

ANTIPLATELET MEDICATIONS IN HEMODIALYSIS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Vascular access failure is a common complication seen among hemodialysis (HD) patients. Antiplatelet (AP) medications are often prescribed to help reduce thrombosis and increase vascular access patency. Studies on AP agents evaluating the bleeding risk for HD patients have produced inconsistent results. We aimed to investigate the utilization of AP medications among patients who undergo hemodialysis (HD). We performed a systematic review and meta-analysis of observational studies on AP medications used in HD therapy.

Methods: This systematic review used Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 as standards. Inclusion criteria for literature eligibility are full-text literature, written in English, and published between 2014 and 2024. Exclusion criteria used for this study were editorials, review articles and identical journal that has been published, and submissions without DOI. Literatures were collected from online reference sources like Pubmed and SagePub.

Result: In the PubMed database, the results of our search brought up 23 articles, whereas the results of our search on SagePub brought up 19 articles. The results of the search conducted for the last year of 2014 yielded a total 9 articles for PubMed and 5 articles for SagePub. In the end, we compiled a total of 5 papers, 4 of which came from PubMed and 1 of which came from SagePub. We included five research that met the criteria.

Conclusion: AP medications are given in HD patients with high cardiovascular comorbidities to increase vascular patency and prevent thrombosis. Aspirin and P2Y12 inhibitors (PI) such as clopidogrel are commonly used. AP medications might cause shortened longevity of AV access for HD patients. The benefits of AP therapy for cardiovascular protection needs to be evaluated along with its possible effect on AVG outcomes.

Keyword: Anti platelet medications, antiplatelet therapy, hemodialysis

INTRODUCTION

Patients with uncontrolled end-stage renal disease (ESRD) commonly undergo dialysis or transplantation for treatment. The arteriovenous fistula (AVF), introduced by Brescia et al. in 1966, has emerged as the preferred choice for vascular access in hemodialysis (HD) patients over other options such as arteriovenous grafts (AVG) and catheters. This preference is attributed to the AVF's lower incidence of infection and complications compared to alternative methods. Consecutively, over 2 million individuals rely on maintenance haemodialysis (HD) which progressively increases by around 10% each year.¹

Several studies have demonstrated a significant decrease in mortality among individuals who undergo hemodialysis (HD) using arteriovenous fistula (AVF) or arteriovenous graft (AVG) as their mode of access, as compared to those using intravenous dialysis catheters. However, the occurrence of thrombosis is not uncommon in AVF and is even more prevalent in AVG. This complication is believed to occur due to venous intimal hyperplasia, characterized by the infiltration of smooth muscle cells that narrow the lumen of the blood vessel and express cytokines such as endothelin, platelet-derived growth factor (PDGF), and tumor growth factor (TGF)-beta. If left untreated, this process can lead to complete blockage and thrombosis of the vascular access. Oxidative stress and inflammation contribute to the accelerated formation of new tissue inside the blood vessels (neo-intima). Medical interventions, such as the administration of clopidogrel and aspirin (ASA), are commonly employed to counteract this stress, reduce platelet aggregation, and potentially improve the patency and functionality of the vascular access. Antiplatelet agents (AP) are commonly administered to haemodialysis patients to prevent ischemic events following percutaneous interventions and to reduce the risk of arteriovenous graft thrombosis.^{1,2}

Moreover, patients and healthcare providers consider the establishment of a secure and efficient vascular entry through an arteriovenous fistula or graft to be of utmost importance for individuals undergoing hemodialysis. Preventing complications and negative outcomes related to vascular access failure is crucial due to its association with morbidity and mortality. Insufficient restructuring of blood vessels and excessive growth of inner tissue leading to narrowing (stenosis) and frequent formation of blood clots (thrombosis) play a pivotal role in the development of access failure. To mitigate this risk, AP medications can be administered to prevent vascular access failure.³

The use of AP has the potential to enhance the chances of maintaining functional vascular access. Results from a randomized double-blind study involving 877 patients showed significantly reduced occurrence of blood clot formation (thrombosis) in arteriovenous fistulas (AVFs) when clopidogrel was administered one day after the creation of the fistula and continued for a duration of 6 weeks compared to a placebo. Likewise, extensive studies conducted on large populations have also shown the advantageous effects of antiplatelet therapy on the long-term viability of primary unassisted arteriovenous grafts (AVGs).⁴

Patients undergoing HD are generally deemed to be at higher risk of bleeding due to platelet dysfunction, altered interactions between platelets and blood vessel walls, and other factors that inhibit normal platelet adhesion and aggregation. The use of heparin during dialysis further contributes to the elevated risk of bleeding. Additionally, prolonged aspirin therapy is significantly associated with an increased likelihood of experiencing hemorrhagic events.² Increased risk of bleeding in patients undergoing chronic hemodialysis is also attributed to various factors, including the buildup of uremic toxins, anemia, secondary hyperparathyroidism, platelet activation caused by extracorporeal circulation, and the use of anticoagulants during dialysis.⁵

However, hemodialysis patients still receive prescriptions for antiplatelet agents (AP) and/or oral anticoagulants (AC) knowingly with the risk of bleeding due to the high occurrence of cardiovascular comorbidities among this population. It is noteworthy that cardiovascular mortality rates are significantly higher among dialysis patients with a tenfold increase, and even greater (40 times) for individuals with both diabetes and renal failure. Additionally, hemodialysis patients frequently receive heparin to prevent clot formation within the extracorporeal system during their dialysis sessions. Consequently, utilization of these medications collectively contributes to an elevated risk of bleeding in this population.⁵

Studies on antiplatelet agents evaluating the bleeding risk for HD patients have produced inconsistent results. Numerous observational studies indicated that the bleeding risk associated with antiplatelet agents did not show any significant alterations in HD patients. Therefore, this study was conducted to analyse the role of antiplatelet medications and its substantial risk in HD patients.²

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we review assessed evidence on antiplatelet medications in hemodialysis. This is done to provide an explanation and improve the handling of patient’s treatments. The main purpose of this paper is to show the relevance of the difficulties that have been identified as a whole.

The inclusion criteria for this study are: 1) The paper needs to be written in English; 2) The studied papers include several that were published between 2014, and 2024. The exclusion criteria for this study are: 1) Editorials; 2) Submissions that do not have a DOI; 3) Review articles that have already been published; and 4) Identical entries of published journal.

Search Strategy

We used "antiplatelet", "medications", "hemodialysis" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: (*"antiplatelet"[All Fields] OR "antiplatelets"[All Fields]*) AND (*"medic"[All Fields] OR "medical"[All Fields] OR "medicalization"[MeSH Terms] OR "medicalization"[All Fields] OR "medicalizations"[All Fields] OR "medicalize"[All Fields] OR "medicalized"[All Fields] OR "medicalizes"[All Fields] OR "medicalizing"[All Fields] OR "medically"[All Fields] OR "medicals"[All Fields] OR "medicated"[All Fields] OR "medication s"[All Fields] OR "medics"[All Fields] OR "pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medication"[All Fields] OR "medications"[All Fields]*) AND (*"haemodialysis"[All Fields] OR "renal dialysis"[MeSH Terms] OR ("renal"[All Fields] AND "dialysis"[All Fields]) OR "renal dialysis"[All Fields] OR "hemodialysis"[All Fields]*) AND (*ff:ft[Filter]*) AND (*ff:ft[Filter]*) AND (*2014:2024[pdat]*) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

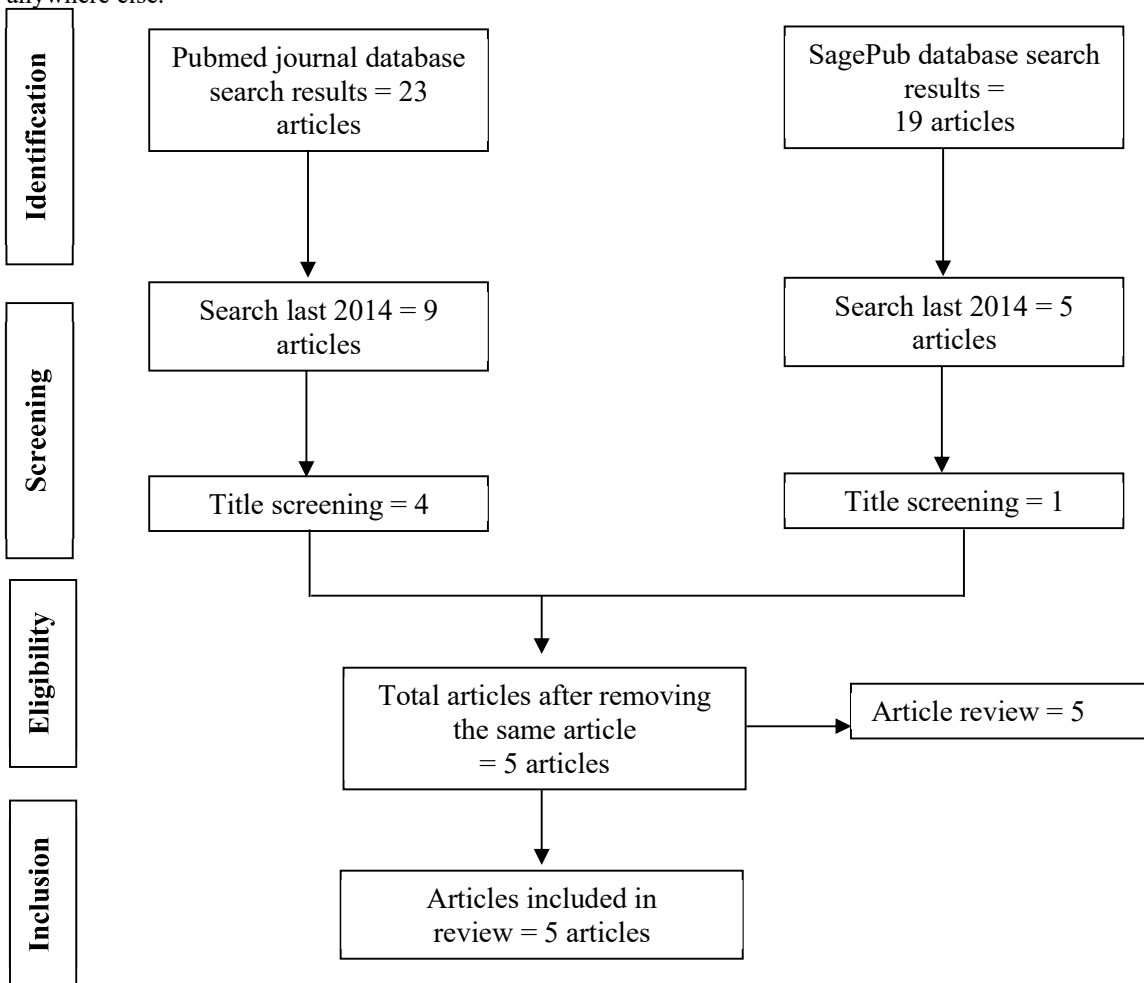


Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 23 articles, whereas the results of our search on SagePub brought up 19 articles. The results of the search conducted for the last year of 2014 yielded a total 9 articles for PubMed and 5 articles for SagePub. In the end, we compiled a total of 5 papers, 4 of which came from PubMed and 1 of which came from SagePub. We included five research that met the criteria.

Locham, et al.¹ (2018) showed that antiplatelet therapy was associated with lower in-hospital mortality. Aspirin and P2Y12-inhibitor use among AVG patients demonstrated improved PP rates compared to no antiplatelet therapy. We recommend the use of antiplatelet therapy especially in patients on AVG.

Nagaraj, et al.⁴ (2023) showed that AP therapy may provide secondary patency gains for previously thrombosed grafts compared to no AP therapy; however, this did not reach statistical significance, presumably related to small sample size.

Table 1. The literature include in this study

Author	Origin	Method	Sample	Result
Locham et al, 2018. ¹	Multicenter	Retrospective study	24,847 patients	A total of 24,847 patients undergoing HD access creation were identified (78% AVF). Anti Platelet Therapy (APT) was noted among 49 and 46% of AVG and AVF patients, respectively. In MLR analysis, patients on no-APT vs. APT had a 12-fold increased risk of in-hospital mortality (odds ratio (OR) 11.79, [95% confidence interval 5.30–26.26]) and the risk of developing steal syndrome was higher among patients discharged on APT (OR 1.81, [1.19–2.76]). In patients undergoing AVF, primary patency (PP) was similar between APT and no-APT. However, in patients undergoing AVG, PP rates at 12 months were significantly higher for APT: ASA (47 vs. 41%) and PI (51 vs. 41%) than for no-APT (p=0.008). At MCR analysis, the loss of PP at 12 months was 13% lower in ASA users (hazard ratio (HR) 0.87, [0.77–0.97], p=0.02) and 24% lower in PI users (HR 0.76, [0.57–0.99], p=0.046) compared to no-APT.
Nagaraj et al., 2023. ⁴	Single center	Retrospective Study	63 patients	A total of 109 declots were technically successful and performed in 63 individual patients. The majority of procedures were performed in upper arm grafts (71%, n=45). Dual antiplatelet (DAPT) was prescribed after 52 declots (48%), single antiplatelet was prescribed after 36 declots (33%), and anticoagulation was prescribed after 31 declots (28%). Median thrombosis free survival was 37 days (range 1–412 days) in the no antiplatelet group, 84 days (range 1–427 days) in the single antiplatelet group, and 93 days (range 3–407 days) in

				the DAPT group. Anti-platelet medications trended towards protective of AVG thrombosis in multivariate analysis (hazard ratio 0.84, 95% confidence interval 0.60–1.19); however, this did not reach statistical significance (P=0.33). A total of 4 major and 5 minor bleeding events occurred.
Collete et al., 2016. ⁵	France	Cohort study	502 patients	Among 502 patients included, 227 (45.2%) received an Anti Platelet (AP), 68 (13.5%) an Anti Coagulant (AC), 81 (16.1%) a combination AP + AC, and 126 (25.1%) were untreated. As compared with untreated patients, those given AP (HR 5.52, 95% CI [3.11–9.80]), AC (HR: 4.15, 95% CI: [3.46–4.99]), and AP + AC (HR: 5.59, 95% CI [2.62–11.91]) were at greater risk of major bleeding events.
Shimizu et al., 2019. ⁶	Japan	Retrospective study	644 patients	At a median follow-up of 49 months, bleeding events occurred in 76 (12.3%) patients. Critical bleeding events of BARC type 3 or 5 occurred more frequently in HD (HD vs. non-HD: 16.7% vs. 7.1%; p = 0.004). Most events tended to occur within 6 months post PCI. Multivariate analysis demonstrated that HD [hazard ratio (HR) 2.50, 95% confidence interval (CI) 1.03–3.16; p = 0.04], body mass index (BMI) (HR 0.91, 95%CI 0.87–0.99, p = 0.02), and serum albumin (HR 0.35, 95%CI 0.34–0.96, p = 0.03) were independent predictors of bleeding events. MACCE also occurred more frequently in HD (HD vs. non-HD: 53.9% vs. 29.3%; p < 0.001). Multivariate analysis demonstrated that pre-dialysis systolic blood pressure (HR 1.03, 95%CI 1.00–1.06, p = 0.02) and high-sensitive C-reactive

				protein level (HR 1.76, 95%CI 1.06–2.72, p = 0.03) were independent predictors of bleeding events in HD.
Yeh et al., 2017. ⁷	Taiwan	Retrospective study	420 patients	From the propensity-score-matched quasi-randomized study, initiation of antiplatelet drugs after first surgical thrombectomy in HD patients did not prevent the recurrence of surgical thrombectomy (log-rank p = 0.81), but significantly decreased the longevity of the access (log-rank p = 0.034). Multivariate Cox model demonstrated that prescription of antiplatelet drugs significantly increased the risk of graft failure (adjusted hazard ratio 2.13, p = 0.025).

Collette, et al.⁵ (2016) showed that the risk of major bleeding is higher in patients receiving an oral AC compared with untreated patients and those receiving an AP agent. A combination of the two drugs does not seem to increase the risk.

Shimizu, et al.⁶ (2018) showed that HD displayed more adverse bleeding and ischemic events compared with non-HD. Therefore, practitioners should reconsider the current regimen of DAPT in this patient cohort to prevent critical bleeding complications and spates of ischemic events.

Yeh, et al.⁷ (2017) showed that adjunctive prescription with antiplatelet medications in HD patients after surgical thrombectomy did not prevent recurrent thrombosis of AV access, but significantly jeopardized the longevity of AVG after surgical thrombectomy.

DISCUSSION

Vascular access failure is a common complication seen among HD patients. Antiplatelet medications are often prescribed to help reduce thrombosis and increase vascular access patency. AP reduces neointimal hyperplasia and graft thrombosis through a combination of anti-inflammatory properties and inhibition of platelet aggregation. The type of AP agent and the prescribed number of AP agents appear to be related to the bleeding risk for HD patients.¹

In HD patients, AP agents may lead to more bleeding events because of platelet dysfunction and differences in haemodynamic stability. However, hemodialysis patients still receive prescriptions for AP and/or oral anticoagulants (AC) knowingly with the risk of bleeding due to the high occurrence of cardiovascular comorbidities among this population. Existing data show mixed results regarding AP therapy for HD patients and the consensus is still not clear to decide on an individual basis.^{1,2,5}

Thrombosis is a frequent complication of AVG. KDOQI guidelines suggest low-dose aspirin and dipyridamole for primary patency after weighing an individual’s risk to benefit ratio. Aspirin and P2Y12 inhibitors (PI) such as clopidogrel are also commonly used as an antiplatelet agent to improve vascular access durability. PI agents are shown to improve primary patency in HD patients. Compared to no antiplatelet therapy, aspirin use decreased the risk of loss of primary patency by 13% and P2Y12 inhibitors decreased it by 24% in HD patients with AVG access. On the contrary, Australian CARI guidelines recommend against clopidogrel utilization to assist with primary patency due to increased bleeding risk. In the present study, AP therapy may provide secondary patency gains for previously thrombosed grafts compared to no AP therapy, however presumably due to the small sample size it did not reach statistical significance.^{1,4}

Up to 40% of patients with chronic kidney disease may have some degree of resistance or non-responsiveness to clopidogrel. Aggressive neo-intimal hyperplasia alters flow dynamics and AP drug resistance may be implicated in treatment response with clopidogrel. Few studies showed that there were improvements in AVG patency with combined AP therapy using dipyridamole and aspirin. However, single use of aspirin did not reproduce the same results regarding AVG patency.⁴

Patients with chronic kidney disease (CKD) are at an increased risk of cardiovascular morbidity and mortality. Furthermore, patients with CKD who are receiving AP therapy after percutaneous coronary intervention (PCI) are also at an increased risk of both major adverse cardiac events and bleeding complications. Dual-antiplatelet therapy (DAPT) after PCI is necessary to prevent stent thrombosis and subsequent ischemic events. HD displayed more adverse bleeding and ischemic events compared with non-HD. HD was an independent predictor of adverse bleeding events during DAPT after PCI. Furthermore, both serum hs-CRP level and pre-dialysis SBP were independent bleeding predictors in HD. Therefore, the current DAPT regimen needs to be reconsidered in HD patients.⁶

The increased cost and morbidity associated with HD patients partly resulted from the repeated procedures for maintaining AVG patency. A functional AVG is vital for patients with ESRD for maintaining HD. Several trials reported that the primary unassisted patency of AVG could be improved with antiplatelet treatment by preventing thrombosis in newly placed AV accesses. However, studies showed that AP therapy might cause shortened longevity of AV access for HD patients. In this present study, initiation of antiplatelet treatment in comparison with zero antiplatelet treatment after surgical thrombectomy caused a significant but modest increase in the loss of AVG longevity without decreasing the need for recurrent surgical thrombectomy. This study suggests that the benefits of AP therapy for cardiovascular protection needs to be evaluated along with its possible effect on AVG outcomes.⁷

CONCLUSION

AP medications are often prescribed to help reduce thrombosis and increase vascular access patency. AP therapy are given in HD patients with high cardiovascular commorbidities to prevent thrombosis and ischemia. Aspirin and P2Y12 inhibitors (PI) such as clopidogrel are commonly used as an antiplatelet agent to improve vascular access durability. However, studies showed that AP therapy might cause shortened longevity of AV access for HD patients. The benefits of AP therapy for cardiovascular protection needs to be evaluated along with its possible effect on AVG outcomes.

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