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Editor's Choice – Dual Antiplatelet Therapy Improves Outcome in Diabetic Patients Undergoing Endovascular Femoropopliteal Stenting for Critical Limb Ischaemia

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WHAT THIS PAPER ADDS

This study shows a benefit of dual antiplatelet therapy after femoropopliteal stenting in diabetic patients with critical limb ischaemia (CLI) without bleeding complications, but no benefit after balloon angioplasty or subintimal angioplasty. This may help the clinician to better select the right antiplatelet treatment after endovascular femoropopliteal intervention.

Objective: The purpose of this study was to analyse the effect of dual antiplatelet therapy (DAPT) compared to aspirin on outcome after endovascular interventions in patients with CLI.

Methods: This was a population based retrospective nationwide cohort analysis. Several linked national databases in Sweden: Swedish National Vascular Registry, Prescribed Drug Registry and National Discharge Registry. A total of 1941 patients (median age 79; range 43–103 years; women 58%) were identified with CLI who had undergone primary femoropopliteal endovascular intervention between 2006 and 2012. Of these, 599 (31%) patients were treated after the intervention with DAPT (aspirin and clopidogrel) and 1342 (69%) patients were treated with aspirin only. Percutaneous transluminal angioplasty (PTA) was performed in 1131 patients (58%), stenting in 633 patients (33%), and subintimal angioplasty (SAP) in 177 patients (9%).

Results: DAPT was given after PTA, stenting, and SAP to 17% ($n = 188$), 53% ($n = 334$), and 44% ($n = 77$) of the patients, respectively. During the study period, 77 patients (13%) with DAPT and 228 patients (17%) with aspirin underwent a major amputation. Patients receiving DAPT after stenting had a lower rate of amputation (HR 0.56; 95% CI 0.36–0.86) than patients receiving aspirin alone. In the subgroup analysis, the protective effect of DAPT on amputation seemed to be confined to patients with diabetes mellitus receiving a stent (HR 0.26; 95% CI 0.13–0.52; $p < .001$). DAPT after PTA or SAP did not influence limb salvage, and there was no overall difference in mortality. There was no significant difference in bleeding complications between DAPT and aspirin.

Conclusion: DAPT with aspirin and clopidogrel compared to aspirin alone was associated with a lower amputation rate but not a higher bleeding rate in patients with diabetes and CLI after endovascular femoropopliteal stenting.

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INTRODUCTION

The use of antiplatelet agents to improve the results after vascular intervention in the lower limbs has not been not fully investigated. After percutaneous transluminal angioplasty (PTA), subintimal angioplasty (SAP), or insertion of stents in the femoropopliteal arteries, a life-long antiplatelet medication (aspirin or clopidogrel) is recommended to promote patency.[1] The supporting evidence for antiplatelet therapy after endovascular intervention in limb ischaemia is mainly extrapolated from what is known from the coronary circulation.[2] Although clopidogrel is often added as a second antiplatelet agent to enhance patency after endovascular peripheral interventions, there is little direct evidence to support the benefit of this dual antiplatelet therapy (DAPT).[3] Vascular interventionists commonly provide a periinterventional loading dose (300–600 mg) of clopidogrel in addition to aspirin and then continue with DAPT (clopidogrel 75 mg and aspirin 75–100 mg once daily) for up to 3 months after infrainguinal PTA, particularly if a stent is placed.[4,5] However, recent evidence based clinical practice guidelines suggest single antiplatelet therapy rather than DAPT for patients undergoing peripheral intervention.[6]

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There are few contemporary studies of adequate size and endpoints that guide clinicians regarding the type of antiplatelet therapy following infrainguinal endovascular procedures. The increasing use of drug coat coated balloons and stents also demands more studies on this topic. The main purpose of this study was to analyse the combination of clopidogrel and aspirin versus aspirin alone after endovascular femoropopliteal intervention in patients with critical limb ischaemia (CLI) and the effect on amputation, bleeding, and death.

MATERIALS AND METHODS

Study design

This was a nationwide population based cohort study including data from several national registries. All patients with CLI and primary endovascular intervention in the femoropopliteal arteries performed in Sweden between January 1, 2006, and December 31, 2012, were identified from the Swedish National Vascular Registry (Swedvasc). CLI was defined as ischaemic rest pain, and or non-healing ischaemic ulcer or gangrene (Grade IV, V, and VI in the Rutherford classification).[7] Exclusion criteria were young age $<$ 40 years, former intervention of the contralateral limb, former amputation of a lower limb, intra-arterial thrombolysis, and length of stay in hospital $>$ 30 days. The cohort was crossmatched with the Swedish Prescribed Drug Registry (PDR) giving information of post-interventional antiplatelet treatment either with a combination of aspirin and clopidogrel (DAPT) or with aspirin alone. Patients treated with other antiplatelet agents such as prasugrel or ticagrelor (which is normally prescribed after coronary stenting and acute coronary syndrome), or oral anticoagulants or heparin like substances (prescribed for cardio-embolic prophylaxis because of atrial fibrillation or a prosthetic heart valve) after discharge from the hospital were excluded. The primary outcome was major amputation or mortality, and the secondary outcome was bleeding complications obtained from the National Discharge Registry (NDR). The study was approved by the local ethics committee.

Data sources

Swedvasc covers $>$95% of the open and endovascular vascular interventions in Sweden.[8] Data from 35 hospitals performing endovascular procedures is registered in a web based standardised formulary containing information about patient characteristics, operative methods, and outcome.

The Swedish NDR was established in 1964 and has had complete national coverage since 1987. It is a part of the National Patient Registry and is governed by the National Board of Health and Welfare (NBHW). It is mandatory for all physicians, privately or publicly funded, to report to the register. The patients are linked to the register by their unique 12 digit personal identity number. From 1997 onwards, surgical day care procedures have been reported to the NBHW. Currently, more than 99% of all hospital discharges in Sweden are registered in the NDR. Since 1997, diagnoses in the NDR have been coded according to the International Classification of Disease. Since 1997 a Swedish version of the Nordic Medico-Statistical Committee (NOMESCO) classification of surgical procedures has been in use. This classification is based on five character codes. Current procedures are listed in the Swedish Classification of Surgical and Medical Procedures.[9] The NDR is highly validated, showing a correct diagnosis after vascular interventions for lower limb ischaemia in 545 of 546 cases (positive predictive value 99.8%).[10]

The PDR is a national pharmaceutical registry maintained by the National Board of Health and Welfare. It contains data on all issued pharmaceuticals including identity, amount, and cost. This information has been available since July 2005 and covers all pharmacies nationwide. Risk factors were retrieved from Swedvasc and completed with data from the PDR (medications) and the NDR (diagnosis) to avoid missing data or misregistrations. Owing to missing data in the vascular registry on smoking habits (23% vs. 25% missing data in each treatment group) which could not be improved using other registries, this variable was not included in the final multivariate analysis. Follow-up was until December 31, 2013, or until an event such as major amputation or death. Major amputation was defined as an amputation of the lower limb above the ankle. Bleeding complication was defined as an occurrence of one of the following listed diagnoses from the NDR: gastrointestinal, intracranial, or epidural/subdural bleeding; bleeding into pericardium, eye, genitals, urinary tract, respiratory tract; redo surgery for profound bleeding; haemothorax; haemarthrosis; post-operative bleeding; bleeding caused by antithrombotic therapy; or bleeding unspecified.

Definition of antithrombotic prescriptions drugs

All claimed prescriptions of antithrombotic medications were identified according to the Anatomical Therapeutic Classification system from the PDR after discharge from the primary endovascular intervention. Patients were classified as having been exposed to the medication if they had started the medicine within 14 days of discharge, or if they were on medication prior to admission and continuing beyond the intervention.

Statistical analysis

Values were expressed as median $\pm$ interquartile range unless otherwise specified.

For pairwise comparison, the Student's *t* test was used. The risks of amputation and death were analysed for all patients discharged within 30 days of the operation using Cox regression models. The time since operation was chosen as the underlying timescale, but follow-up of the patients started at Day 14 after surgery if their first dispensing of a study drug occurred prior to this day or at the time of the first dispensing of a study drug if it occurred after Day 14, that is, allowing for staggered entry in order to avoid immortal time bias. Univariate analysis was performed with Cox regression using only treatment group as independent variable and amputation or death as dependent variables. The

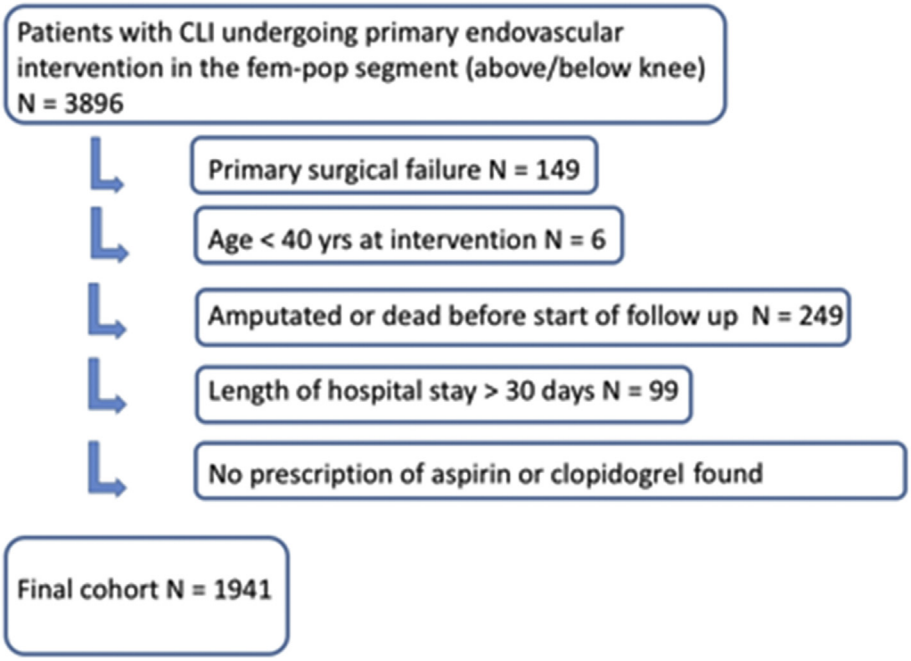


Figure 1. Study cohort: inclusion/exclusion criteria.

multivariate models included all variables deemed to be of biological and clinical importance for the risk of amputation and mortality (age, gender, diabetes mellitus [DM], hypertension, cerebrovascular disease, renal failure, heart disease, statin treatment, endovascular method, and treatment year). Non-proportional hazards were investigated by inclusion of pseudo time dependent covariates where hazard ratios for clopidogrel versus aspirin only were estimated for the different time intervals of follow-up (1—6, 7—12, 13—24, and >24 months) and no significant differences were detected. Results were presented as hazard ratios (HRs) with 95% confidence interval (CI).

Adjusted survival curves for the risk of amputation were estimated by the fixed covariate method standardised to the mean covariates for the whole study group. The survival curves were obtained from the estimated cumulative hazard functions in a stratified Cox regression model with treatment and operation method as strata, this implies estimation of separate baseline hazard function for each study group allowing for potential non-proportional hazards to be displayed. Kaplan—Meier plots were used for presentation of overall amputation and mortality rate. Data analysis was performed using PASW SPSS, version 18.0 (IBM, Somers, NY), and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA.).

RESULTS

Patient population and procedures

In total 3896 patients were identified with CLI who underwent primary endovascular intervention in the femoropopliteal segment (above or below the knee) in Sweden between 2006 and 2012. After excluding for primary surgical failure, patient age below 40 years, amputation or death before the start of follow-up (30 days), length of hospital stay > 30 days and no prescriptions found for aspirin or clopidogrel, 1941 patients (median age 79, range 43—103 years, women 58%) were included in the study cohort (Fig. 1). These patients had undergone endovascular intervention with PTA (n = 1131; 58%), stent/stent graft (n = 633; 33%), or SAP (n = 177; 9%).

Peri-procedural DAPT use

Post-interventional antiplatelet therapy with DAPT (aspirin and clopidogrel) was prescribed to 599 (31%) patients and aspirin to 1342 (69%) patients. Demographic data in the two antiplatelet treatment groups are presented in Table 1. In the DAPT group, there were more patients with smoking (51% vs. 44%, p = .02) and statin treatment (60% vs. 52%, p = .0006), but fewer patients with heart disease (40% vs. 48%, p = .0005). There was no difference in severity of CLI between the two groups, with ischaemic ulcer/gangrene in 74% vs. 75% (p = 0.71) of patients. In total, DAPT was given after PTA, stenting, and SAP to 17% (188/1131), 53% (334/633), and 44% (77/177) of the patients, respectively, with significantly more patients undergoing stenting or SAP in the DAPT group (p < .0001). The overall use of DAPT in patients increased from 14% (32/237) in 2006 to 33% (101/305) in 2012. Treatment duration with DAPT was up to 28 days for 215 patients (36%), between 29 and 99 days for 50 patients (8%), and 100 days or more for 334 patients (56%). The median follow-up time in the aspirin group was 2.0 years (interquartile range 0.8—3.7) and in the DAPT group 1.9 years (interquartile range 0.9—3.2).

DAPT and clinical outcomes

In total, 305 (16%) patients had been amputated and 743 patients (38%) had died before the end of follow-up. The number of major amputations and deaths after DAPT and aspirin only are presented in Table 2. In the univariate

analysis, there was a lower overall rate of amputation after DAPT (HR 0.77, 95% CI 0.59–0.99) but this was non-significant in the multivariate analysis. After stenting, DAPT was associated with a lower rate of amputation than aspirin in the multivariate analysis (HR 0.56, 95% CI 0.36–0.86) (Fig. 2). The rate of amputation after PTA or SAP did not differ significantly between the treatment groups (Figs. 3 and 4). An extended treatment duration (≥100 days after intervention) of DAPT after stenting was not significantly better than a shorter treatment (<100 days) (HR 0.54 vs. HR 0.59, $p = .77$).

In patients with DM, the use of DAPT after stenting was associated with a significantly lower risk of amputation (HR 0.26, 95% CI 0.13–0.52) than aspirin alone (Table 3 and

Table 1. Patient characteristics. DAPT (clopidogrel and aspirin) versus aspirin only.

	DAPT ($n = 599$)	Aspirin ($n = 1342$)	p
Age at surgery (years)	78 (70–84)	80 (71–85)	.322
Age group at surgery			
40–59 years	31 (5%)	69 (5%)	.101
60–69 years	113 (19%)	221 (16%)	
70–79 years	187 (31%)	376 (28%)	
80–89 years	231 (39%)	555 (41%)	
≥ 90 years	37 (6%)	121 (9%)	
Gender			
Male	251 (42%)	555 (41%)	.821
Female	348 (58%)	787 (59%)	
Severity of ischaemia			
Ischaemic ulcer/gangrene	442 (74%)	1001 (75%)	.709
Rest pain	157 (26%)	341 (25%)	
Smoking (ongoing or quit < 5 years)			
Yes	303 (51%)	590 (44%)	.024
No	159 (27%)	413 (31%)	
Missing	137 (23%)	339 (25%)	
Diabetes			
Yes	242 (40%)	603 (45%)	.063
No	357 (60%)	739 (55%)	
Hypertension			
Yes	488 (81%)	1054 (79%)	.140
No	111 (19%)	288 (21%)	
Renal failure			
Yes	49 (8%)	133 (10%)	.227
No	550 (92%)	1209 (90%)	
Cerebrovascular disease			
Yes	59 (10%)	169 (13%)	.083
No	540 (90%)	1173 (87%)	
Heart disease			
Yes	237 (40%)	645 (48%)	<.001
No	362 (60%)	697 (52%)	
Statin treatment			
Yes	363 (60%)	700 (52%)	<.001
No	236 (40%)	642 (48%)	
Year of surgery			
2006	32 (5%)	205 (15%)	<.001
2007	62 (10%)	193 (14%)	
2008	90 (15%)	179 (13%)	
2009	76 (13%)	184 (14%)	
2010	118 (20%)	201 (15%)	
2011	120 (20%)	176 (13%)	
2012	101 (17%)	204 (15%)	
Endovascular method			
PTA	188 (31%)	943 (70%)	<.001
Stent	334 (56%)	299 (22%)	
Sap	77 (13%)	100 (8%)	
Clopidogrel after surgery			
≤ 28 days	215 (36%)	n.a	n.a
29–99 days	50 (8%)	n.a	
≥ 100 days	334 (56%)	n.a	
Length of stay (days)	1 (1–2)	1 (1–3)	.361
Years of follow-up (years)	1.9 (0.9–3.2)	2.0 (0.8–3.7)	

Note. Age at surgery, length of stay, and years of follow-up are expressed as median and interquartile range. Data are presented as *N* (%) unless stated otherwise. DAPT = dual antiplatelet therapy; PTA = percutaneous transluminal angioplasty; SAP = subintimal angioplasty.

Table 2. Amputation and mortality by antiplatelet treatment.

	DAPT ($n = 599$)	Aspirin only ($n = 1342$)
Major amputation N (%)		
Yes	77 (13%; 95% CI 0.10–0.16)	228 (17%; 95% CI 0.15–0.19)
No	522 (87%)	1114 (83%)
Mortality *N* (%)		
Yes	172 (29%; 95% CI 0.25–0.32)	571 (43%; 95% CI 0.40–0.45)
No	427 (71%)	771 (57%)

Events before end of follow-up (December 31 2013). DAPT = Dual antiplatelet therapy (clopidogrel and aspirin).

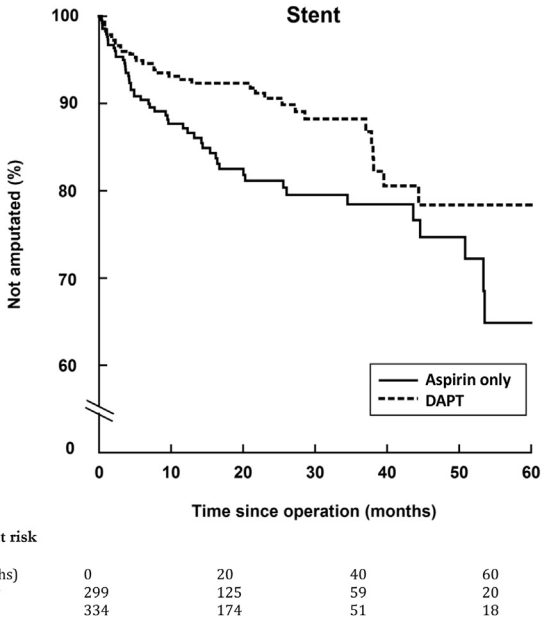
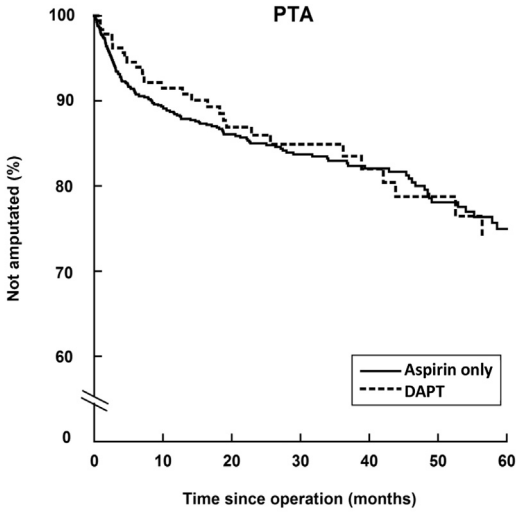


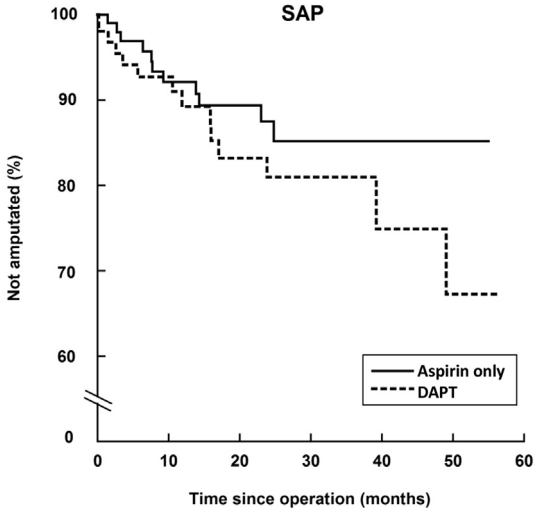
Figure 2. Freedom from amputation by antiplatelet treatment after femoropopliteal stenting. DAPT = dual antiplatelet therapy.



Numbers at risk

Time (months)	0	20	40	60
Aspirin only	943	479	266	118
DAPT	188	106	61	22

Figure 3. Freedom from amputation by antiplatelet treatment after femoropopliteal balloon angioplasty (PTA). DAPT = dual antiplatelet therapy; PTA = percutaneous transluminal angioplasty.



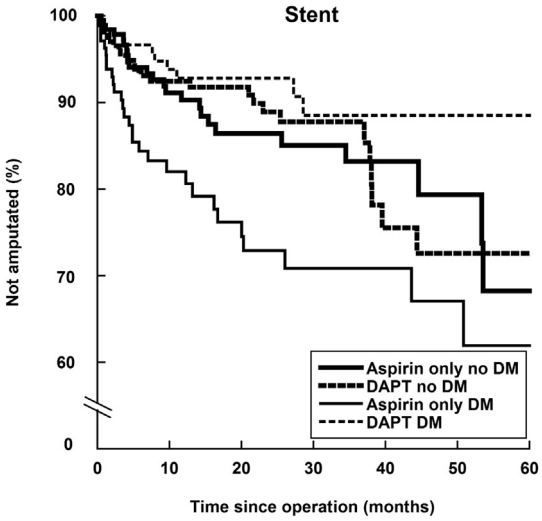
Numbers at risk

Time (months)	0	20	40	60
Aspirin	100	51	18	0
DAPT	77	38	12	0

Figure 4. Freedom from amputation by antiplatelet treatment after femoropopliteal SAP. DAPT = dual antiplatelet therapy; SAP = subintimal angioplasty.

Fig. 5). For non-diabetic patients after stenting there was no difference (HR 0.99, 95% CI 0.60—1.65). The interaction of DAPT effect on amputation between the two groups (DM vs. non-DM) was highly significant, $p < .001$. No difference between DM and non-DM in the DAPT effect was seen either for SAP ($p = .38$) or PTA ($p = .46$).

There was no significant interaction between statin treatment and the effect of antiplatelet treatment (DAPT/aspirin) for any method (stenting $p = .43$; SAP $p = .63$; PTA $p = .65$). In total, there were 220 bleeding complications: 148 (11%) for aspirin and 72 (12%) for DAPT. There was no



Numbers at risk for the 4 groups

Time (months)	0	20	40	60
Aspirin DM	120	51	25	7
Aspirin no DM	179	74	34	13
Clopidogrel DM	130	72	20	5
Clopidogrel no DM	204	102	31	13

Figure 5. Freedom from amputation by antiplatelet treatment and diabetes mellitus after femoropopliteal stenting. DAPT = dual antiplatelet therapy; DM = diabetes mellitus.

increased overall risk of bleeding in the univariate or in the multivariate analysis. Analyzing bleeding complications within 6 months of intervention, there was no significant increased risk of bleeding events for the DAPT group (4.7% vs. 3.3%) (HR 1.4, 95% CI 0.86—2.29).

Finally, overall mortality was lower after DAPT in the univariate analysis (HR 0.72, 95% CI 0.61—0.86), but in the multivariate analysis there was no difference in mortality between the two treatment groups (HR 0.83, 95% CI 0.69—1.00) (Table 3 and Fig. 6).

DISCUSSION

This nationwide population based registry study showed a lower rate of major amputation for patients treated with a combination of aspirin and clopidogrel (DAPT) after endovascular femoropopliteal stenting than treatment with aspirin alone. However, for patients undergoing PTA or SAP, DAPT was not associated with a better outcome. In the subgroup analysis the significant effect on DAPT seemed to be confined to patients with DM undergoing stenting. However, DAPT had no effect on mortality, and there was no difference in bleeding complications between DAPT and aspirin only.

Peripheral arterial disease (PAD) has a prevalence of 18% in the population above 60 years of age, and of these about 1% suffer from CLI.[11] The role of aspirin/acetylsalicylic acid for secondary prevention in atherosclerotic vascular disease is well established with the Antiplatelet Trialists Collaborative meta-analysis of 143 randomised controlled trials and 73,000 patients showing a 27% risk reduction for stroke, myocardial infarction, and vascular death.[12] Clopidogrel has been shown to have an even greater antiplatelet effect; the CAPRIE trial showed a 24% relative risk reduction of

Table 3. Cox regression analysis of DAPT (clopidogrel and aspirin) versus aspirin only.

	Univariate	Multivariate[a]
Amputation		
Overall	HR 0.77 (95% CI 0.59–0.99)	HR 0.79 (95% CI 0.60–1.04)
PTA		HR 0.92 (95% CI 0.61–1.37)
Stent		HR 0.56 (95% CI 0.36–0.85)
SAP		HR 1.53 (95% CI 0.68–3.42)
Stent with DAPT < 100 days		HR 0.59 (95% CI 0.33–1.05)
Stent with DAPT ≥ 100 days		HR 0.54 (95% CI 0.32–0.90)
Diabetes + stent		HR 0.26 (95% CI 0.13–0.52)
Non-diabetes + stent		HR 0.99 (95% CI 0.60–1.65)
Diabetes + PTA		HR 0.81 (95% CI 0.48–1.39)
Non-diabetes + PTA		HR 1.10 (95% CI 0.61–1.99)
Diabetes + SAP		HR 1.18 (95% CI 0.43–3.29)
Non-diabetes + SAP		HR 1.95 (95% CI 0.75–5.08)
Mortality		
Overall	HR 0.72 (95% CI 0.61–0.86)	HR 0.83 (95% CI 0.69–1.00)
PTA		HR 0.82 (95% CI 0.62–1.08)
Stent		HR 0.92 (95% CI 0.70–1.22
SAP		HR 0.55 (95% CI 0.29–1.02)
Bleeding		
Overall	HR 1.12 (95% CI 0.85–1.49)	HR 1.08 (95% CI 0.79–1.47)
1–6 months		HR 1.40 (95% CI 0.86–2.29)
7–12 months		HR 0.67 (95% CI 0.33–1.38)

CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; PTA = percutaneous transluminal angioplasty; SAP = subintimal angioplasty.

[a] Adjusting for age group, gender, diabetes, hypertension, cerebrovascular disease, renal failure, heart disease, statin treatment and year of surgery.

ischaemic events overall for patients with peripheral arterial disease treated with clopidogrel versus aspirin.[13]

Endovascular femoropopliteal interventions in patients with CLI remain challenging with respect to mid- and long-term outcomes including limb salvage.[14,15] The use of adjuvant antiplatelet agents to improve the results of peripheral angioplasty and stenting is not yet clearly defined.[16] Specific trials comparing aspirin with DAPT in lower limb endovascular interventions are sparse.[17] The heterogeneity of PAD makes it challenging to draw conclusions about subgroups. The improved antiplatelet effect using DAPT after stenting is consistent with the evidence from studies in patients undergoing coronary stenting.[18] The supporting evidence for adjuvant antiplatelet therapy after peripheral arterial interventions has previously been largely extrapolated from that related to the coronary circulation. However, comparing and extrapolating interventional coronary data to infrainguinal interventions is complicated given the differences in artery size, procedure and stent types, and outcomes related to reocclusion.[19] Many studies have used restenosis, re-occlusion, or target

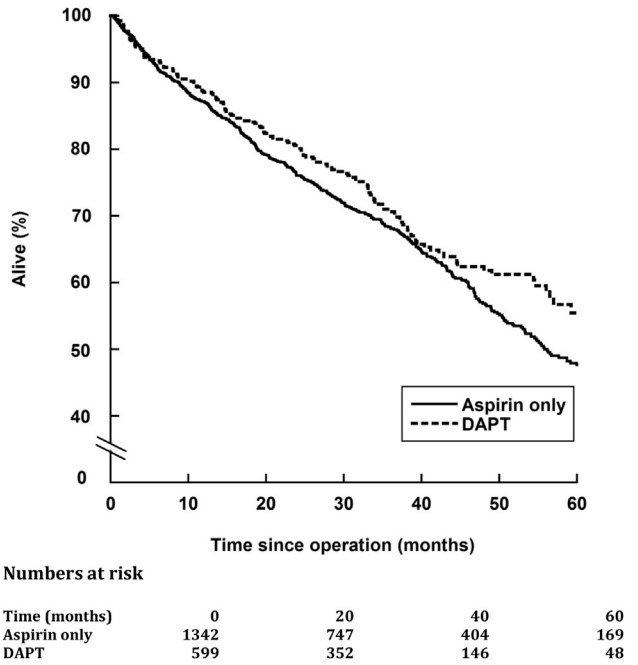


Figure 6. Freedom from mortality by antiplatelet treatment after endovascular femoropopliteal intervention. DAPT = dual antiplatelet therapy.

lesion revascularisation (TLR) as the primary endpoint, which are surrogates for the important patient outcomes such as major amputation used in this study.[20]

Another randomised study showed that DAPT reduced post-interventional platelet activation in patients with PAD treated by endovascular intervention.[21] The study was not powered for a clinical endpoint, but patients who received DAPT had a lower rate of TLR 6 months after the intervention. None of the TLR was caused by thrombotic occlusion of previously recanalised arteries. However, after stopping clopidogrel at 6 months, there was no significant difference in TLR 12 months after treatment. In several randomised controlled trials investigating bare metal stenting and balloon angioplasty in the femoropopliteal region, the DAPT duration varied from 1 to 3 months.[7,8,22–24] This study did not have sufficient power to show if an extended treatment period with DAPT, 100 days or longer, was associated with a lower risk of amputation than a shorter treatment period. In a recent retrospective review including a majority of patients with intermittent claudication, DAPT duration did not seem to affect rates of major adverse limb events (MALE).[25] Patients with underlying coronary artery disease were here prescribed a longer duration of DAPT (>3 months).

It was surprising that only about half of the patients on a national level undergoing stenting in the femoropopliteal segment had adjuvant DAPT, although there were an increasing number of patients treated with DAPT during the study period. Patients with CLI have advanced atherosclerotic disease but a more aggressive short-term antiplatelet therapy in this study was, as expected, not associated with a significant effect on overall mortality. A large study (CHARISMA) performed in a high risk cardiovascular

population, including PAD, showed no overall benefit of the combination of antiplatelet drugs (aspirin and clopidogrel) compared with aspirin alone on the outcome of myocardial infarction, stroke, and cardiovascular death.[26]

Retrospective register based studies are limited by the type and quality of the registered data. Selection bias may well exist which could have influenced the choice of antiplatelet regimen. The PDR covers medicines dispensed at the pharmacy only; therefore, no information on antiplatelet therapy for patients treated in hospitals or rehabilitation centres for more than 30 days was used. These patients were excluded from the study but could be suspected to have more comorbidities and more severe peripheral vascular disease. Also there is no information on whether patients have actually taken their medications. Furthermore, sufficient information on smoking habits was lacking because of missing data in the registry. It was therefore decided not to include smoking in the multivariate analysis. For all the other risk factors, data could be merged from the other registries to avoid missing data. Data on drug eluting balloons and stents were not included in the National Vascular Registry until 2014. The vascular registry also does not provide any information on lesion length, stenosis percentage, or distal outflow.

In conclusion, this population based nationwide study shows a significantly lower rate of major amputations with adjuvant DAPT, without an increased risk of bleeding complications, in patients with DM and CLI undergoing femoropopliteal stenting. DAPT was not associated with an improved outcome after balloon or subintimal angioplasty or in non-diabetic patients after stenting. The registry data have several limitations that need to be considered when interpreting the results including drug compliance and important anatomical and lesion characteristics. There is a continuous development of new antiplatelet drugs and stent technology. In patients with PAD undergoing endovascular interventions, there is a need for further studies with adequate clinical endpoints analyzing post-interventional antiplatelet therapy with special focus on new antiplatelet agents, doses, duration, and especially the interactions with DM.

CONFLICT OF INTEREST

None.

FUNDING

None.

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