


# Safety Comparison of Monotherapy Aspirin to Dual Antiplatelet Therapy Following Coronary Artery Bypass Surgery

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## Abstract

**Background:** Dual antiplatelet therapy (DAPT) is recommended over single antiplatelet therapy (SAPT) in patients following coronary artery bypass grafting (CABG). The compilation of evidence has focused on the efficacy of DAPT to limit risk of graft occlusion, however the safety, especially in the on-pump CABG population, is less well described. The aim of this study was to assess the safety of DAPT versus SAPT after on-pump CABG.

**Methods:** This was a single-center, retrospective cohort analysis of adult patients following isolated on-pump CABG between January 2012 and December 2019 not on oral anticoagulation at discharge. The primary endpoint was occurrence of a composite bleeding event identified by pre-specified ICD codes. Secondary endpoints consisted of 30-day and 1-year mortalities along with individual bleeding components.

**Results:** Of the 2341 patients included 1250 patients were in the SAPT arm and 1091 patients in the DAPT arm. The study populations differed by age, prior MI, PAD, and CHF status/stage. Bleeding events occurred in a total of 70 patients (3.0%), with 36 patients (2.9%) in the SAPT arm and 34 patients (3.1%) in the DAPT arm ( $P = .74$ ). 30-day (SAPT 0.7% vs DAPT 0.4%) and 1-year (SAPT 3.3% vs DAPT 2.3%) mortality were not significantly different between groups. The most frequent bleed event was in the gastrointestinal tract.

**Conclusion:** In this study, DAPT was not associated with an increase in composite bleeding compared to SAPT. This study could reduce the barrier to prescribing of DAPT given previous efficacy data.

## Keywords

coronary artery bypass graft surgery, CABG, antiplatelets, medication safety bleeding, clopidogrel, and aspirin

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## Introduction

Approximately 371 000 coronary artery bypass grafting (CABG) procedures are performed annually in the United States as the standard of care in patients with complex multivessel heart disease, especially those with comorbid diabetes.<sup>1-4</sup> Complications include graft occlusion/loss of patency, myocardial infarction, stroke, and bleeding.<sup>5</sup> The primary prevention for these complications include antiplatelet therapy that has been shown to prevent loss of graft patency and prevent ischemic events after CABG but carries with it the potential to increase bleeding risk.<sup>6,7</sup> Accordingly, aspirin monotherapy has long been considered the standard of care following CABG.

In 2016 the American College of Cardiology/American Heart Association Guideline Focused Update on Duration of

Dual Antiplatelet Therapy in Patients with Coronary Artery Disease issued recommendations to utilize dual antiplatelet therapy (DAPT) over single antiplatelet therapy (SAPT) in patients following CABG.<sup>8</sup> The compilation of data suggested that DAPT further reduced rates of graft occlusion with a

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trend toward reduction in major adverse cardiac events (MACE) when compared to SAPT.<sup>9–11</sup> Evaluation of practice changes to adopt DAPT post-CABG demonstrate consistent benefit in a large population comparison.<sup>12–16</sup> The increased efficacy of preventing thrombotic events is not clearly weighed against the potential bleeding events due to varying bleeding definitions and only secondary analysis of safety. The aim of this study was to assess rates of bleeding in patients receiving DAPT versus patients receiving SAPT following on-pump CABG.

## Methods

This was a single-center, retrospective cohort study of adult patients ( $\geq 18$  years of age) who received on-pump, isolated CABG between January 1, 2012 and September 30, 2019 at Mayo Clinic in Rochester, MN and were discharged with instructions to take aspirin monotherapy or DAPT. During the study period this center performed an average of 673 on-pump CABG procedures annually. Antiplatelet therapy practices switched temporally around 2017 following release of the 2016 guideline recommendations.<sup>8</sup> After 90 days of DAPT patients were recommended to continue aspirin 81 mg daily monotherapy if they had no other indication to continue DAPT for longer. Aspirin monotherapy at discharge was either 325 mg daily or 81 mg daily depending on surgeon preference. The practice was to utilize aspirin 325 mg prior to the practice change and converted to 81 mg after. Few patients were discharged on aspirin monotherapy after the 2017 practice change. Clopidogrel was the predominate P2Y12 inhibitor prescribed in patients receiving DAPT. Patients were only discharged on a proton pump inhibitor (PPI) if they were taking prior to admission or developed a gastrointestinal bleed. Patients were identified through the institution's prospectively managed Society of Thoracic Surgeons (STS) database. Available patient characteristics were extracted through STS. Bleeding outcomes were classified by International Classification of Disease (ICD)-9 and ICD-10 codes (Supplemental Table 1). All events were validated by the study team and all living patients had, at minimum, a phone or virtual visit at one year regardless of if they had an outside primary care provider. Patients were excluded if they were prescribed oral anticoagulation at discharge, had contraindications to either aspirin or P2Y12 inhibitors, were suspected or confirmed pregnant, incarcerated, or declined the MN Research Authentication. This study was approved by the Mayo Clinic Institutional Review Board (IRB 20-007877).

## Outcomes

The primary endpoint was the occurrence of a composite of a bleeding event (Gastrointestinal (GI) bleed, intracranial bleed, hemoperitoneum, any bleeding and/or readmission for bleed within 1 year post-operatively) with secondary endpoints comprising of the individual types of bleeding included in the composite. Re-operation bleeding during the index admission was not included in the composite primary endpoint but was

recorded. Other secondary outcomes included 30-day and 1-year mortality.

## Statistical Analysis

Data was summarized using frequencies and percentages for categorical data, and either means and standard deviations or medians and interquartile ranges for continuous data. Univariate and multivariable logistic regression were used to assess the association between receiving DAPT versus SAPT and having a bleeding event within one year. Secondary outcomes were compared between groups using either a Chi-square or Fisher's exact test. All tests were two-sided, and  $P$ -values  $\leq .05$  were considered statistically significant. Statistical analyzes were performed using SAS version 9.4 software (SAS Institute, Inc.; Cary, NC).

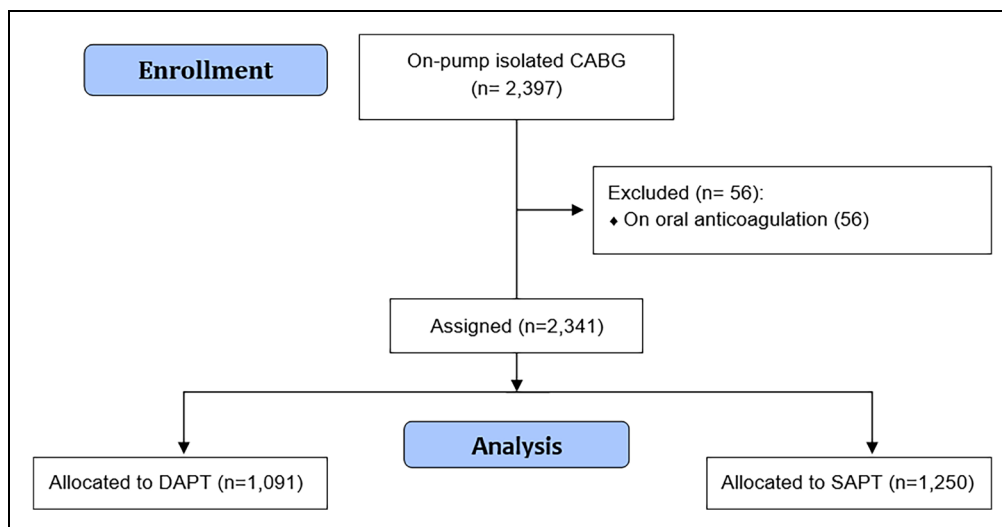
Our assumption that 65% of patients would have received SAPT and 35% had receive DAPT, and that 5% of those who received SAPT would have a bleeding event within one year, with a level of significance of 0.05, we estimated we would need 978 SAPT patients and 528 DAPT patients in order to have 80% power to detect an increase of 4% or more in those receiving DAPT compared to SAPT.

## Results

### Study Population

A total of 2341 adult patients were identified having undergone isolated, on-pump CABG and after excluding 56 for discharge on oral anticoagulation we allocated 1250 patients receiving post-operative SAPT and 1091 patients receiving post-operative DAPT (Figure 1). A total of 313 patient in the SAPT arm had an aspirin dose of 324 or 325 mg (25.0%) and the rest received 81 mg. All patients in the DAPT arm received aspirin 81 mg with a total of 17 patients receiving ticagrelor (0.02%) and all other patients receiving clopidogrel. Baseline characteristics were mostly similar between the two groups (Table 1). Patients receiving SAPT were older (median age 68: IQR 60-74, vs 65: IQR 58-72;  $P = <.001$ ), and had a higher number classified as NYHA class IV (17.2% vs 11%;  $P = <.001$ ). Patients who received DAPT had a higher incidence of prior myocardial infarction (MI) (52.2% vs 45.7%,  $P = .002$ ), peripheral artery disease (PAD) (17.4% vs 12.7%,  $P = .002$ ), and confirmed previous smoking history (46.7% vs 22.4%;  $P = .001$ ). The median length of stay after surgery was 5 days [Interquartile range (IQR) 4-6] and 5 days (IQR 5-7) in the SAPT and DAPT group respectively.

Most patients underwent elective CABG but patients receiving DAPT had more urgent surgery (38.9% vs 35.9%,  $P = .046$ ) while SAPT had more emergent surgery (2.4% vs 1%,  $P = .046$ ). A majority of patients received at least one internal mammary artery (Table 1). Patients receiving DAPT were more likely to have previously undergone a percutaneous coronary intervention (PCI) procedure (33.1% vs 27.5%,  $P = .003$ ). Patients receiving SAPT had longer perfusion time (min, 88 vs



**Figure 1.** Consort diagram.

85,  $P = .007$ ) (Table 1). Prior to discharge, reoperation bleeding events occurred in 29 (2.3%) and 12 (1.1%) of DAPT patient respectively ( $P = .043$ ).

### Outcomes

The primary composite outcome occurred in a total of 70 patients (3%), with 36 patients (2.9%) receiving SAPT and 34 patients (3.1%) receiving DAPT experiencing a bleeding event within 12 months of the procedure ( $P = .74$ ) (Table 2). Bleeding events at 90 days occurred in 27 patients (1.14%) in the SAPT arm and 16 patients (0.68%) in the DAPT arm.

The most common bleed type between the SAPT and DAPT arms was GI bleed (1.6% vs 2.3%,  $P = .29$ ). A multivariable analysis was conducted which did not demonstrate an increased risk of bleeding with DAPT versus SAPT (Table 2). Variables that were identified to be associated with bleeding were older age, renal failure, and PAD. A decreased bleed risk was associated with dyslipidemia (Table 2).

### Discussion

The results of this study found that the use of DAPT was not associated with increased rates of composite bleeding when compared to the use of SAPT in patients that underwent isolated on-pump CABG. The most common observed post-discharge bleeding event was a GI bleed with numerically higher number in the patient who received DAPT. That finding while not statistically significant is consistent with other DAPT medical management evidence.<sup>17</sup> While the use outpatient antacid therapy was not able to be assessed in this study, it warrants future research as a preventive measure for this bleeding event. With previous evidence showing a reduction in MACE post-CABG in combination with the lack of safety signal observed in this study suggest a net clinical benefit of DAPT when used post-CABG.<sup>16</sup>

The use of DAPT versus SAPT after CABG stemmed from a retrospective observation of reduced myocardial infarction events in patients treated with clopidogrel with aspirin from a Danish administrative database study.<sup>14</sup> Since then a variety of CABG populations, mostly undergone off-pump bypass procedures with venous graphs, have shown benefit for the use of DAPT over SAPT for graft patency.<sup>12,18</sup> While the efficacy of DAPT appears well established in the off-pump populations, subsequent small studies in the on-pump population were inconsistent at showing reduction in MACE or graft occlusion.<sup>12,19–21</sup> A large register study of over 18 000 patients evaluated the efficacy of reported MACE events at 6 months for DAPT versus SAPT post-isolate CABG. This population study showed DAPT use was associated with a reduction in ischemic events overall and across all subgroup analysis.<sup>16</sup>

The current evidence has bleeding included as a secondary endpoint with most studies showing no difference in bleed risk, but one randomized trial demonstrated an increased bleed risk with DAPT.<sup>9</sup> A separate small randomized trial, specifically assessing an on-pump CABG population ( $n = 100$ ), found no difference in bleeding rates between DAPT and SAPT therapies.<sup>12</sup> Since 2016 few studies have evaluated the use of DAPT and safety outcomes in the specific on-pump CABG population. A recent trial ( $n = 496$ ) of patients undergoing on-pump CABG observed a trend toward increased bleeding with the use of DAPT, though not statistically significant.<sup>15</sup> This study varied from ours as it studied patients receiving only saphenous vein grafts treated with ticagrelor while our population included those receiving vein or arterial graft(s) mainly treated with clopidogrel, which when compared in acute coronary syndrome patients clopidogrel has a lower incidence of bleeding.<sup>15,22</sup> The size of the recent trial may have also limited the ability to detect a difference in bleeding. When comparing bleeding events in over 2300 patients in our trial the bleeding rates were not different and can reassure the risk of clopidogrel post-CABG may not outweigh the previously demonstrated benefit.

**Table 1.** Baseline and Surgical Characteristics.

Variable	DAPT (n = 1091)	SAPT (n = 1250)	P-Value
Age <sup>*</sup>	65 (58, 72)	68 (60, 74)	<.001
Race <sup>a</sup>			.35
Caucasian	1005 (92.1)	1173 (93.8)	
Black	6 (0.5)	10 (0.8)	
Asian	24 (2.2)	20 (1.6)	
Other	43 (3.9)	35 (2.8)	
Unknown	13 (1.2)	12 (1.0)	
Sex, male <sup>a</sup>	880 (80.7)	1003 (80.2)	.80
Height (cm) <sup>b</sup>	173 (167, 179)	173 (166, 179)	.73
Weight (kg) <sup>b</sup>	90 (77, 103)	89 (77, 102)	.83
Body Mass Index <sup>b</sup>	29.8 (26.4, 34.1)	29.8 (26.6, 33.7)	.91
Hypertension <sup>a</sup>	930 (85.2)	1026 (82.5)	.077
Dyslipidemia <sup>a</sup>	1039 (95.2)	1193 (96.0)	.38
Diabetes <sup>a</sup>	450 (41.2)	503 (40.5)	.70
Congestive Heart Failure <sup>a</sup>	110 (10.1)	153 (12.3)	.090
NYHA class <sup>a</sup>			<.001
I	122 (21.6)	131 (13.4)	
II	169 (29.9)	335 (34.3)	
III	212 (37.5)	344 (35.2)	
IV	62 (11.0)	168 (17.2)	
Prior Myocardial Infarct <sup>a</sup>	568 (52.2)	568 (45.7)	.002
Prior Cerebrovascular Accident <sup>a</sup>	74 (6.8)	73 (5.9)	.37
Smoking <sup>a</sup>			<.001
Current	170 (15.6)	169 (13.5)	
Previous	509 (46.7)	280 (22.4)	
Never	372 (34.1)	217 (17.4)	
Unknown	40 (3.7)	584 (46.7)	
Peripheral Artery Disease <sup>a</sup>	190 (17.4)	158 (12.7)	.002
Renal Failure <sup>a</sup>	58 (5.3)	64 (5.1)	.85
<b>Surgery Variable</b>	<b>DAPT (n = 1091)</b>	<b>SAPT (n = 1250)</b>	<b>P-Value</b>
Status, n (%)			.046
Elective	655 (60.0)	769 (61.6)	
Urgent	424 (38.9)	449 (35.9)	
Emergent	11 (1.0)	30 (2.4)	
Emergent Salvage	1 (0.1)	1 (0.1)	
Previous Sternotomy, n (%)	26 (2.4)	38 (3.0)	.33
Previous PCI, n (%)	361 (33.1)	343 (27.5)	.003
Perfusion time (min), median (IQR)	85 (67, 104)	88 (71, 108)	.007
Cross clamp time (min), median (IQR)	65 (49, 79)	63 (49, 79)	.26
Internal Mammary artery <sup>c</sup> , n (%)			<.001
1	441 (67.7)	807 (75.6)	
2	10 (1.5)	15 (1.4)	
3	180 (27.6)	204 (19.1)	
4	20 (3.1)	42 (3.9)	
Radial Artery Used <sup>d</sup> , n (%)			.003
1	65 (14.8)	11 (6.1)	
2	375 (85.2)	170 (93.9)	
Hospital Length of Stay, post-operatively <sup>b</sup> , n (%)	5 (5.7)	5 (4.6)	

\*denotes number (interquartile range);

<sup>a</sup>denotes number (%);

<sup>b</sup>denotes median (interquartile range);

<sup>c</sup>only available in 1737 (651 DAPT and 1086 SAPT);

<sup>d</sup>only available in 631 (440 DAPT and 191 SAPT).

Our multivariable analysis for composite bleed lends further evidence that renal dysfunction (estimated Glomerular Filtration Rate < 45 ml/min/1.73m<sup>2</sup>) is an attributable risk factor for bleeding during and after CABG procedures. Chronic kidney disease has been associated with a 1.5× higher bleeding event rate in medical patients and surgery could exacerbate that risk even

further.<sup>23</sup> Observed platelet dysfunction from intrinsic impaired abnormalities and activation may make the chronic kidney disease patient group a high risk group for DAPT post CABG.<sup>24</sup> The WILL-BLEED Score also showed renal dysfunction as a risk despite antiplatelet therapy choice for major bleeding associated with CABG.<sup>25,26</sup> More research is needed in this group to

**Table 2.** Results.

Outcome	DAPT (n = 1091)	SAPT (n = 1250)	P-Value
<i>Primary</i>			
Composite bleeding, n (%)	34 (3.1)	36 (2.9)	.74
<i>Secondary</i>			
Gastrointestinal bleed, n (%)	25 (2.3)	20 (1.6)	.29
Intracranial bleed, n (%)	2 (0.2)	2 (0.2)	>.99
Bleeding from other site, n (%)	5 (0.5)	12 (1.0)	.22
Hemoperitoneum, n (%)	2 (0.2)	2 (0.2)	>.99
30-day mortality, n (%)	4 (0.4)	9 (0.7)	.25
1-year mortality, n (%)	25 (2.3)	41 (3.3)	.15
Multivariable Model for Composite Bleeding Outcome			
	Adjusted Odds Ratio (95% CI)		P-value
Treatment (DAPT vs SAPT)	1.06 (0.65-1.72)		.83
Age (per year)	1.04 (1.01-1.06)		.009
Hypertension (Y vs N)	2.14 (0.83-5.50)		.11
Dyslipidemia (Y vs N)	0.39 (0.16-0.95)		.038
PAD (Y vs N)	2.42 (1.43-4.10)		.001
Renal failure (Y vs N)	3.69 (1.88-7.25)		<.001

\*OR > 1 means more likely to have bleeding event.

validate their optimal antiplatelet therapy, but for now that group may benefit more from SAPT post CABG due to the risk of bleeding.

This study has several limitations. First, our patient population consisted primarily of older Caucasian males which may decrease the applicability of our results to other patient populations. Second, pharmacotherapy regimens were only assessed at the time of discharge. Outpatient prescription fill history and the use of over the counter medications, including those associated with a reduction in bleeding, after discharge was unavailable.<sup>27</sup> Additionally, we were only able to assess the use oral anticoagulation therapy at time of discharge and new start anticoagulants as an outpatient were not captured. The use of ICD coding for identification of outcomes may have led to underreporting of events as we were only able to manually verify events we found.<sup>28</sup> Lastly, the event rate we found was lower than anticipated based on our estimates from event rates found in other literature, but each event was validated to ensure it was a bleeding event. The limited event rate did also prevent any additional regression analysis.

## Conclusion

The results of this study found the routine use of DAPT post-CABG was not associated with a statistical difference in composite bleeding compared to SAPT with aspirin. These findings, in combination with previous evidence suggesting improved graft patency and decreased MACE, provides further evidence that routine use of DAPT is a safe alternative to SAPT following CABG.

## Author's Individual Contribution

*Scott D. Nei:* This author contributed substantially to the conception, design of the content, and drafting of the manuscript for important intellectual content.

*Kyle S. Wamsley:* This author contributed substantially to the conception, design of the content, and drafting of the manuscript for important intellectual content.

*Kristin C. Mara:* This author contributed substantially to the conception, design of the content, and drafting of the manuscript for important intellectual content.

*John M. Stulak:* This author contributed substantially to the conception, design of the content, and drafting of the manuscript for important intellectual content.

*Joseph J. Ziemiński:* This author contributed substantially to the conception, design of the content, and drafting of the manuscript for important intellectual content.

## Declaration of Conflicting Interests

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## Ethical Approval

All applicable institutional and/or national guidelines were followed.

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## Supplemental Material

Supplemental material for this article is available online.

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