# Cardiovascular Topics

# The effects on clinical outcomes of administering medications together or separately in prolonged dual antiplatelet therapy after peripheral revascularisation

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## Abstract

**Background:** In the current guidelines, dual antiplatelet therapy [acetylsalicylic acid (ASA) + clopidogrel] is recommended for at least three months after peripheral iliac stenting. In this study, we investigated the effect on clinical outcomes of adding ASA in different doses and at different times after peripheral revascularisation.

**Methods:** Seventy-one patients were administered dual antiplatelet therapy after successful iliac stenting. Group 1, consisting of 40 patients, was given 75 mg of clopidogrel plus 75 mg of ASA in a single dose in the morning. In group 2, separate doses of 75 mg of clopidogrel (in the morning) and 81 mg of $1 \times 1$ ASA (in the evening) were started in 31 patients. The demographic data and bleeding rates of the patients after the procedure were recorded.

**Results:** The groups were found to be similar in terms of age, gender and accompanying co-morbid factors ($p > 0.05$). The patency rate was 100% in the first month in both groups, and it was above 90% at the sixth month. When one-year patency rates were compared, although the first group had higher rates (85.3%), no significant difference was found ($p < 0.05$). However, there were 10 (24.4%) bleeding events in group 1, and five (12.2%) of these were in the gastrointestinal system, resulting in reduced haemoglobin levels ($p = 0.038$).

**Conclusion:** ASA doses of 75 mg or 81 mg did not affect one-year patency rates. However, higher bleeding rates were observed in the group that received both clopidogrel and ASA treatment simultaneously (in the morning) despite the lower dose of ASA.

**Keywords:** peripheral arterial revascularisation, dual antiplatelet therapy, acetylsalicylic acid dosing, outcome, bleeding

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Peripheral arterial disease (PAD) involving the extremity arteries is defined as narrowing and occlusion of the antegrade flow of the main arteries. Although PAD has various causes, such as underlying vasculitis, dysplastic events, thrombosis, embolism and trauma, the most common is atherosclerotic vascular occlusion.[1] This condition, which is not symptomatic at first, starts with intermittent claudication and is accompanied by other findings related to extremity ischaemia as it progresses.

PAD may be a precursor marker for systemic atherosclerosis, so timely diagnosis and treatment are important. Following diagnosis with imaging methods, treatment covers a wide spectrum, ranging from simple lifestyle changes to medical treatment and surgery.[1,2]

Balloon angioplasty and stenting have produced very successful results before surgery in cases that do not respond to medical therapy, especially for PAD involving aorto-iliac disease and femoral occlusion.[3] However, medical treatment is important, especially after the procedure.[3,4] In the Turkish Peripheral Artery and Vein Diseases 2021 guidelines, single anti-aggregant therapy was recommended, especially after aorto-iliac and femoral endovascular procedures, and after standard combination therapy with acetylsalicylic acid (ASA) (75–100 mg/day) and clopidogrel (75 mg/day) for at least four weeks.[5]

There are different views on how long dual antiplatelet therapy (DAPT) should last. Although it has been argued that there is no difference between high and low ASA doses, there is a consensus that the ideal dose range is generally 75–100 mg for ASA and 75 mg for clopidogrel.[5,6]

In this study, the clinical outcomes were investigated of administering prolonged dual antiplatelet therapy, APA and clopidogrel, either together in one tablet or separately in two tablets to patients who underwent endovascular treatment for PAD. The aim was to reveal the results of prolonged treatment, and specifically, the effects of taking ASA in combination with clopidogrel as a single tablet or as two separate tablets at different times.

## Methods

Patients admitted to our clinic between January 2021 and July 2022 due to PAD were evaluated prospectively. Based on the Trans-Atlantic Inter-Society Consensus Document II classification, 112 patients with primary stenting TASC II A & B iliac lesions were identified.[7] Seventy-one of these patients who were treated with dual antiplatelet therapy and followed up for one year were included in the study.

Patients who did not agree to participate in the study, whose records and controls could not be reached during the follow-up period, who did not complete the one-year follow-up period or for whom vascular patency was not provided were excluded from the study. In addition, patients were excluded if they had contra-indications for dual antiplatelet therapy or the presence of distal type occlusive peripheral artery disease, took additional bleeding agents (such as anticoagulant agents), or required continuous chemotherapy.

Ethical approval was obtained from the Non-Invasive Research Ethics Committee of the Faculty of Medicine before the study (approval no. 04-11.2022). Informed consent forms were signed by all participants, and their consent to participate in the study was obtained.

Demographic variables, concomitant diseases, patency rates, main blood tests for determining the pre-treatment blood levels of patients and bleeding complications (major and minor) were recorded.

Each patient, whose lesion had previously been detected using computed tomographic angiography, was taken to a conventional angiography room. A 7-F sheath was placed using the Seldinger method after local anaesthesia. It was placed in the ipsilateral antegrade or retrograde position or on the contralateral limb, depending on the position of the lesion, as the intervention site. Thereafter, each lesion was passed using 0.035 hydrophilic wires (InWIRE; INVAMED, Ankara, Turkey), and in all patients, percutaneous transluminal angioplasty was applied with an appropriately sized Extender drug-eluting balloon (INVAMED, Ankara, Türkiye). Finally, an appropriately sized balloon-expandable cobalt–chromium stent was implanted in each lesion site (Myra BMS, Meril Life Sciences, Gujarat, India).

Dual antiplatelet treatment was initiated for all patients after the procedure. The 71 patients were divided randomly into two groups. A single tablet containing 75 mg of ASA and 75 mg of clopidogrel (Klogel-A 75/75 mg, Neutec İlac San, Sakarya, Turkey) was prescribed to the patients in group 1 (n = 40). Meanwhile, group 2 (n = 31) received 75 mg of clopidogrel in the morning (Planor; Koçak Farma, Tekirdağ, Turkey) and 81 mg of ASA separately in the evening (Ecopirin Pro, Abdi İbrahim İlaç Sanayi ve Ticaret AŞ, İstanbul, Turkey).

Our clinic's usual procedure is to continue this dual antiplatelet treatment for at least six months. However, this period was extended to one year in the patients who participated in this study.

## Statistical analysis

In this study, continuous data were subjected to normal distribution analysis by evaluating five parameters (mean ± standard deviation, kurtosis/skewness, Q-Q plot, histogram and Shapiro–Wilk test results). Parameters with scores of 3.5 or above were considered normally distributed and presented as means ± standard deviation, and the independent samples $t$-test was applied in pairwise comparisons. Parameters with scores below 3.5 in the normal distribution analysis were assumed not to be normally distributed and are presented as medians (minimum–maximum), and the Mann–Whitney $U$-test was applied in pairwise comparisons.

In the expected and observed frequency analysis of discrete data, the chi-squared test was applied in 2 × 2 tables, while a multi-eyed chi-squared test was applied in 3 × 2 tables. In the study, $\alpha = 0.05$ was accepted and $p < \alpha$ was evaluated as statistically significant. The SPSS 23.00 package program was used in the statistical analysis.

## Results

There were no gender or age differences between the groups ($p > 0.05$). The groups were found to be similar in terms of concomitant situations (hypertension, diabetes mellitus, family history and smoking habits) and main blood parameters, except triglycerides. There were 36 (87.8%) patients in group 1 and 23 (76.7%) in group 2, for whom this was the first interventional procedure. The participants' demographical variables are presented in Table 1.

| Table 1. Comparison of demographical variables between the groups | | | |
|---|---|---|---|
| Variables | Group I (n = 41) | Group II (n = 30) | p-value* |
| Age (years), mean ± SD | 61.30 ± 9.22 | 61.40 ± 12.51 | 0.972 |
| Gender (male), n (%) | 36 (87.8) | 25/80.0 | 0.120 0.729** |
| Hypertension, n (%) | 15 (36.5) | 12/40.0 | 0.000 0.999** |
| Diabetes mellitus, n (%) | 15 (36.5) | 12/40.0 | 0.000 0.999** |
| Smoking history, n (%) | 20 (48.7) | 13/43.3 | 0.269 0.604** |
| Family history, n (%) | 17 (41.4) | 9/30.0 | 1.232 0.267** |
| | 5 (12.8) | 7/23.3 | 0.445 0.505** |
| Blood tests | | | |
| Haemoglobin (g/dl), mean ± SD | 12.87 ± 1.97 | 13.20 ± 1.88 | 0.511 |
| Platelets ($10^{-3}$/μl), mean ± SD | 255.93 ± 72.14 | 259.13 ± 58.62 | 0.851 |
| Main corpuscular volume (fl), mean (median) | 87.90 (71.70–102.90) | 86.75 (32.80–97.50) | 0.584 |
| Main platelet volume (fl), mean (median) | 8.60 (6.70–14.50) | 8.30 (6.90–11.70) | 0.329 |
| Platelet distribution width (fl), mean (median) | 16.70 (15.70–19.30) | 16.50 (15.40–18.70) | 0.168 |
| Creatinine (mg/dl), mean (median) | 1.05 (0.50–3.20) | 0.90 (0.60–7.70) | 0.121 |
| Low-density lipoprotein cholesterol, mg/dl, (mean ± SD) | 132.27 ± 43.27 | 136.65 ± 46.68 | 0.720 |
| High-density lipoprotein cholesterol (mg/dl), mean ± SD | 35.31 ± 7.94 | 38.50 ± 8.58 | 0.238 |
| Triglycerides (mg/dl), mean (median) | 135 (84–679) | 103 (51–317) | 0.017 |

*$p < 0.05$ is statistically significant, **Chi-squared test (Yates).
SD, standard deviation.

| Table 2. Comparison of follow-up findings between the two groups | | | |
|---|---|---|---|
| Follow up | Group I (n = 41) | Group II (n = 30) | p-value* |
| One-month patency, n (%) | 41 (100) | 30 (100) | 0.000 1.000** |
| Six-month patency, n (%) | 39 (95.6) | 29 (96.6) | 0.0019 0.892** |
| One-year patency, n (%) | 35 (85.3) | 24 (80.0) | 0.120 0.729** |
| Total bleeding complaints, n (%) | 10 (24.4) | 2 (6.7) | 4.32 |
| Minor bleeding (ecchymosis, bruising) | 5/12.2 | 0/0 | 0.038$ |
| Major GIS bleeding (leading to reduced haemoglobin levels) | 5/12.2 | 2/6.7 | 0.237# |

*$p < 0.05$ is significant, **Chi-squared test (Yates), $Pearson's test, #Fisher's exact test. GIS, gastrointestinal system.

When we looked at the stent patency rates, the early patency was found to be 100% in both groups, and it was above 90% at the sixth month. When the one-year patency rates were compared, although the first group had higher rates (85.3%), no significant difference was found. A comparison of patency rates is provided in Table 2.

There were 10 (24.4%) bleeding events in group 1, five (12.2%) of which occurred in the gastrointestinal system (GIS), resulting in reduced haemoglobin levels. On the other hand, bleeding events were observed in two (6.7%) cases in group 2, both of which involved major bleeding from the GIS ($p = 0.237$). The bleeding events are presented in Table 2.

## Discussion

Our study presents the one-year results of two groups receiving ASA in slightly different doses (75 vs 81 mg) as part of dual antiplatelet therapy. To the best of our knowledge, this is the first study to compare the use of dual antiplatelet therapy in the form of two separate tablets taken at two different times daily (75 mg of clopidogrel in the morning and 81 mg of ASA in the evening) with a combination preparation taken as a single dose (75 mg of ASA plus 75 mg of clopidogrel in the morning). Our results show that the form taken as a single tablet in the morning had slightly higher patency rates but also yielded a higher incidence of major bleeding in the long term.

Although antiplatelet therapy has become a standard protocol in PAH, there is still no clear consensus on how long this process should be continued and which molecules and doses provide optimal treatment.[8,9] Moreover, in the medical management of PAH, apart from the role of antiplatelet therapy in preventing major cardiovascular events, post-interventional plans for the advanced stages of the disease have not been clearly established.

While discussions continue about the role of DAPT in standard treatment in recent guidelines, the advantages of its use after revascularisation have been emphasised.[10,11] The data on prolonged DAPT application, especially after revascularisation, have also been discussed. It has been emphasised that discontinuation of DAPT before six months may be associated with early restenosis, and it has been suggested that prolonging it for more than six months may provide a prolonged patency rate.

Although DAPT administered over six months reduced the risk of major cardiovascular events, prolonged treatment was associated with greater incidences of all-cause death, re-interventions for target lesions and major amputation.[8-12] In our study, DAPT treatment was applied for one year in both groups and followed up.

Abdullah et al. found that 12-month primary patency rates after peripheral revascularisation with drug eluting stents (DES) ranged from 54 to 85%, regardless of additional factors.[13] DES has been reported to be more advantageous than bare stents.

Singh et al. presented baseline demographic variables, medications, co-morbidity and procedure-related findings in their study investigating different combinations of single anti-aggregant, DAPT and anticoagulation after peripheral vascular intervention.[14] While advanced age and male gender predominated in their study, as in ours, the frequency of diabetes and smoking was higher in their study. In this study, DAPT prescription after peripheral intervention was reported as over 90%.[14]

Kronlage et al. investigated the results of long- and short-term DAPT treatment. The one-year open rates were 83.94% short-term versus 79.8% long-term DAPT. As a result, they stated that long-term DAPT treatment had no effect.[15] In our study, DAPT was applied to all groups for 12 months, and the patency rate was found to be more than 80% in both groups.

In the review by Tsai et al., many comprehensive studies are discussed, and it was emphasised that DAPT application after peripheral intervention provided benefits in terms of patency rate, need for re-intervention, amputation rates and major cardiovascular events.[16] In the same study, it was emphasised that DPT did not increase major bleeding compared to monotherapy, but it did cause an increase in minor bleeding. However, data on the relationship between treatment duration and bleeding rates were not presented.[16]

In the study by Mauri et al., one-year DAPT treatment after peripheral revascularisation was compared with ASA treatment alone. It was determined that stent thrombosis as well as major cerebral and cardiovascular events were significantly reduced in the DAPT group. This study also focused on the relationship between prolonged DAPT administration and increased bleeding rates.[17]

The most important parameter of concern in the prolonged DAPT regimen is the increased risk of bleeding.[18] The MIRROR study compared six months of DAPT and ASA monotherapy and found no difference in major bleeding rates.[19] Cho et al. also found no increase in the frequency of major bleeding after prolonged DAPT.[8] In our study, the effects of DAPT regimens taken simultaneously (in a single preparation) or in two separate doses, on major bleeding were evaluated in addition to the effectiveness of prolonged treatment. It was determined that the simultaneous intake of ASA and clopidogrel may cause more bleeding. A similar exploration of this issue has not been found in the literature.

In pharmacokinetic and pharmacodynamic investigations, the time taken for 100 mg of oral ASA to reach its maximum plasma concentration ($t_{max}$: 1.00 hour) has been reported as one hour on average.[20] This time was determined as 1.17 hours for 75 mg of oral clopidogrel ($t_{max}$: 1.17 hours).[21] The times for these molecules to reach similar peak plasma concentrations may be associated with increased bleeding times in concomitant administration. However, more comprehensive studies should be designed to clarify the mechanism of action behind the increased bleeding.

One of the major limitations of this study is the relatively small study population. Larger cohorts would be useful for confirmation of the results. Another limitation is that the results presented here were collected from a single centre. Multicentre studies would produce more comprehensive conclusions.

## Conclusion

Prolonged DAPT treatment, either in a single tablet or two separate doses, seems to be similarly effective in preventing stent restenosis. However, single-tablet administration seems to increase major bleeding events. Therefore, even if the use of a single tablet is advantageous, patients at risk should be followed closely and stringent anti-bleeding measures should be taken. Comprehensive studies are needed to definitively understand the pharmacodynamic effects discussed here.

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