Title

The Impact of Postoperative Dual Antiplatelet Therapy on Outcomes of Endovascular Therapies in Patients with Chronic-Limb Threatening Ischemia in the Vascular Quality Initiative-Medicare-Linked Database

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Title: The Impact of Postoperative Dual Antiplatelet Therapy on Outcomes of Endovascular Therapies in Patients with Chronic-Limb Threatening Ischemia in the Vascular Quality Initiative-Medicare-Linked Database

Short title: Dual Antiplatelet Therapy in Endovascular Therapies for Chronic-Limb Threatening Ischemia

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Meeting: This study was presented at the Vascular Annual Meeting (VAM) at National Harbor, MD (June 14-17, 2023) as a poster competition.

Article Highlights

Type of research: Multicenter retrospective analysis of prospectively collected Vascular Quality Initiative-Medicare-Linked data

Key Findings: We found that 58.3% of patients undergoing endovascular therapy for infrainguinal occlusive disease presenting with chronic limb-threatening ischemia in the VQI-VISION registry received dual antiplatelet therapy (DAPT) following discharge. DAPT was associated with improved amputation-free survival (AFS) for up to five years, as well as improved overall survival (OS) and limb salvage for up to one year. Additionally, P2Y12 inhibitor alone was associated with improved OS and AFS up to five years compared to aspirin alone.

Take home message: Our findings support the use of dual antiplatelet therapy or P2Y12 inhibitor following endovascular therapy for infra-inguinal chronic limb-threatening ischemia, as it was associated with significantly improved amputation-free survival up to five years.

Table of Contents Summary: We found that 58.3% of patients undergoing endovascular therapy for infrainguinal occlusive disease presenting with chronic limb-threatening ischemia in the VQI-VISION registry received dual antiplatelet therapy (DAPT) following discharge. DAPT or P2Y12 inhibitor was associated with improved amputation-free survival for up to five years.

Conflicts of Interests: SZ, MH, and MPM have nothing to disclose (Educational grant to support postdoctoral fellow was obtained but not used for this study). MBM was PI/Co-PI for the studies as follows when he was at Johns Hopkins: BEST CLI, Zilver PTX IDE; Zilver PTX post-approval study, The ACTIVE (Use of the Assurant® Cobalt Iliac Stent System in the Treatment of Iliac Vessel Disease) Study, and CLEVER study. ACG has nothing to disclose.

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Abstract

Objectives: The beneficial effects of dual antiplatelet therapy (DAPT) compared to single antiplatelet therapy (SAPT) have been well established in coronary and carotid endovascular interventions; however, no consensus exists to the role of DAPT in lower extremity endovascular therapies (ET). We aimed to investigate the impact of postoperative DAPT following ET in patients presenting with chronic limb-threatening ischemia (CLTI) in the Vascular Quality Initiative-Medicare-Linked (Vascular Implant Surveillance and Interventional Outcomes Network [VISION]) database.

Methods: The study was a multicenter retrospective analysis of prospectively collected VQI-Medicare-Linked data. The VISION database was queried for all ETs performed for infrainguinal occlusive disease between 2011 and 2019. The patients were stratified by discharge antiplatelet regimen (DAPT vs. SAPT). SAPT patients received either aspirin or P2Y12 inhibitors whereas DAPT patients received both. The primary outcome was 1- and 5-year amputation-free survival (AFS). The secondary outcomes included 1- and 5-year overall survival, limb salvage (freedom from major amputation), and freedom from reintervention. Kaplan-Meier survival estimates and Cox regression were used for analysis.

Results: The study included two cohorts: SAPT (N=10,086, 41.7%) and DAPT (N=14,081, 58.3%). The patients in SAPT cohort were older than their DAPT counterparts and were more likely to have congestive heart failure and chronic kidney disease. While the patients in the DAPT cohort were more likely to have diabetes and coronary artery disease. In survival analyses, compared to SAPT, 1-year AFS in the DAPT cohort was 67.9% vs. 63.7% (P<.001) and 5- year AFS was 30.4% vs. 24.6% (P<.001). After adjusting for potential confounders, DAPT was associated with reduced hazards of major amputation or death at 1-year (adjusted hazard ratio [aHR]=0.82; 95% confidence interval [CI], 0.75-0.89; P<.001) and 5-year (aHR=0.91; 95% CI, 0.84-0.99; P=0.027). DAPT was also associated with lesser hazards of death (aHR=0.90; 95% CI, 0.81-0.99; P=0.048) and major amputation (aHR=0.86; 95% CI,

0.79-0.93; P<.001) at 1-year but not 5-year. Reintervention was not impacted by the antiplatelet therapy strategy. In our sub-analysis, we found superior five-year overall and amputation-free survivals in patients receiving DAPT compared to aspirin alone and also in patients receiving P2Y12 inhibitor alone compared to aspirin alone. However, the outcomes of DAPT vs. P2Y12 inhibitor alone were not significantly different.

Conclusions: In this large Medicare-linked national analysis, we found that DAPT is associated with improved AFS up to five years following ET in patients with CLTI compared to SAPT. However, there was no difference between DAPT and P2Y12 inhibitor alone. Additionally, P2Y12 inhibitor was associated with improved AFS up to five years compared to aspirin. Our findings support the use of DAPT or P2Y12 inhibitor following ETs performed in the lower extremity for CLTI; however, further prospective studies are required to confirm our findings.

Introduction

Patients with infrainguinal peripheral artery disease (PAD) presenting with chronic limb-threatening ischemia (CLTI) are at significant risk of both limb loss and death. Revascularization is recommended for these patients (1). Based on the recent Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischemia (BEST-CLI) trial, bypass with a single-segment great saphenous vein is superior to endovascular therapy (ET) in terms of major adverse limb event or death. However, in certain patients who are at high surgical risk or have suboptimal autogenous grafts or distal run-off, ET becomes an alternative option (2–5). The type of antiplatelet therapy following ET is one of the factors that impact the outcomes in patients treated for CLTI (6).

Within the cardiology practice, there is strong evidence supporting the use of dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) in patients with coronary artery disease (CAD). DAPT generally consists of aspirin combined with a P2Y12 inhibitor. The patient's ability to tolerate and adhere to at least 30 days of DAPT after bare metal stent (BMS) placement and 12 months after drug-eluting stent (DES) placement is a critical factor in determining whether PCI is appropriate for treating patients with CAD (7–9). Studies on PCI have demonstrated that extending DAPT beyond one year after DES placement, compared to aspirin alone, significantly reduces the risk of stent thrombosis and major adverse cardiovascular and cerebrovascular events. However, this prolonged DAPT is also associated with an increased risk of bleeding (10).

The most recent guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend the use of DAPT, consisting of low-dose aspirin and a P2Y12 inhibitor, following ET in patients with CLTI, with a class 2a level of recommendation (11). Additionally, the guidelines from the Society for Vascular Surgery (SVS) suggest considering

DAPT (aspirin plus clopidogrel) for patients who have undergone infrainguinal ET for CLTI, recommending a duration of at least one month, with a class C level of recommendation (12). Studies supporting the use of DAPT following ET for infrainguinal CLTI are not as extensive as those for CAD (13–16). Most of the recommendations for DAPT after ET are extrapolated from coronary studies resulting in the “soft guideline recommendations”. Therefore, we aimed to investigate the long-term outcomes following ET for infrainguinal CLTI in patients discharged on DAPT compared to those discharged on single antiplatelet therapy (SAPT), utilizing data from the Vascular Quality Initiative (VQI)-Medicare-Linked database.

Methods

Data

We utilized the Vascular Implant Surveillance and Interventional Outcomes Network (VISION) database. VISION matches Medicare claims data to the VQI registry, which is the most comprehensive registry for vascular surgery procedures in North America. Over 1,000 centers across the United States and Canada participate in VQI, and the registry has captured more than 1.2 million procedures to date (17,18). The primary aim of VQI is to improve the quality of vascular surgery care (19,20). More information about VQI can be found at www.vqi.org. VISION (https://www.mdepinet.net/vision) matches VQI data to Medicare claims using ICD-10 (International Classification of Diseases, 10th Revision) and CPT (Current Procedural Terminology) codes, linking SVS VQI registry data to Medicare claims to generate unique registry-claims linked datasets. These datasets combine the clinical detail from the VQI with long-term outcome variables derived from Medicare claims. VISION data is used to generate center-specific feedback reports, known as Survival, Reintervention, and Surveillance (SRS) reports, and to analyze device performance and long-term outcomes of vascular surgical techniques. Use of the data is governed by a Data Use Agreement (DUA) between Weill Cornell Medical College and the Centers for Medicare & Medicaid Services (CMS) (21,22). The protocol

for this study was approved by the SVS Research Advisory Committee (RAC) under approval number 4996. This study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational research.

Patients

We utilized the Peripheral Vascular Intervention (PVI) pathway from the VQI-VISION data covering the period from 2011 to 2019. Only patients with occlusive disease undergoing intervention for infrainguinal CLTI were included. Patients treated for claudication, acute limb ischemia, or aneurysmal disease were excluded. Additionally, those undergoing concomitant aortic or suprainguinal procedures, common femoral artery intervention, infrapopliteal artery stenting, or concomitant endarterectomy were excluded. Patients with prior major amputations were also excluded. Since Medicare-matched data was used, patients with insurance other than Medicare and Medicaid were also excluded. The study sample was then stratified based on discharge antiplatelet therapy: DAPT vs. SAPT (Figure 1). SAPT was defined as receiving either aspirin or a P2Y12 inhibitor post-intervention, while DAPT was defined as receiving both aspirin and a P2Y12 inhibitor post-intervention. The duration of discharge SAPT or DAPT was not recorded in the VQI/VISION data.

Background variables

Background variables include age, sex, race, ethnicity, smoking status (never, former, current), comorbidities (obesity, hypertension, diabetes mellitus [DM], CAD, congestive heart failure [CHF], chronic pulmonary obstructive disease [COPD], and chronic kidney disease [CKD]), prior procedures (coronary revascularization, carotid revascularization, inflow intervention, ipsilateral bypass or PVI, contralateral bypass or PVI), preoperative medications (aspirin, P2Y12 inhibitor, statin, and anticoagulant), contrast volume, fluoroscopy time, urgency of procedure, number of arteries treated, type of CLTI (rest pain vs. tissue loss), level of revascularization

(femoropopliteal, infrapopliteal, and femorotibial), type of ET (angioplasty, angioplasty + stenting, angioplasty + atherectomy, and angioplasty + stenting + atherectomy), and discharge medications (statin and anticoagulant).

Femoropopliteal interventions were defined as those involving the femoral, popliteal, or both the femoral and popliteal arteries. Infrapopliteal interventions referred to procedures targeting the tibiopedal arteries. Femorotibial interventions encompassed procedures involving arteries from both the femoropopliteal and infrapopliteal territories.

Based on the VQI registry, obesity was defined as a preoperative body mass index (BMI) of ≥ 30 kg/m^2. Hypertension was defined as a preoperative blood pressure of ≥ 140/90 mmHg or a documented history of either controlled or uncontrolled hypertension. Diabetes mellitus was defined as a preoperative diagnosis, including patients managed by diet, oral medications, insulin, or a combination of these treatments. CAD was defined as any history of angina or myocardial infarction (MI). CHF was defined as a history of either asymptomatic or symptomatic CHF, regardless of severity. COPD was defined as any diagnosis of COPD, regardless of whether the patient was receiving medication or home oxygen therapy. CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 (23).

Outcomes

The primary outcome was amputation-free survival (AFS). The secondary outcomes included overall survival (OS), limb salvage (LS), and freedom from reintervention (FFR). Death was defined as mortality from any cause and was captured in the VISION database using the denominator file from Medicare claims. Limb salvage was defined as freedom from major amputation. Major amputation and reintervention data were also derived from Medicare claims using VISION follow-ups. Major amputation was defined as any below-knee or above-knee amputations above the level of the ankle using the current procedural terminology (CPT) codes. Reintervention was defined as any open or endovascular redo intervention in the

femoropopliteal or infrapopliteal regions following the index ET using the CPT codes. All outcomes were analyzed at one-year and five-year follow-up intervals.

Statistical analyses

Categorical variables were reported as frequencies and percentages, while continuous variables were expressed as medians with interquartile ranges. Kaplan-Meier survival estimates, along with log-rank tests, were used to assess one-year and five-year outcomes. Multivariate analysis was conducted using Cox regression, with confounders selected through backward stepwise regression ($P<0.1$) and based on clinical relevance (24). Regardless of the stepwise selection results, age, sex, race, procedure urgency, and type of CLTI were included in all models. Models were clustered by center identification codes. Schoenfeld residuals were used to evaluate the proportional hazards assumption of the Cox models. When a fit Cox model was not achieved, a stratified Cox model was utilized. Adjusted hazard ratios (aHR) were reported with 95% confidence intervals (CI). Statistical significance was determined at $P<0.05$. Sub-analyses of outcomes were also performed based on the level of ET (femoropopliteal vs. infrapopliteal vs. femorotibial), type of CLTI (rest pain vs. tissue loss), and ET type using the Cox regression models. Further analyses of the outcomes were also conducted comparing DAPT vs. the type of SAPT (aspirin alone, P2Y12 inhibitor alone, and SAPT + anticoagulant). Additionally, results of P2Y12 inhibitors alone were compared to aspirin alone. All analyses were conducted using Stata version 18 (StataCorp LLC, College Station, Texas).

Results

Baseline characteristics

The study included two cohorts: SAPT (N=10,086, 41.7%) and DAPT (N=14,081, 58.3%). In the SAPT cohort, 5,972 patients (59.2%) received only discharge aspirin, while 4,114 (40.8%) received only a P2Y12 inhibitor. Patients in the SAPT cohort were older than their DAPT

counterparts (74 [67, 82] vs. 72 [65, 81]; P<.001). SAPT patients were also more likely to have CHF (33.4% vs. 29.6%; P<.001) and CKD (59.4% vs. 57.1%; P<.001). In contrast, patients in the DAPT cohort were more likely to be Hispanic or Latino (7.9% vs. 6.3%; P<.001) and current smokers (20.2% vs. 17.8%; P<.001). DAPT patients were also more likely to have diabetes (70.5% vs. 67.2%; P<.001) and CAD (53.9% vs. 48.0%; P<.001). Table 1 lists the baseline characteristics between the DAPT and SAPT cohorts. All baseline variables had less than 6% missing data. The rate of SAPT has decreased from 55.6% in 2011 to 43.5% in 2019, while the rate of DAPT has increased from 44.4% in 2011 to 56.5% in 2019 (Figure 2). The mean follow-up time was 643.9 ± 586.5 days.

One-year outcomes

In survival analyses, 1-year OS was 76.6% vs. 73.4% in the DAPT and SAPT cohorts, respectively (P<.001). One-year AFS in the DAPT and SAPT cohorts was 67.9% vs. 63.7% (P<.001) (Table 2). After adjusting for potential confounders, DAPT was associated with reduced hazards of major amputation or death at 1 year (aHR=0.82; 95% CI, 0.75-0.89; P<.001). DAPT was also associated with lower hazards of death (aHR=0.90; 95% CI, 0.81-0.99; P=0.048) and major amputation (aHR=0.86; 95% CI, 0.79-0.93; P<.001) at 1 year. Reintervention was not impacted by the antiplatelet therapy for 1 year (Table 3).

Five-year outcomes

In survival analyses, 5-year OS was 36.9% vs. 30.6% in the DAPT and SAPT cohorts, respectively (P<.001) (Figure 3A and Table 2). Five-year LS was 76.4% vs. 74.5% in the DAPT and SAPT cohorts, respectively (P=0.001) (Figure 3B and Table 2). Compared to SAPT, 5-year AFS in the DAPT cohort was 30.4% vs. 24.6% (P<.001) (Figure 3C and Table 2). Five-year FFR was 38.4% vs. 41.0% in the DAPT and SAPT cohorts, respectively (P<.001) (Figure 3D and Table 2). After adjusting for potential confounders, DAPT was associated with reduced hazards

of major amputation or death at 5 years (aHR=0.91; 95% CI, 0.84-0.99; P=0.027). Reintervention was not impacted by the antiplatelet therapy at 5 years (Table 3).

Sub-analysis of the outcomes stratified by level of intervention

In the sub-analysis of outcomes based on the level of ET, DAPT was associated with decreased hazards of major amputation or death in femoropopliteal interventions both at 1 year (aHR=0.91; 95% CI, 0.84-0.98; P=0.010) and 5 years (aHR=0.93; 95% CI, 0.86-0.99; P=0.036). Moreover, DAPT was associated with decreased hazards of major amputation at 1 year (aHR=0.80; 95% CI, 0.68-0.93; P=0.003) and 5 years (aHR=0.85; 95% CI, 0.75-0.96; P=0.012) in the femoropopliteal region. DAPT was associated with decreased hazards of reinterventions in the femoropopliteal region (aHR=0.92; 95% CI, 0.85-0.99; P=0.024) and increased hazards of reinterventions in the infrapopliteal region (aHR=1.11; 95% CI, 1.01-1.21; P=0.025) at 5 years. DAPT was also associated with decreased hazards of major amputation in femorotibial (aHR=0.87; 95% CI, 0.77-0.98; P=0.022) interventions at 5-year (Table 4).

Sub-analysis of the outcomes stratified by type of CLTI

In the sub-analysis of outcomes based on the type of CLTI, DAPT was associated with decreased hazards of death (aHR=0.84; 95% CI, 0.73-0.97; P=0.014), major amputation (aHR=0.80; 95% CI, 0.65-0.98; P=0.033), and major amputation or death (aHR=0.81; 95% CI, 0.72-0.91; P=0.001) in patients with rest pain up to 5 years. In patients with tissue loss, DAPT was only associated with decreased hazards of major amputation (aHR=0.92; 95% CI, 0.85-0.99; P=0.042) up to 5 years (Table 5).

Sub-analysis of the outcomes stratified by type of ET

In the sub-analysis of outcomes based on the type of ET, DAPT was associated with decreased hazards of death (aHR=0.87; 95% CI, 0.76-0.99; P=0.045), major amputation (aHR=0.78; 95%

CI, 0.64-0.96; P=0.017), and major amputation or death (aHR=0.88; 95% CI, 0.78-0.99; P=0.031) in patients receiving angioplasty + stenting at 1 year. In patients receiving angioplasty + atherectomy, DAPT was only associated with decreased hazards of major amputation (aHR=0.81; 95% CI, 0.67-0.99; P=0.036) at 1 year. Moreover, DAPT was associated with decreased hazards of major amputation or death in patients receiving angioplasty alone (aHR=0.92; 95% CI, 0.86-0.99; P=0.024) and angioplasty + stenting (aHR=0.89; 95% CI, 0.82-0.98; P=0.016) up to 5 years (Table 6).

Analysis of the outcomes by the type of SAPT

One-year and five-year outcomes in DAPT vs. Aspirin alone, DAPT vs. P2Y12 inhibitor alone, DAPT vs. SAPT + Anticoagulant, and P2Y12 inhibitor alone vs. aspirin alone were analyzed and are presented in Table 7. We found superior five-year overall and amputation-free survivals in patients receiving DAPT compared to aspirin alone and also in patients receiving P2Y12 inhibitor alone compared to aspirin alone. However, the outcomes of DAPT vs. P2Y12 inhibitor alone were not significantly different.

Discussion

We found that 58.3% of patients undergoing ET for infrainguinal occlusive disease presenting with CLTI received DAPT. DAPT was associated with improved AFS for up to five years, as well as improved OS and LS for up to one year. The superiority of AFS persisted in femoropopliteal interventions but not in infrapopliteal and femorotibial interventions. Additionally, DAPT was associated with increased FFR in femoropopliteal interventions and with increased LS in femorotibial interventions for up to five years. Patients presenting with rest pain had superior outcomes with DAPT in terms of OS, LS, and AFS. However, the superiority of DAPT over SAPT in patients with tissue loss persisted only for LS. Moreover, the superiority of DAPT over

SAPT in terms of better AFS was persistent when the intervention was angioplasty alone or angioplasty + stenting up to five years. In patients receiving angioplasty + atherectomy, the superiority of DAPT was observed only for one-year LS. The sub-analysis of DAPT vs. SAPT based on the type of SAPT (P2Y12 inhibitor or aspirin) demonstrated that DAPT was superior to aspirin alone in terms of five-year overall and amputation-free survivals but no difference was observed between DAPT and P2Y12 inhibitor alone. Additionally, P2Y12 inhibitor alone was superior to aspirin alone in terms of five-year overall and amputation-free survivals.

The choice of SAPT vs. DAPT after PVI depends on several factors, and there is no clearly defined consensus regarding this matter. Nevertheless, patient-related factors that have been shown to be associated with DAPT prescription post-PVI include male sex, smoking, CAD, claudication, CLTI, more than one treated artery, outflow artery involvement, stent use, and the presence of procedural complications (25). However, the most common determinant of DAPT prescription postoperatively is the continuation of a prior prescription of DAPT. The benefit of using antiplatelets goes back to the reasoning of increased thrombotic complications after instrumentation and intimal disruption taking place during lower extremity endovascular intervention, hence patients are prescribed antiplatelet agents to limit aggregation and target lesion thrombosis (26). However, we found that patients receiving DAPT post-discharge were less likely to receive preoperative anticoagulant (11% vs. 34.9%). Therefore, concerns about bleeding or already being on an anticoagulant will impact the decision to start DAPT as well.

Owing to significant practice variation in the use of antithrombotic therapy after PVI, a group from Australia distributed a discrete choice experiment questionnaire among 300 vascular surgeons in Australia and New Zealand (27). Multinomial logistic regression models were used to analyze what variables affected the decision-making process to prescribe a second antithrombotic agent, and the preferred choice of antithrombotic (clopidogrel 75 mg daily or rivaroxaban 2.5 mg twice daily) as well as aspirin 100 mg daily. Results show that prescribing a second antithrombotic was more likely after femoropopliteal stenting compared with angioplasty

(OR=1.89, 95% CI, 1.20-2.13), and in CLTI compared with intermittent claudication (OR=1.58, 95% CI, 1.20-2.13).

Results from the MIRROR (Management of peripheral arterial interventions with mono or dual antiplatelet therapy) randomized trial comparing dual antiplatelet therapy vs. aspirin alone on local platelet activation, showed that in a sample size of 80 patients, DAPT reduces peri-interventional platelet activation and improves functional outcome without higher bleeding complications. However, 30% of patients receiving clopidogrel were resistant to it and all clopidogrel patients who needed target lesion revascularization were from the resistant group (28). At 6 months follow-up, this advantage of DAPT did not persist after stopping clopidogrel and the authors of this trial concluded that prolonged dual therapy (>6 months) should be considered in patients who are at high risk for restenosis (29). However, the benefits should be interpreted in the context of increased risk of bleeding.

A large multi-institutional study by Ramanan et al. using data from the VQI registry (2003-2018), showed that on Kaplan-Meier analyses, patients on SAPT had a higher risk of 1-year major amputation, lower OS (84% vs. 87%, P<.001) and AFS (82% vs .85%, P<.001) compared with those on DAPT which mirrored results of our study (14). Furthermore, the SAPT group was at higher risk for reintervention compared with the DAPT group (15.9% vs. 13%; P=.0012). After adjusting to potential confounders, DAPT was associated with improved OS but not major amputation at 1 year which is what we were able to demonstrate as per our analysis. DAPT in another study was also found to be an independent predictor of improved limb salvage at 2 years (HR=0.83; 95% CI, 0.79-0.87; P<.007) (30). Another observational study of 629 patients revealed that DAPT vs. aspirin SAPT was associated with a decreased risk of adverse cardiovascular events (aHR=0.65; 95% CI, 0.44-0.96) and overall mortality (aHR=0.55; 95% CI, 0.35-0.89). However, there was no association found between DAPT use and the risk of major amputation (aHR=0.69; 95% CI, 0.37-1.29) (31). Nevertheless, our study provides more rigorous analysis considering the impact of CLTI severity (rest pain vs. tissue loss), level of

revascularization (femoropopliteal, infrapopliteal, and femorotibial), as well as longer follow up time up to 5 years using Medicare-matched data.

The benefits of DAPT should be balanced against increased risk of bleeding. Level-one evidence in patients receiving drug eluting stents for coronary interventions (12 months vs. 30 months of DAPT) have shown increased moderate to severe bleeding risk (P=0.001) (10). This can impact the decision-making regarding administration of MATP or DAPT in infrainguinal endovascular interventions.

It should also be considered that the rate of discharge anticoagulation administration in this study was 41.3% in the SAPT cohort compared to 11.9% in the DAPT cohort. Most practitioners do not administer triple therapy, so the beneficial effects of DAPT observed in our study occurred despite the lower rate of anticoagulation therapy.

The sub-analyses of our study revealed that DAPT is superior in terms of LS, AFS, and FFR up to five years in femoropopliteal ETs. However, in femorotibial ETs, it showed only superior LS up to five years. No benefits of DAPT were found in infrapopliteal-only ETs. Additionally, superior AFS was sustained in patients receiving angioplasty or angioplasty + stenting up to five years, while only superior one-year LS was observed in angioplasty + atherectomy. This suggests that the high-risk anatomy of the infrapopliteal region and smaller artery diameters make them vulnerable to poor outcomes despite receiving DAPT. Furthermore, patients who undergo atherectomy tend to have an overall high-risk profile and do not show improved AFS with DAPT despite better LS at one year.

To understand the observed benefits of DAPT and P2Y12 inhibitor alone compared to aspirin alone, it is essential to consider the mechanism of actions of the antiplatelet medications in reducing thrombosis and re-occlusion rates following endovascular interventions. P2Y12 inhibitors target different pathway than aspirin to more effectively prevent thrombus formation. P2Y12 inhibitors block the P2Y12 receptor, preventing adenosine diphosphate (ADP)-mediated

platelet activation, while aspirin irreversibly inhibits cyclooxygenase-1 (COX-1), reducing thromboxane A2 synthesis and platelet aggregation.

In our study, the observed superiority of DAPT in terms of LS, AFS, and FFR up to five years in femoropopliteal ETs supports its efficacy in these specific vascular beds. The high-risk anatomy of the infrapopliteal region and the smaller vessel diameters pose unique challenges, where the protective effects of DAPT are diminished, as reflected in our findings. In these cases, the benefits of DAPT may be limited due to the inherently high susceptibility of these regions to restenosis and re-occlusion despite aggressive antiplatelet therapy. Furthermore, the lower rate of discharge anticoagulation in the DAPT cohort (11.9% compared to 41.3% in the SAPT cohort) highlights the effectiveness of DAPT even without the additional antithrombotic support of anticoagulation. Although more aggressive therapy could be beneficial in areas susceptible to restenosis and occlusion (e.g., the infrapopliteal region), we found greater benefits in the femoropopliteal regions compared to the infrapopliteal region. This highlights the high-risk anatomy of the infrapopliteal region, where even DAPT may not provide optimal outcomes. Additionally, we excluded patients who underwent infrapopliteal stenting, which could have influenced this finding. It is also important to note that in our sub-analysis, DAPT was not superior to a P2Y12 inhibitor alone, suggesting that it may be the P2Y12 inhibitor, not DAPT, that is linked to improved outcomes. Interestingly, comparing a P2Y12 inhibitor alone to aspirin also revealed superior OS and AFS, further reflecting the beneficial effect of P2Y12 inhibition. The specific needs of patients with smaller vessels and those undergoing procedures like atherectomy must also be considered. While DAPT does provide improved 1-year LS, the higher-risk profile and complex anatomy of these patients may diminish the long-term benefits of DAPT, as shown by the lack of sustained AFS improvement in these subgroups. These findings underscore the importance of individualized treatment decisions, taking into account anatomy, procedure type, and patient-specific risk factors to optimize outcomes. Overall, DAPT appears to offer a valuable therapeutic advantage in select cases, especially in larger vessels and with

certain ETs, but should be carefully balanced with the bleeding risk, particularly in female patients and those with high-risk profiles.

We found superior outcomes with DAPT compared to SAPT, DAPT compared to aspirin alone, and P2Y12 inhibitor alone compared to aspirin alone. Although DAPT is superior to SAPT based on our analysis, the superiority of DAPT over P2Y12 inhibitor alone was not observed. Therefore, the results of this analysis should be interpreted with caution, as the observed benefits may be due to the P2Y12 inhibitor rather than DAPT. Although DAPT is superior to SAPT, this is primarily due to the P2Y12 inhibitor. P2Y12 alone is superior to ASA. DAPT is not superior to P2Y12 alone.

Limitations

The present study has several limitations. First, it is a retrospective analysis of prospectively collected data with Medicare linkage, introducing the possibility of confounding by indication and bias from the non-random allocation of intervention groups. Second, although we employed Cox regression to adjust for available covariates in the VQI-VISION database, some degree of confounding from unmeasured variables is inevitable (32). Third, despite the VQI's reliance on professional and trained personnel for data entry, issues such as missing data and coding errors, common in any registry, were unavoidable. Fourth, the assessment of reinterventions during follow-ups in this Medicare-linked study was not restricted to ipsilateral interventions due to limitations in CPT and ICD coding for determining laterality. As a result, some patients may have undergone contralateral reintervention unrelated to the index procedure, preventing us from assessing major adverse limb events (MALE) during follow-up. The same limitation may apply to major amputation but presumably this would be comparable for both SAPT and DAPT. Fifth, the duration of postoperative DAPT use was not captured in the VQI database. Sixth, we were unable to include DAPT use during follow-ups due to a large amount of missing data. Seventh, the indication for discharge DAPT was not captured, meaning that some patients may

have been prescribed DAPT for other reasons, such as prior PCI. Eighth, we were unable to measure patients' compliance for preoperative and discharge medications and patients in the DAPT cohort might have been more compliant than their SAPT counterparts. Ninth, this study utilized Medicare-linked data, limiting the generalizability of the results to younger populations (33). Lastly, since this study is a retrospective analysis of prospectively collected data; it demonstrates associations rather than providing level-one evidence. Furthermore, the duration of DAPT was not addressed in this study. Therefore, we cannot make recommendations regarding the optimal duration of DAPT following infrainguinal endovascular interventions.

Conclusions

Our findings support the use of DAPT or P2Y12 inhibitor following ETs for CLTI in the occlusive arterial disease of the lower extremities, as it was associated with significantly improved AFS up to five years. The benefits of DAPT were evident in enhancing both OS and LS within the first year. However, the results of the present study should be interpreted with caution since there is no long-term benefit for major amputation or reintervention. Additionally, DAPT was associated with improved FFR in femoropopliteal interventions for up to five years. These findings highlight the potential of DAPT to improve long-term outcomes in a substantial portion of patients with CLTI undergoing ET. Moreover, the superiority of DAPT compared to aspirin alone was persistent, but it was not observed when compared to P2Y12 inhibitor alone. Additionally, the P2Y12 inhibitor was superior to aspirin alone. Therefore, the observed benefits may result from the beneficial effects of P2Y12 inhibitors rather than combination therapy. While these results are promising, they also underscore the need for further prospective, randomized studies to validate our conclusions, optimize treatment strategies, and better understand the specific patient populations who may benefit most from DAPT in the post-ET setting. Ultimately, such studies will help refine clinical guidelines and improve long-term outcomes for patients with CLTI.

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Table 1: Baseline variables

Variable	DAPT N=14,081 (58.3%)	SAPT N=10,086 (41.7%)	P-Value
Age (Years)	72 (65, 81)	74 (67, 82)	**<.001**
Gender (Female)	6,028 (42.8)	4,221 (41.8)	0.138
Race (Non-White)	3,943 (28.0)	2,775 (27.5)	0.408
Ethnicity (Hispanic or Latino)	1,117 (7.9)	639 (6.3)	**<.001**
Smoking			**<.001**
Never	4,979 (35.4)	3,909 (38.8)	
Former	6,243 (44.4)	4,372 (43.4)	
Current	2,839 (20.2)	1,789 (17.8)	
Comorbidities			
Obesity	4,578 (32.6)	3,337 (33.2)	0.319
Hypertension	12,915 (92.0)	9,255 (92.0)	0.970
Diabetes Mellitus	9,930 (70.5)	6,773 (67.2)	**<.001**
CAD	7,582 (53.9)	4,844 (48.0)	**<.001**
CHF	4,165 (29.6)	3,366 (33.4)	**<.001**
COPD	3,368 (23.9)	2,515 (24.9)	0.068
CKD	8,005 (57.1)	5,963 (59.4)	**<.001**
Prior Procedures			
CABG/PCI	6,179 (44.1)	3,622 (36.1)	**<.001**
CEA/CAS	472 (3.4)	286 (2.8)	**0.024**
Inflow intervention	1,435 (10.2)	795 (7.9)	**<.001**
Ipsilateral bypass or PVI	4,908 (34.9)	2,960 (29.4)	**<.001**
Contralateral bypass or PVI	3,746 (26.7)	2,127 (21.2)	**<.001**
Preoperative Medications			
Aspirin	11,922 (84.7)	5,737 (56.9)	**<.001**
P2Y12 Inhibitor	7,906 (56.2)	2,638 (26.2)	**<.001**
Statin	10,269 (72.9)	6,710 (66.6)	**<.001**
Anticoagulant	1,546 (11.0)	3,518 (34.9)	**<.001**
Contrast volume (mL)	80 (50, 120)	70 (45, 109)	**<.001**
Fluoroscopy time (min)	18.2 (11.4, 28.1)	16.5 (10.4-25.9)	**<.001**
Urgent/Emergent	3,334 (23.7)	2,607 (25.9)	**<.001**
Number of arteries treated	2 (1, 2)	1 (1, 2)	**<.001**
Indication			**<.001**
Rest pain	3,429 (24.3)	2,144 (21.3)	

Tissue loss	10,652 (75.6)	7,942 (78.7)	
Level			**<.001**
Femoropopliteal	6,475 (46.0)	4,259 (42.2)	
Infrapopliteal	3,142 (22.3)	2,964 (29.4)	
Femorotibial	4,464 (31.7)	2,863 (28.4)	
Type of treatment			**<.001**
Angioplasty	6,241 (44.9)	5,567 (56.7)	
Angioplasty + stenting	4,160 (30.0)	2,195 (22.4)	
Angioplasty + atherectomy	2,621 (18.9)	1,703 (17.3)	
Angioplasty + stenting + atherectomy	861 (6.2)	349 (3.6)	
Discharge Medications			
Statin	11,171 (79.3)	7,334 (72.4)	**<.001**
Anticoagulant	1,681 (11.9)	4,160 (41.3)	**<.001**

CABG, coronary artery bypass graft; *CAD*, coronary artery disease; *CAS*, carotid artery stenting; *CEA*, carotid endarterectomy; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *DAPT*, dual antiplatelet therapy; *PCI*, percutaneous coronary intervention; *PVI*, peripheral vascular intervention; *SAPT*, single antiplatelet therapy

Data presented as median (interquartile range) or count (%)

Table 2: Crude rates of one-year and five-year outcomes in DAPT vs. SAPT cohorts

Outcomes	1-Year			5-Year		
	DAPT	SAPT	P-Value	DAPT	SAPT	P-Value
Overall survival	76.6	73.4	**<.001**	36.9	30.6	**<.001**
Limb Salvage	86.7	84.7	**<.001**	76.4	74.5	**0.001**
Amputation-fee survival	67.9	63.7	**<.001**	30.4	24.6	**<.001**
Freedom from reintervention	60.9	63.4	**<.001**	38.4	41.0	**<.001**

DAPT, dual antiplatelet therapy; *SAPT*, single antiplatelet therapy

Data presented as percentage.

Table 3: Multivariate analysis of one-year and five-year outcomes in DAPT vs. SAPT cohorts (Reference = SAPT)

Outcomes	**1-Year**		**5-Year**	
	aHR (95% CI)	P-Value	aHR (95% CI)	P-Value
Death	0.90 (0.81-0.99)	**0.048**	0.91 (0.81-1.03)	0.127
Major Amputation	0.86 (0.79-0.93)	**<.001**	0.99 (0.80-1.24)	0.996
Major Amputation/Death	0.82 (0.75-0.89)	**<.001**	0.91 (0.84-0.99)	**0.027**
Reintervention	1.02 (0.88-1.19)	0.761	0.88 (0.74-1.05)	0.158

aHR, adjusted hazard ratio; *CI,* confidence interval; *DAPT*, dual antiplatelet therapy; *SAPT*, single antiplatelet therapy

Table 4: Sub-analysis of one-year and five-year outcomes in DAPT vs. SAPT cohorts stratified by level of revascularization (Reference = SAPT)

Outcomes		**1-Year**		**5-Year**	
		aHR (95% CI)	P-Value	aHR (95% CI)	P-Value
Femoropopliteal	Death	0.96 (0.87-1.06)	0.409	0.96 (0.89-1.04)	0.315
	Major Amputation	0.80 (0.68-0.93)	**0.003**	0.85 (0.75-0.96)	**0.012**
	Major Amputation/Death	0.91 (0.84-0.98)	**0.010**	0.93 (0.86-0.99)	**0.036**
	Reintervention	0.87 (0.79-0.96)	**0.004**	0.92 (0.85-0.99)	**0.024**
Infrapopliteal	Death	1.02 (0.88-1.17)	0.819	0.96 (0.86-1.07)	0.448
	Major Amputation	0.97 (0.83-1.12)	0.669	1.01 (0.87-1.16)	0.929
	Major Amputation/Death	0.98 (0.88-1.10)	0.706	0.92 (0.84-1.01)	0.101
	Reintervention	1.07 (0.96-1.19)	0.233	1.11 (1.01-1.21)	**0.025**
Femorotibial	Death	0.98 (0.87.1.11)	0.807	0.96 (0.87-1.06)	0.403
	Major Amputation	0.82 (0.72-0.92)	**0.001**	0.87 (0.77-0.98)	**0.022**
	Major Amputation/Death	0.92 (0.84-1.01)	0.090	0.93 (0.86-1.00)	0.051
	Reintervention	1.05 (0.95-1.17)	0.298	1.05 (0.96-1.15)	0.259

aHR, adjusted hazard ratio; *CI,* confidence interval; *DAPT*, dual antiplatelet therapy; *SAPT*, single antiplatelet therapy

Table 5: Sub-analysis of one-year and five-year outcomes in DAPT vs. SAPT cohorts stratified by type of CLTI (Reference = SAPT)

Outcomes		**1-Year**		**5-Year**	
		aHR (95% CI)	P-Value	aHR (95% CI)	P-Value
Rest Pain	Death	0.79 (0.66-0.95)	**0.015**	0.84 (0.73-0.97)	**0.014**
	Major Amputation	0.68 (0.53-0.86)	**0.002**	0.80 (0.65-0.98)	**0.033**
	Major Amputation/Death	0.76 (0.65-0.88)	**<.001**	0.81 (0.72-0.91)	**0.001**
	Reintervention	1.03 (0.90-1.17)	0.681	1.08 (0.98-1.20)	0.121
Tissue loss	Death	1.03 (0.95-1.10)	0.485	0.98 (0.93-1.04)	0.579
	Major Amputation	0.89 (0.81-0.97)	**0.009**	0.92 (0.85-0.99)	**0.042**
	Major Amputation/Death	0.96 (0.91-1.02)	0.234	0.95 (0.90-1.00)	0.052
	Reintervention	0.96 (0.90-1.03)	0.308	0.98 (0.93-1.04)	0.595

aHR, adjusted hazard ratio; *CI,* confidence interval; *CLTI,* chronic limb-threatening ischemia; *DAPT*, dual antiplatelet therapy; *SAPT*, single antiplatelet therapy

Table 6: Sub-analysis of one-year and five-year outcomes in DAPT vs. SAPT cohorts stratified by the type of endovascular therapy (Reference = SAPT)

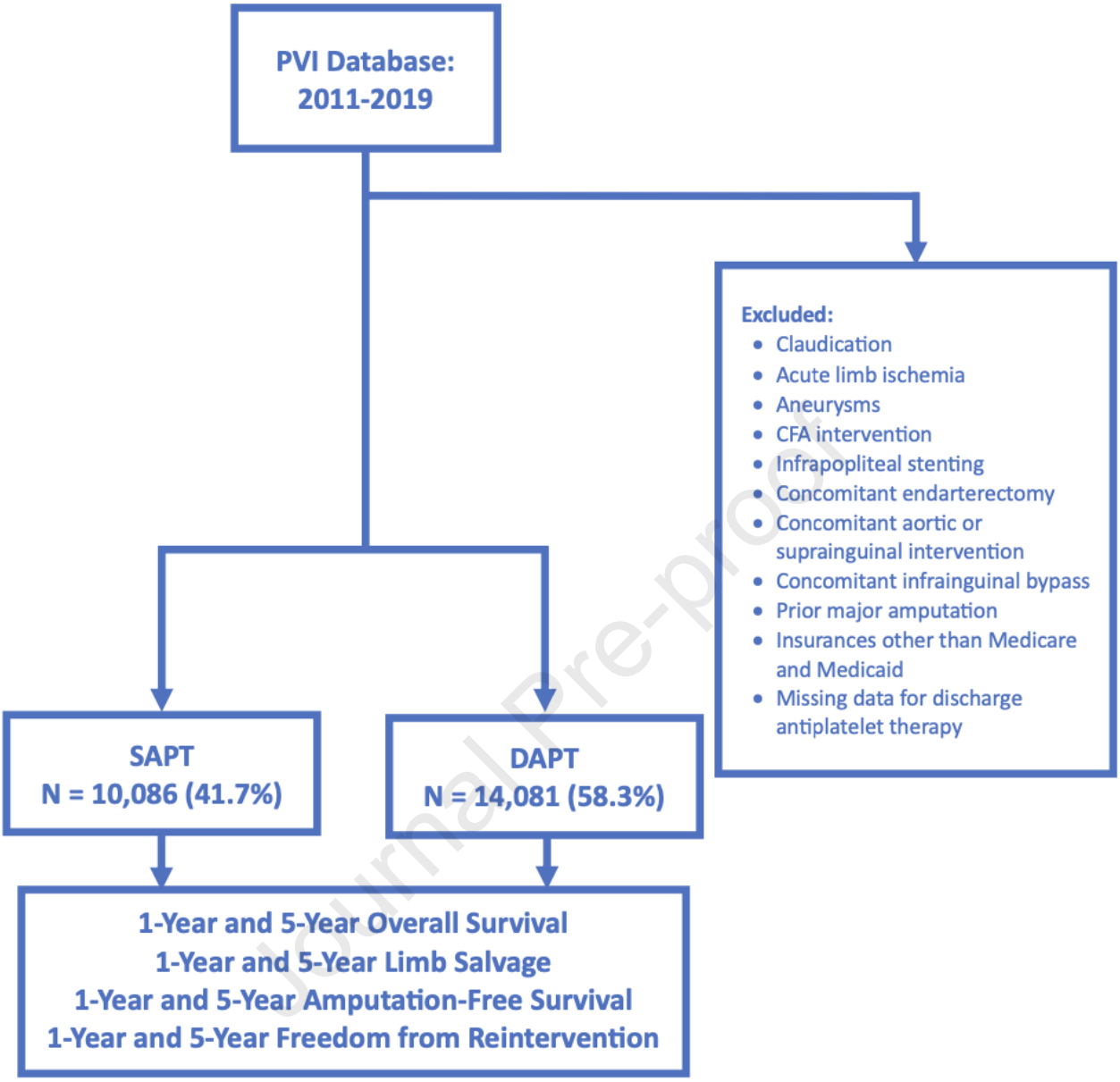
Outcomes		**1-Year**		**5-Year**	
		aHR (95% CI)	P-Value	aHR (95% CI)	P-Value
Angioplasty	Death	0.98 (0.88-1.08)	0.668	0.95 (0.87-1.04)	0.267
	Major Amputation	0.90 (0.80-1.01)	0.066	0.90 (0.81-1.00)	0.060
	Major Amputation/Death	0.94 (0.87-1.02)	0.117	0.92 (0.86-0.99)	**0.024**
	Reintervention	1.01 (0.93-1.11)	0.738	1.05 (0.98-1.14)	0.174
Angioplasty + stenting	Death	0.87 (0.76-0.99)	**0.045**	0.92 (0.83-1.02)	0.104
	Major Amputation	0.78 (0.64-0.96)	**0.017**	0.89 (0.76-1.04)	0.148
	Major Amputation/Death	0.88 (0.78-0.99)	**0.031**	0.89 (0.82-0.98)	**0.016**
	Reintervention	0.98 (0.86-1.11)	0.764	1.00 (0.90-1.10)	0.943
Angioplasty + atherectomy	Death	1.01 (0.86-1.19)	0.862	0.98 (0.88-1.11)	0.788
	Major Amputation	0.81 (0.67-0.99)	**0.036**	0.89 (0.75-1.05)	0.169
	Major Amputation/Death	0.95 (0.84-1.07)	0.383	0.96 (0.87-1.06)	0.395
	Reintervention	0.97 (0.84-1.11)	0.639	0.95 (0.85-1.08)	0.452
Angioplasty + stenting + atherectomy	Death	1.22 (0.91-1.63)	0.176	1.04 (0.83-1.29)	0.728
	Major Amputation	0.68 (0.42-1.13)	0.137	0.95 (0.60-1.50)	0.815
	Major Amputation/Death	1.16 (0.88-1.54)	0.295	1.06 (0.86-1.31)	0.568
	Reintervention	1.03 (0.78-1.35)	0.838	1.09 (0.85-1.41)	0.488

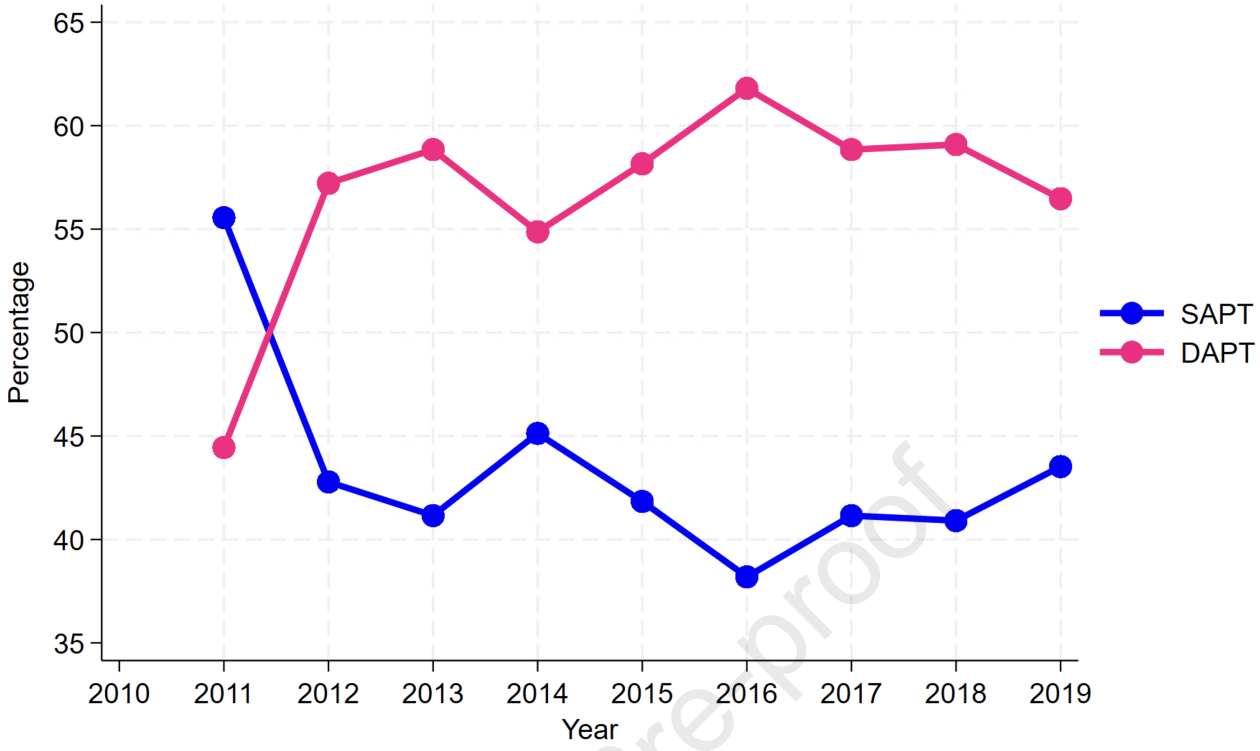
aHR, adjusted hazard ratio; *CI,* confidence interval; *DAPT*, dual antiplatelet therapy; *SAPT*, single antiplatelet therapy

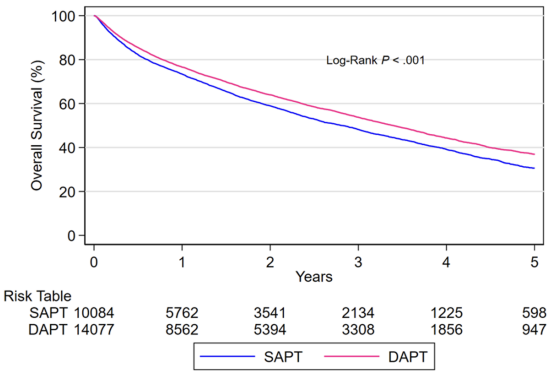
Table 7: Analysis of one-year and five-year outcomes in DAPT vs. Aspirin alone, DAPT vs. P2Y12 inhibitor alone, and DAPT vs. SAPT + Anticoagulant

Outcomes	**1-Year**		**5-Year**	
	aHR (95% CI)	P-Value	aHR (95% CI)	P-Value
DAPT vs. Aspirin alone; Reference: Aspirin alone				
Death	0.84 (0.75-0.95)	**0.004**	0.85 (0.74-0.99)	**0.033**
Major Amputation	0.83 (0.76-0.90)	**<.001**	0.97 (0.75-1.24)	0.783
Major Amputation/Death	0.77 (0.69-0.86)	**<.001**	0.87 (0.79-0.96)	**0.004**
Reintervention	0.96 (0.80-1.16)	0.693	0.86 (0.70-1.06)	0.150
DAPT vs. P2Y12 inhibitor alone; Reference: P2Y12 inhibitor alone				
Death	1.06 (0.86-1.31)	0.597	1.03 (0.83-1.28)	0.772
Major Amputation	0.94 (0.80-1.11)	0.472	1.04 (0.74-1.45)	0.836
Major Amputation/Death	0.97 (0.84-1.11)	0.640	1.01 (0.89-1.14)	0.897
Reintervention	1.06 (0.82-1.38)	0.649	0.95 (0.72-1.24)	0.694
DAPT vs. SAPT + Anticoagulant; Reference: SAPT + Anticoagulant				
Death	1.21 (0.91-1.61)	0.181	0.83 (0.66-1.03)	0.086
Major Amputation	0.88 (0.78-0.99)	**0.031**	0.91 (0.67-1.24)	0.550
Major Amputation/Death	1.08 (0.88-1.33)	0.459	0.84 (0.73-0.97)	**0.019**
Reintervention	0.88 (0.57-1.36)	0.568	1.12 (0.80-1.57)	0.504
P2Y12 inhibitor alone vs. Aspirin alone; Reference: Aspirin alone				
Death	0.78 (0.62-0.98)	**0.035**	0.70 (0.51-0.97)	**0.030**
Major Amputation	0.88 (0.74-1.03)	0.113	0.73 (0.47-1.13)	0.159
Major Amputation/Death	1.03 (0.83-1.29)	0.783	0.86 (0.75-0.98)	**0.028**
Reintervention	0.76 (0.49-1.17)	0.209	1.07 (0.73-1.55)	0.727

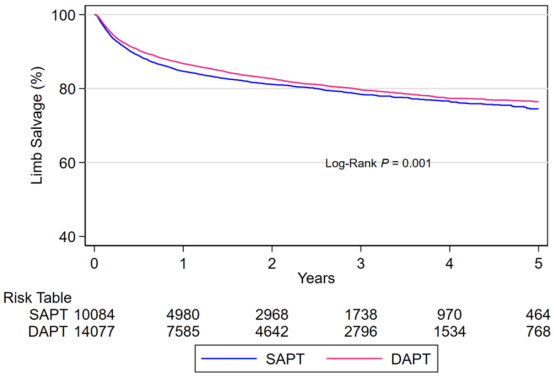
aHR, adjusted hazard ratio; *CI,* confidence interval; *DAPT*, dual antiplatelet therapy; *SAPT*, single antiplatelet therapy







(A)



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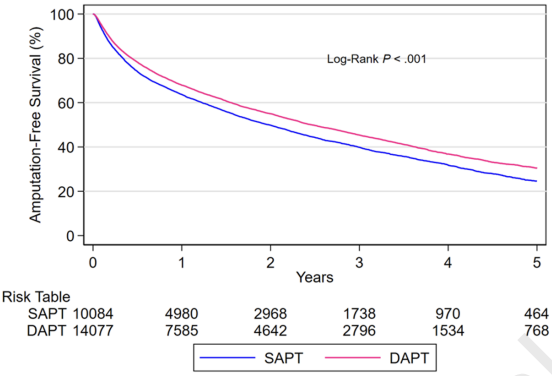
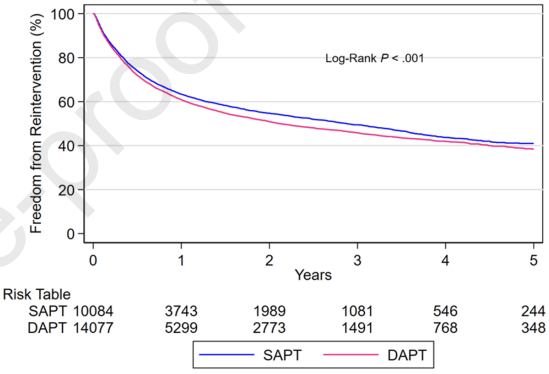


(C)



(D)

Figure legends

Figure 1: Flowchart of the analyzed PVIs (*DAPT*, dual antiplatelet therapy; *PVI*, peripheral vascular intervention; *SAPT*, single antiplatelet therapy).

Figure 2: Trend of DAPT and SAPT from 2011 to 2019 in the Vascular Quality Initiative-Medicare-Linked database (*DAPT*, dual antiplatelet therapy; *SAPT*, single antiplatelet therapy)

Figure 3: Overall survival (A), limb salvage (B), amputation-free survival (C) and freedom from reintervention (D) in patients receiving DAPT vs. SAPT (*DAPT*, dual antiplatelet therapy; *SAPT*, single antiplatelet therapy)