease; EF = ejection fraction; IMA = internal mammary artery; NSTEMI = non-ST elevation myocardial infarction; NYHA = New York Heart Association; STEMI = ST elevation myocardial infarction; STS = Society of Thoracic Surgeons.

* STS mortality risk not included in propensity matching algorithm.

Table 4
Postoperative complications between unmatched cohorts of patients receiving either aspirin monotherapy or dual antiplatelet therapy following CABG

Variable	Aspirin (n = 1246)	DAPT (n = 4236)	p
All-cause reoperation	55 (4.41%)	139 (3.28%)	0.057
Reoperation for bleeding	22 (1.77%)	61 (1.44%)	0.408
Blood transfusion	317 (25.44%)	1276 (30.12%)	0.001
Prolonged ventilation	77 (6.18%)	212 (5.00%)	0.103
Pneumonia	26 (2.09%)	67 (1.58%)	0.225
Renal failure	22 (1.77%)	64 (1.51%)	0.525
Permanent stroke	12 (0.96%)	35 (0.83%)	0.821
Transient ischemic attack	1 (0.08%)	21 (0.50%)	0.041
Sepsis	13 (1.04%)	6 (0.14%)	<0.001
Superficial wound infection	21 (1.69%)	32 (0.76%)	0.003

Table 5
Postoperative complications between propensity-matched cohorts of patients receiving either aspirin monotherapy or DAPT following CABG

Variable	Aspirin (n = 1242)	DAPT (n = 2320)	p
All-cause reoperation	55 (4.43%)	83 (3.58%)	0.210
Reoperation for bleeding	22 (1.77%)	36 (1.55%)	0.622
Blood transfusion	316 (25.44%)	711 (30.65%)	0.001
Prolonged mechanical ventilation	77 (6.20%)	106 (4.57%)	0.036
Pneumonia	26 (2.09%)	32 (1.38%)	0.109
Renal failure	22 (1.77%)	36 (1.55%)	0.622
Permanent stroke	12 (0.97%)	19 (0.82%)	0.798
Transient ischemic attack	1 (0.08%)	13 (0.56%)	0.029
Sepsis	13 (1.05%)	3 (0.13%)	<0.001
Superficial wound infection	21 (1.69%)	15 (0.65%)	0.003

between individual surgeons. Arguments against DAPT in CABG include the fact that there is no physical stent in place that predisposes to thrombus, and the notion that progression of native disease is less relevant as the lesion is bypassed. There are also multiple reports demonstrating that DAPT is not necessarily benign as compared to aspirin monotherapy, and this practice leads to increased bleeding and blood product transfusion rates in CABG patients.[12]

Nonetheless, saphenous vein grafts in particular can be prone to thrombosis or occlusion after CABG. Some studies have suggested saphenous vein graft failure rates as high as 30%-40% in the first year after CABG and up to 70% at 10 years after CABG.[12] An important concept is that although angiographic graft thrombosis or occlusion may be detected, it is entirely a different question whether this is clinically relevant or not. For example, an initial vein graft bypass for a native coronary vessel with chronic total occlusion that fails may have no clinical sequelae due to collateralization. This likely would have minimal if any impact on survival or quality of life of the patient and may not manifest with any symptoms, troponin leak, or adverse impact on ventricular function. In this context, cumulating real-world clinical evidence comparing outcomes of CABG in aspirin monotherapy versus DAPT patients, and in particular MACCE outcomes, is essential to better understanding optimal antiplatelet therapy in this patient subset.

The major finding of our study was that DAPT did not confer a survival or freedom from MACCE advantage as compared to aspirin monotherapy following isolated CABG. In the Clopidogrel after Surgery for Coronary Artery Disease (CASCADE) study, freedom from MACCE and rates of bypass graft stenosis/occlusion were similar between randomized patients receiving aspirin versus aspirin plus clopidogrel at 1 year.[11] Likewise, propensity-matched, post hoc analysis of the Arterial Revascularization Trial demonstrated no differences in 1-year MACCE between patients discharged on DAPT versus aspirin alone.[13] Our study adds to these prior reports in that it provides real-world data without strict inclusion criteria that are often required for clinical trials. Indeed, our study cohort comprised a large percentage of urgent CABGs with unstable angina and non-ST-elevation myocardial infarction representing the most common indications for surgical revascularization.

We also demonstrated higher blood transfusion rates in patients who received DAPT therapy (30.1% vs 25.4%, p = 0.001). However, we did not observe a difference in reoperation for major bleeding. Previous meta-analysis by Agarwal and colleagues did not demonstrate a difference in major bleeding events (RR 1.1, CI 0.94 to 1.29, p = 0.22,

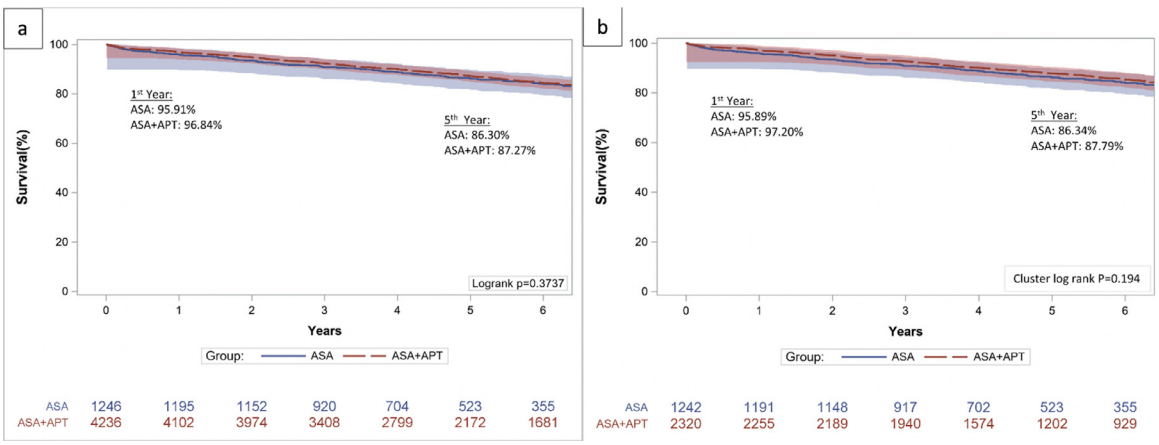

Figure 1. Overall survival following isolated CABG in patients receiving either aspirin monotherapy versus DAPT in (A) unmatched comparison and (B) propensity-matched comparison.

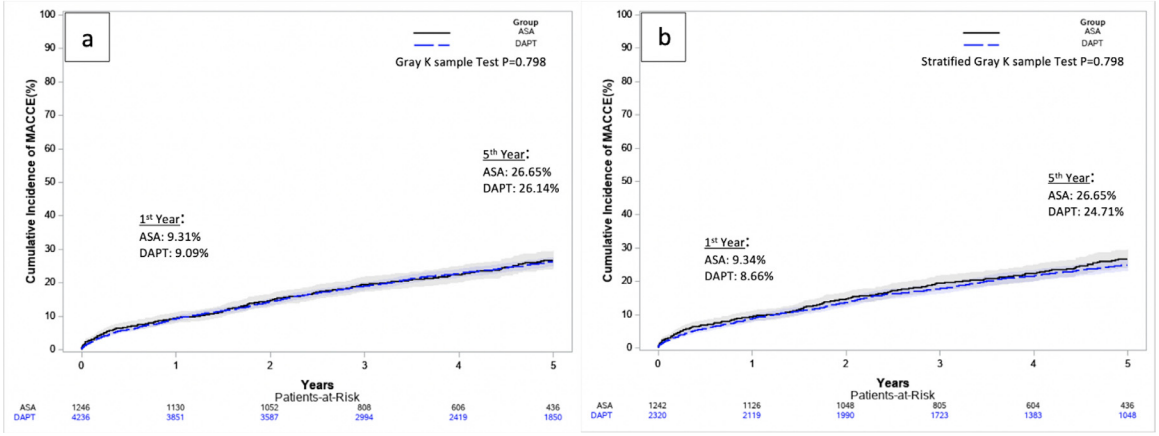

Figure 2. Cumulative incidence for MACCE readmission following isolated CABG in patients receiving either aspirin monotherapy versus DAPT in (A) unmatched comparison and (B) propensity-matched comparison.

$I^2 = 0\%$) between aspirin monotherapy and DAPT.[7] It is possible that though transfusion requirement may increase with usage of DAPT over aspirin, especially in the postoperative period, it does not manifest in major bleeding events requiring intervention other than transfusion. Additionally, in real world practice, antiplatelet agents are sometimes held in the very acute postoperative period when significant bleeding is a concern, and thus it is possible that reoperation for bleeding in the acute postoperative period may be unrelated to antiplatelet agents. However, non-operative bleeding may nevertheless be important clinically as blood transfusions have been correlated with increased major infection risk during the first 65 days after cardiac surgery.[14]

Also relevant in the discussion of aspirin monotherapy versus DAPT in CABG is whether certain subpopulations more prone to MACCE would benefit selectively from DAPT utilization. For instance, diabetes mellitus has been shown to be associated with higher MACCE rates following CABG.[15] Interestingly, a post hoc, nonrandomized analysis

Table 6
Long-term outcomes following CABG in propensity-matched patients receiving either aspirin monotherapy versus DAPT, and description of 5-year post-CABG myocardial infarction

Variable	Aspirin (n = 1242)	DAPT (n = 2320)	p
Follow-up (years)	4.48 (2.95- 6.19)	5.13 (3.49- 7.23)	<0.001
Hospital length of stay (days)	7.50 (6.00-10.00)	8.00 (6.00-10.00)	0.339
One-year MACCE	290 (23.35%)	531 (22.89%)	0.755
Five-year MACCE	116 (9.34%)	201(8.66%)	0.500
One-year stroke	13 (1.05%)	25 (1.08%)	0.932
Five-year stroke	41 (3.30%)	108 (4.66%)	0.054
One-year myocardial infarction	35 (2.82%)	71 (3.06%)	0.685
Five-year myocardial infarction	69 (5.56%)	160 (6.90%)	0.120
One-year repeat revascularization	48 (3.86%)	83 (3.58%)	0.664
Five-year repeat revascularization	123 (9.90%)	194 (8.36%)	0.124
Five-year all-cause readmission	517 (41.63%)	1044 (45.00%)	0.052
Five-year cardiac readmission	435 (35.02%)	899 (38.75%)	0.028
Five-year heart failure readmission	158 (12.72%)	327 (14.09%)	0.255
Five-year myocardial infarction	**Aspirin (n = 69)**	**DAPT (n = 160)**	
Anatomic territory			
Anterior	11 (15.94%)	39 (24.38%)	
Lateral	20 (28.99%)	37 (23.13%)	
Posterior	17 (24.64%)	26 (16.25)	
Unknown	21 (30.43%)	73 (45.63%)	
Previous grafting to affected territory			
LIMA	6 (8.70%)	13 (8.13%)	
RIMA	0 (0.00%)	2 (1.25%)	
Radial artery	0 (0.00%)	0 (0.00%)	
SVG	32 (46.38%)	63 (39.38%)	
Territory not grafted	10 (14.49%)	9 (5.63%)	
Unknown	21 (30.43%)	73 (45.63%)	

LIMA = left internal mammary artery; MACCE = major adverse cardiac and cerebrovascular events; RIMA = right internal mammary artery; SVG = saphenous vein graft.

of the FREEDOM trial compared aspirin monotherapy versus DAPT in diabetic CABG patients and found no difference in cardiovascular or bleeding events, leading the authors to conclude that DAPT may not be clinically warranted in this subset.[16]

Some groups have also argued that another cohort that may benefit from DAPT are those CABG patients with aspirin resistance. We do not routinely obtain resistance assays in our practice although some surgeons do this regularly. Data regarding aspirin resistance in CABG is conflicting, with incidence of resistance ranging from 5% to 35% and some studies showing an correlation between resistance and lower saphenous vein graft patency with other studies demonstrating no impact.[17,18]

The current study has several limitations. First, this was a nonrandomized observational study, and as such, may be subject to selection bias. Though we did perform propensity matched analysis that resulted in well-balanced groups, there may be unmeasured confounding variables that impact the outcomes of this study. Second, in our practice, patients are uniformly placed on 81 mg daily of aspirin should monotherapy be used, and 81 mg aspirin daily and 75 mg clopidogrel daily should a DAPT regimen be used. However, dosages or choice of alternative antiplatelet agent other than aspirin may have varied in a small subset of these patients. Patients treated with a higher dosage of aspirin preoperatively were typically resumed on this higher dosage. Patients of whom had been managed with alternative antiplatelet agents to clopidogrel in the preoperative setting were typically resumed on their preoperative agent in addition to aspirin. Although this potentially small subpopulation may create inconsistency within treatment arms, it reflects a real-world practice in which a surgical group should employ a strategy of universal aspirin monotherapy or DAPT following CABG procedures. Additionally, a notable proportion of patients experienced a change in their antiplatelet regimen in the postoperative period, or addition of anticoagulants for other medical reasons. Medical regimens were determined by active medication lists at various timepoints in the post-CABG period. As such, there is potential for discrepancy between medications listed as "active" in a patient's electronic health record and what they may actually be taking at home. Because aspirin is often bought over the counter and does not require a provider prescription, it is possible the proportion of patients taking this medication in the outpatient setting may be underestimated.

In this propensity-matched analysis of 3,562 patients undergoing isolated CABG, the postoperative use of dual antiplatelet therapy did not confer any advantage in terms of overall survival or rates of MACCE as compared to aspirin monotherapy. Patients on DAPT had higher postoperative blood transfusion rates. This real-world data suggests that DAPT may not be clinically warranted after isolated CABG.

Authors' Contributions

Nicholas Hess: Conceptualization, Data curation, Writing – original draft, review and editing; Ibrahim Sultan: Writing – review and editing; Yisi Wang: Formal statistical analysis; Floyd Thoma: Data curation, formal statistical analysis; Arman Kilic: Conceptualization, supervision, writing – review and editing

Disclosures

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Supplementary materials

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