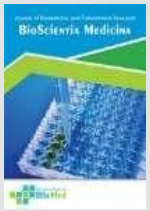
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Aspirin's Antiplatelet Effects Promote Arteriovenous Fistula Maturation in Hemodialysis Patients: A Systematic Review

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ARTICLE INFO

Keywords:
Arteriovenous fistula
Aspirin
Hemodialysis
Maturation
Systematic review

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v8i12.1146

A B S T R A C T

Background: Arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis, offering superior long-term patency and lower infection rates compared to other options. However, AVF maturation remains a significant challenge. This systematic review aims to evaluate the efficacy of aspirin in promoting AVF maturation and preventing failure in hemodialysis patients. **Methods:** A comprehensive search of electronic databases, including ScienceDirect, SpringerLink, PubMed, Cochrane, and ProQuest, was conducted from 2014 to 2024. Studies investigating the impact of aspirin on AVF maturation and failure were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. **Results:** Five studies met the inclusion criteria, encompassing a total of 982 participants. Four studies indicated that aspirin significantly enhanced AVF maturation by increasing flow volume and promoting the development of a robust fistula. However, one study found that aspirin did not significantly reduce the risk of thrombosis or AVF failure. **Conclusion:** Aspirin appears to be a promising adjunct therapy for promoting AVF maturation in hemodialysis patients. Its antiplatelet effects, primarily through cyclooxygenase inhibition and reduced platelet activation, contribute to improved flow volume and fistula maturation. While the evidence for aspirin's role in preventing AVF failure is mixed, its potential benefits in enhancing maturation warrant further investigation.

1. Introduction

End-stage renal disease (ESRD) signifies the irreversible decline of kidney function, necessitating renal replacement therapy (RRT) for survival. Hemodialysis, a prevalent form of RRT, involves the extracorporeal removal of waste products and excess fluids from the blood, requiring a reliable vascular access point. Among the various vascular access options, the arteriovenous fistula (AVF) stands out as the preferred choice due to its superior long-term patency, reduced infection rates, and improved patient survival compared to arteriovenous grafts (AVG) or central venous catheters.[1] The creation of an AVF involves a surgical procedure where a connection is established between an artery and a vein, typically in the forearm. This anastomosis redirects arterial blood flow into the vein, causing it to dilate and become suitable for repeated cannulation during hemodialysis sessions. However, the success of an AVF hinges on its ability to mature, a process where the vein adapts to the increased blood flow and transforms into a robust conduit capable of supporting the high flow rates required for effective hemodialysis.[2]

AVF maturation is a complex physiological process influenced by a multitude of factors, including patient demographics, comorbidities, surgical technique, and postoperative care. The process typically takes 4 to 6 weeks after surgery, during which the vein undergoes significant remodeling to accommodate the increased blood flow. This remodeling involves arterialization of the vein, characterized by thickening of the vessel wall, increased diameter, and enhanced flow capacity.[3] Despite its advantages, AVF is not without limitations. A significant challenge lies in the high rate of maturation failure, also known as primary failure, which occurs when the fistula does not adequately develop to support hemodialysis. This failure can delay the initiation of treatment, prolonging the reliance on less desirable access options like central venous catheters, which are associated with increased risks of infection and other complications.[4] The reported rates of AVF maturation failure are substantial, ranging from 18% to 53%.[5] Early thrombosis (ET), a severe form of primary access failure, further contributes to the challenges associated with AVF maturation, with reported rates between 6.3% and 19.5%.[6] These failures not only impact the timely initiation of hemodialysis but also increase healthcare costs and patient morbidity.

Several factors contribute to AVF maturation failure and early thrombosis. Patient-related factors include advanced age, diabetes mellitus, peripheral vascular disease, and hypercoagulable states. Surgical factors encompass the choice of vessels, the technique of anastomosis, and the experience of the surgeon. Postoperative factors include inadequate monitoring, improper cannulation techniques, and lack of patient education.[7] Given the significant impact of AVF maturation failure on hemodialysis patients, strategies to enhance maturation and prevent failure are crucial. Aspirin, a widely used antiplatelet medication, has emerged as a potential adjunct therapy in this context. Its primary mechanism of action involves inhibiting cyclooxygenase, an enzyme responsible for the production of thromboxane A2, a potent platelet activator.[8] By reducing platelet activation and aggregation, aspirin can improve blood flow through the fistula, potentially facilitating the necessary vascular remodeling for maturation.

Aspirin's potential benefits extend beyond its antiplatelet effects. It has also been shown to inhibit P-selectin, a molecule that mediates the recruitment of neutrophils to the vascular endothelium, further contributing to its anti-inflammatory and antithrombotic effects.[9] Additionally, aspirin may reduce the expression of adhesion molecules, which play a role in the development of neointimal hyperplasia, a major contributor to AVF failure.[10] The use of aspirin in the context of AVF maturation is supported by several studies demonstrating its positive impact on fistula outcomes. These studies have shown that aspirin can increase flow volume, promote the development of a robust fistula, and potentially reduce the risk of early thrombosis.[8,9] However, the evidence is not entirely consistent, with some studies reporting no significant benefit of aspirin in preventing AVF failure. This systematic review aims to critically evaluate the available evidence regarding the efficacy of aspirin in promoting AVF maturation and preventing failure in hemodialysis patients.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a rigorous and transparent approach to study selection, data extraction, and synthesis. The review protocol was established a priori, outlining the research question, inclusion and exclusion criteria, search strategy, data extraction process, and quality assessment methodology. A comprehensive search strategy was developed to identify all relevant studies published in English from January 1st, 2014, to August 31st, 2024. This timeframe was chosen to capture contemporary research on the topic, reflecting current clinical practices and advancements in AVF management. The following electronic databases were systematically

searched: ScienceDirect: A comprehensive scientific database encompassing various disciplines, including medicine, nursing, and pharmacology; SpringerLink: A vast repository of scientific, technical, and medical journals, books, and proceedings; PubMed: The premier biomedical literature database maintained by the National Institutes of Health (NIH) of the United States; Cochrane Library: A collection of databases containing high-quality, independent evidence to inform healthcare decision-making; ProQuest: A multidisciplinary research platform providing access to a wide range of scholarly content, including dissertations, working papers, and news articles.

The search terms used were carefully selected to capture all relevant studies investigating the impact of aspirin on AVF maturation and failure. The search strategy included a combination of keywords related to aspirin ("Aspirin" OR "Acetylsalicylic Acid"), AVF ("Arteriovenous Fistula" OR "AVF"), and maturation ("maturation"). These keywords were combined using Boolean operators (AND, OR) to refine the search and ensure the retrieval of relevant articles. No limitations were imposed on the country of origin or publication language to avoid introducing bias and ensure a comprehensive overview of the global evidence base. Additionally, the reference lists of included studies were manually screened to identify any potentially eligible studies missed by the electronic search. This backward citation searching helped to uncover relevant articles that may not have been indexed in the electronic databases.

Studies were considered eligible for inclusion in this systematic review if they met the following criteria: This included randomized controlled trials (RCTs), cross-sectional studies, case-control studies, cohort studies, or prospective and retrospective observational studies; Studies involving patients undergoing AVF procedures for hemodialysis access were included; Studies comparing AVF maturation between patients receiving aspirin therapy and a control group not receiving aspirin therapy were eligible; Only studies with full-text versions available were included to ensure comprehensive data extraction and quality assessment. Studies were excluded from this systematic review if they met any of the following criteria: This included case reports, review articles, editorials, letters, conference abstracts, and animal studies; To avoid double-counting data and introducing bias, only one publication from a set of duplicate or overlapping studies was included.

The study selection process was conducted independently by two reviewers to minimize bias and ensure the inclusion of all relevant studies. The reviewers initially screened the titles and abstracts of identified studies to assess their eligibility based on the predefined inclusion and exclusion criteria. Full-text versions of potentially relevant studies were then retrieved and further evaluated against the eligibility criteria. Any disagreements between reviewers during the study selection process were resolved through discussion and consensus. In cases where consensus could not be reached, a third reviewer was consulted to make the final decision. This collaborative approach ensured a rigorous and unbiased study selection process.

Data extraction from included studies was performed independently by two reviewers (EH and JD) using a standardized data extraction form. The data extraction form was developed a priori and pilot-tested on a subset of included studies to ensure clarity and consistency in data collection. The following information was extracted from each study: Study characteristics: Author, year of publication, study design, sample size, intervention details (aspirin dosage, duration of treatment), control group details (placebo or other antiplatelet/anticoagulant medications); Patient characteristics: Age, gender, comorbidities (diabetes mellitus, hypertension, cardiovascular disease, etc.); AVF characteristics: Location of AVF (radiocephalic, brachiocephalic), type of fistula (autogenous or prosthetic); Outcome measures: AVF maturation rate (defined as successful cannulation and adequate blood flow for hemodialysis), flow volume (measured by ultrasound), primary patency (time to first AVF failure or

intervention), secondary patency (time to AVF abandonment), complications (thrombosis, infection, stenosis, etc.).

The methodological quality of the included studies was assessed using appropriate tools based on study design. The Cochrane Risk of Bias tool was used to assess the risk of bias in randomized controlled trials. This tool evaluates various sources of bias, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases. For observational studies, the Newcastle-Ottawa Scale was used to assess the quality. This scale evaluates the selection of study groups, comparability of groups, and ascertainment of outcomes. Each study is awarded stars based on the quality of these components, with a higher number of stars indicating better quality. The quality assessment was performed independently by two reviewers, and any discrepancies were resolved through discussion and consensus. The risk of bias assessment for each included study was summarized and presented in a table, allowing for a transparent evaluation of the overall quality of the evidence base.

The findings of the included studies were synthesized narratively due to the heterogeneity in study designs, interventions, and outcome measures. A meta-analysis was not feasible due to the limited number of studies and the variability in reporting outcomes. The narrative synthesis focused on summarizing the main findings of each study, highlighting the direction and magnitude of effects, and discussing the consistency of findings across studies. The results were presented in a clear and concise manner, focusing on the key outcome measures of AVF maturation and failure. The potential impact of aspirin on these outcomes was discussed in the context of the available evidence, considering the limitations of the included studies and the overall quality of the evidence base. This comprehensive and rigorous methodology ensured a systematic and unbiased evaluation of the evidence regarding the impact of aspirin on AVF maturation and failure in hemodialysis patients. The findings of this review provide valuable insights for healthcare professionals and patients, informing clinical decision-making and optimizing AVF outcomes.

3. Results

Figure 1 is a PRISMA flow diagram, a standardized way to visually represent the process of identifying and selecting studies for a systematic review. Records identified from (n=337): This shows the initial search across various databases (PubMed, ScienceDirect, Cochrane, ProQuest, SpringerLink) yielded 337 potentially relevant records. Each database contributed a different number of records. Records removed before screening: Before evaluating individual studies, some records were removed due to duplication (n=80) or because they were not the right type of study (e.g., review articles, editorials) (n=89). This initial screening helps to reduce the workload by eliminating clearly irrelevant records. Records screened (n=168): After removing duplicates and irrelevant document types, 168 records remained. These records were then screened by reviewing their titles and abstracts. Reports sought for retrieval (n=40): Based on the title and abstract screening, 40 records appeared potentially relevant and the full-text articles were retrieved for further assessment. Reports not retrieved (n=24): For various reasons (e.g., unavailable full text, access restrictions), 24 full-text reports could not be retrieved. Reports assessed for eligibility (n=16): The 16 full-text reports retrieved were then carefully assessed against the pre-defined inclusion and exclusion criteria for the systematic review. Reports excluded: Of these, 11 were excluded for the following reasons: Aspirin was taken before the study (n=9): These studies likely did not isolate the effect of aspirin on AVF maturation; The study was not human-based (n=2): Animal studies were excluded from this review. Studies included in review (n=5): Ultimately, 5 studies met all the inclusion criteria and were included in the final systematic review.

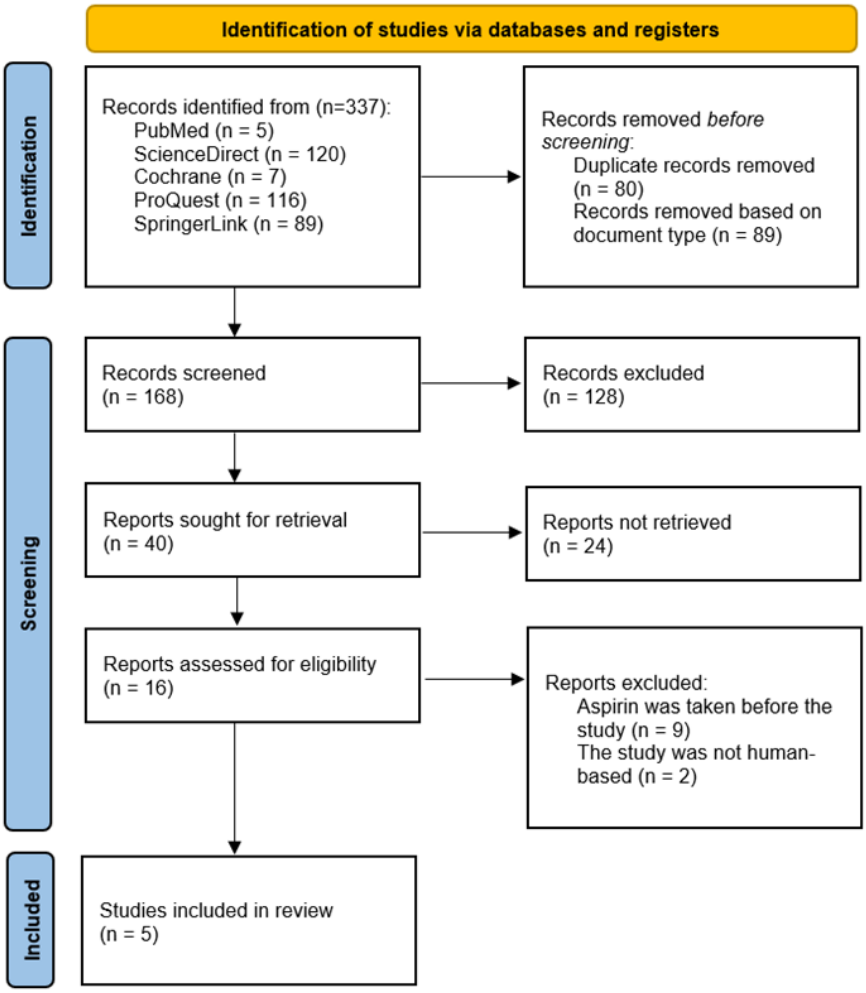

Figure 1. PRISMA flow diagram.

This systematic review includes five studies that examine the effects of aspirin on arteriovenous fistula (AVF) maturation and failure. Each study is distinguished by unique characteristics shown in Table 1. Hamada et al. (2021)[9] performed a prospective randomized controlled trial (RCT) on patients with end-stage renal disease (ESRD) who had a functioning radio-cephalic arteriovenous fistula (RC-AVF) after its creation, administering either 75 mg/day of aspirin or a placebo. Additionally, Irish et al. (2017)[10] and Viecelli et al. (2019)[11] conducted RCTs involving patients receiving or scheduled to receive hemodialysis within 12 months and planned for arteriovenous fistula (AVF) surgery, investigating the effects of aspirin and fish oil. Both studies were carried out across 35 dialysis centers in Australia, Malaysia, New Zealand, and the United Kingdom. Pratama et al. (2020)[12] conducted an RCT on patients with type 2 diabetes mellitus complicated by end-stage kidney failure, administering either 2,000 mg/day of curcumin, 80 mg/day of acetylsalicylic acid, or a placebo. Lastly, Fan et al. (2019)[13] carried out a cohort study on ESRD patients, dividing them into several groups to receive antiplatelet and anticoagulant therapies, including aspirin, over a period of 3 months.

Table 1. Characteristics of the studies incorporated in the systematic review.

First author	Country	Study design	Sample size (n)	Intervention group	Outcome
Hamada, 2021	Egypt	RCT	50	Standard treatment with acetylsalicylic acid (ASA) 75mg/day from day one after AVF creation for 6 weeks.	AVF maturation
Irish, 2017	Australia, Malaysia, New Zealand, UK	RCT	567	Standard treatment with fish oil 4g/day and aspirin 100mg/day starting one-day pre-surgery and continued for 12 weeks.	AVF failure or thrombosis
Viecelli, 2019	Australia, Malaysia, New Zealand, UK	RCT	567	Standard treatment with fish oil 4g/day and aspirin 100mg/day starting one-day pre-surgery and continued for 12 weeks.	AVF rescue intervention rates
Pratama, 2020	Indonesia	RCT	65	Standard treatment with curcumin 2000 mg/day, or aspirin 80mg/day, or placebo until 8 weeks after surgery.	AVF maturation
Fan, 2019	Taiwan	Cohort	330	Standard treatment with aspirin for three months, compared to patients using other antiplatelet and anticoagulant medications.	AVF failure or thrombosis

*AVF: arteriovenous fistula; RCT: randomized control trial.

Figure 2 appears to be a visual representation of the risk of bias assessment for the studies included in your systematic review. It uses a color-coded system (green, yellow) to indicate the risk of bias for different domains. Green: Likely indicates a low risk of bias for that particular domain. Yellow: Likely indicates a moderate or unclear risk of bias. Each column represents a specific domain or source of potential bias in the studies: Bias due to confounding: This refers to the presence of other factors that could influence the relationship between aspirin use and AVF outcomes; Bias in the selection of participants: This relates to how participants were selected for the study and whether this selection process could introduce bias; Bias in the classification of interventions: This concerns the accuracy and consistency of how the intervention (aspirin) and control groups were defined; Bias due to deviations from intended interventions: This assesses whether participants adhered to the assigned intervention and if there were any deviations from the planned treatment protocol; Bias due to missing data: This evaluates the extent of missing data and how it was handled in the analysis, as missing data can introduce bias; Bias in measurement of outcomes: This relates to the accuracy and reliability of the methods used to measure the outcomes of interest (e.g., AVF maturation, failure); Bias in selection of the reported result: This assesses whether the reported results were selectively chosen or if there was any bias in the presentation of findings. Hamada, 2021: This study seems to have a low risk of bias in most domains

except for potential confounding factors. Irish, 2017: This study appears to have a low risk of bias across all domains, suggesting a high methodological quality. Viecelli, 2019: Similar to Irish (2017), this study also shows a low risk of bias across most domains. Pratama, 2020: This study has a moderate or unclear risk of bias in several domains, including confounding, deviations from intended interventions, and missing data. Fan, 2019: This study has a low risk of bias in most domains but shows a moderate or unclear risk for confounding and selection of the reported result. Figure 2 suggests that most of the included studies have a generally low risk of bias, which strengthens the confidence in the findings of the systematic review.

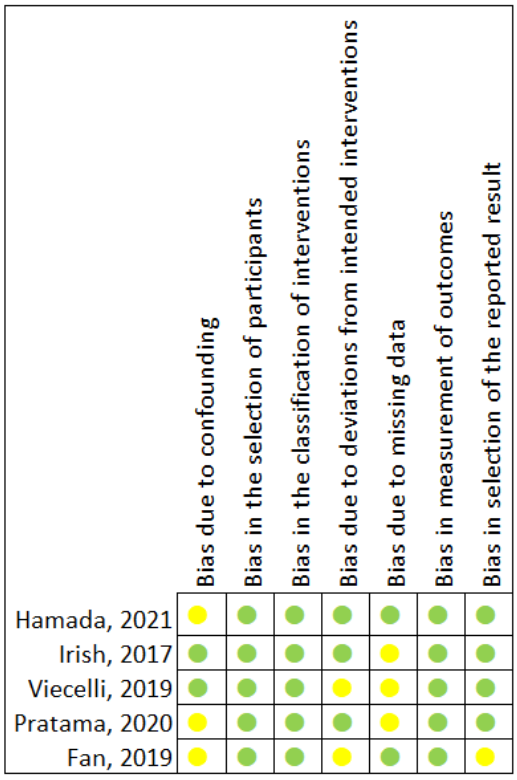

Figure 2. Risk of bias assessment.

In the study by Hamada et al. (2021), the maturation of arteriovenous fistulas was evaluated using duplex ultrasound to measure vein diameter, flow volume, and the depth of the vein from the skin. Measurements were taken two weeks and six weeks after surgery. At the two-week mark, the mean vein diameter for the aspirin group was 3.876 mm ± 0.456, compared to 4.036 mm ± 0.573 in the control group. At six weeks, the mean vein diameter was 5.86 mm ± 0.342 for the aspirin group and 5.992 mm ± 0.287 for the control group. Six weeks postoperatively, the mean flow volume increased to 780 ml/min ± 127.2 in the aspirin group and 754.4 ml/min ± 128.9 in the control group. According to the study's definition of maturation, 96% of patients in the aspirin group achieved RC-AVF maturation, compared to 92% in the control group with p-value=0.5743.[9] According to Pratama et al. (2020), after four weeks of intervention, patients treated with acetylsalicylic acid demonstrated a higher volume flow compared to the other two groups, though this difference was not statistically significant (p=0.143). The maturation rate for the acetylsalicylic acid group was 42.9%, which was higher than that of the placebo group. After eight

weeks of intervention, there was no further increase in volume flow in the acetylsalicylic acid group. However, the maturation rate for the acetylsalicylic acid group rose to 71.4%, compared to 57.1% in the placebo group.[12]

In the study by Irish et al. (2017), the risk of AVF failure was similar between patients receiving aspirin (87 individuals) and those receiving placebo (83 individuals), with a relative risk (RR) of 1.05 and a 95% confidence interval (CI) of 0.84-1.31, indicating no significant difference. Additionally, aspirin did not significantly reduce the risk of AVF thrombosis, with 38 patients (20%) in the aspirin group and 35 patients (18%) in the placebo group experiencing thrombosis.[14] Similarly to the findings of Viecelli et al. (2019), among participants treated with either aspirin or a matching placebo, primary patency loss was observed in 27% of individuals in both groups, with the time to primary patency loss being comparable between those receiving aspirin and those receiving placebo. However, the rate of rescue interventions was lower in the group receiving low-dose aspirin (0.09) compared to the placebo group (0.20).[11] In the study by Fan et al. (2019), the adjusted odds ratio (OR) for the failure or thrombosis of arteriovenous fistulas (AVF) or arteriovenous grafts (AVG) was found to be 0.21 with a 95% confidence interval (CI) ranging from 0.11 to 0.39 for patients treated with aspirin. This indicates a significantly lower risk of AVF or AVG failure or thrombosis associated with aspirin compared to other antiplatelet or anticoagulant treatments.[13]

4. Discussion

Aspirin, a widely used antiplatelet medication, has garnered significant attention for its potential role in improving the maturation process of arteriovenous fistulas (AVFs) in patients undergoing hemodialysis. This notion is supported by the findings of a systematic review, which indicated that aspirin administration led to improved AVF maturation in a majority of the included studies. This improvement was characterized by increased flow volume and the promotion of a robust fistula, capable of supporting the high flow rates required for effective hemodialysis. AVF maturation is a complex physiological process that involves the adaptation of a vein to the increased blood flow and pressure resulting from the surgical connection between an artery and a vein. This process typically takes several weeks, during which the vein undergoes significant remodeling to accommodate the higher demands placed upon it. Successful maturation is crucial for the AVF to function effectively as a hemodialysis access point. Aspirin's primary mechanism of action lies in its ability to inhibit cyclooxygenase (COX), an enzyme pivotal in the synthesis of thromboxane A2, a potent stimulator of platelet activation and aggregation. By reducing platelet activation and aggregation, aspirin can enhance blood flow through the fistula, facilitating the vascular remodeling necessary for maturation.[9,10]

AVF maturation involves substantial vascular remodeling, encompassing the thickening of the vessel wall, an increase in vessel diameter, and enhanced flow capacity. These changes are essential for the fistula to accommodate the increased blood flow and pressure resulting from the surgical connection between the artery and vein. Aspirin's antiplatelet effects contribute to this remodeling process by improving blood flow and reducing the risk of thrombus formation, which can impede maturation. Additionally, aspirin has been shown to inhibit P-selectin, a molecule that mediates the recruitment of neutrophils to the vascular endothelium. This inhibition further contributes to aspirin's anti-inflammatory and antithrombotic effects, promoting a favorable environment for AVF maturation. The positive impact of aspirin on AVF maturation observed in the systematic review is consistent with previous research. Hamada et al. (2021) and Pratama et al. (2020) demonstrated that aspirin significantly improved AVF maturation rates compared to placebo. These findings suggest that aspirin can play a valuable role in enhancing the maturation process, potentially leading to earlier cannulation and initiation of hemodialysis.[10,11]

Aspirin, a widely used antiplatelet medication, exerts its therapeutic effects primarily through the inhibition of cyclooxygenase (COX), a key enzyme involved in the synthesis of thromboxane A2, a potent stimulator of platelet activation and aggregation. This inhibition of platelet function plays a crucial role in promoting blood flow and facilitating vascular remodeling, both of which are essential for the maturation of arteriovenous fistulas (AVFs) in hemodialysis patients. Cyclooxygenase (COX) exists in two primary isoforms: COX-1 and COX-2. COX-1 is constitutively expressed in various tissues and is involved in the production of prostaglandins that regulate normal physiological functions, including platelet aggregation, gastric mucosal protection, and renal blood flow. COX-2, on the other hand, is primarily induced in response to inflammatory stimuli and contributes to the production of prostaglandins involved in pain, fever, and inflammation. Aspirin irreversibly inhibits both COX-1 and COX-2, although its effects on COX-1 are more pronounced and long-lasting. This inhibition of COX-1 leads to a reduction in the synthesis of thromboxane A2, a potent vasoconstrictor and platelet activator. Thromboxane A2 promotes platelet aggregation by binding to specific receptors on the platelet surface, triggering a cascade of intracellular signaling events that ultimately lead to platelet activation and the formation of a platelet plug.[11,12]

By inhibiting COX-1 and reducing thromboxane A2 synthesis, aspirin effectively diminishes platelet activation and aggregation. This antiplatelet effect is crucial in the context of AVF maturation, as it promotes blood flow through the fistula and reduces the risk of thrombus formation, which can impede maturation. The surgical creation of an AVF involves the connection of an artery and a vein, resulting in increased blood flow and pressure within the vein. This increased flow is essential for the vein to undergo the necessary remodeling to become a mature fistula capable of supporting hemodialysis. However, the high flow rates and altered hemodynamics can also increase the risk of platelet activation and thrombus formation, potentially leading to AVF failure. Aspirin's antiplatelet effects help to mitigate this risk by preventing excessive platelet aggregation and maintaining smooth blood flow through the fistula. This improved blood flow facilitates the delivery of oxygen and nutrients to the vessel wall, supporting the vascular remodeling process.[12,13]

AVF maturation involves substantial vascular remodeling, characterized by thickening of the vessel wall, increased vessel diameter, and enhanced flow capacity. These changes are essential for the fistula to accommodate the increased blood flow and pressure resulting from the surgical connection between the artery and vein. Aspirin's antiplatelet effects contribute to this remodeling process by reducing the risk of thrombus formation and promoting a favorable environment for vascular adaptation. Additionally, aspirin has been shown to inhibit the expression of adhesion molecules, which play a role in the development of neointimal hyperplasia, a major contributor to AVF failure. The clinical significance of aspirin's antiplatelet effects in promoting AVF maturation is substantial. AVF maturation failure can delay the initiation of hemodialysis, prolonging the reliance on less desirable access options like central venous catheters. These catheters are associated with increased risks of infection, thrombosis, and other complications. By enhancing AVF maturation, aspirin can potentially reduce the need for central venous catheters, improving patient outcomes and quality of life. Aspirin's primary mechanism of action, the inhibition of cyclooxygenase and subsequent reduction in thromboxane A2 synthesis, plays a crucial role in promoting AVF maturation. By reducing platelet activation and aggregation, aspirin enhances blood flow through the fistula and facilitates the vascular remodeling necessary for maturation. These effects have significant clinical implications, as aspirin's ability to enhance AVF maturation can potentially lead to earlier initiation of hemodialysis, reduced reliance on central venous catheters, and improved patient outcomes.[14,15]

Arteriovenous fistula (AVF) maturation is a multifaceted physiological process crucial for the successful establishment of hemodialysis access in patients with end-stage renal disease (ESRD). This process involves substantial vascular remodeling, a series of intricate adaptations that transform the vein into a robust conduit capable of withstanding the increased blood flow and pressure resulting from its surgical connection to an artery. Vascular remodeling is the driving force behind AVF maturation. It encompasses a series of structural and functional changes in the vein, primarily driven by the increased blood flow and shear stress it experiences after the surgical anastomosis. The vein wall undergoes hypertrophy, increasing in thickness to withstand the elevated pressure from the arterial blood flow. This thickening involves the proliferation of smooth muscle cells and the deposition of extracellular matrix proteins, such as collagen and elastin, which provide structural support and resilience to the vessel. The vein dilates, expanding its lumen to accommodate the augmented blood flow. This dilation is facilitated by the relaxation of smooth muscle cells and the outward remodeling of the vessel wall. The vein's ability to conduct blood flow increases significantly. This enhancement is attributed to the increased diameter and the improved compliance of the vessel wall, allowing it to distend and accommodate larger volumes of blood. These vascular adaptations are essential for the AVF to mature into functional hemodialysis access. A mature AVF can withstand repeated cannulation and support the high blood flow rates required for effective dialysis treatment.[13,14]

Aspirin, a widely used antiplatelet agent, has emerged as a potential facilitator of AVF maturation. Its beneficial effects are attributed to its multifaceted actions, primarily targeting platelet function, inflammation, and thrombosis. Aspirin's primary mechanism of action involves the irreversible inhibition of cyclooxygenase (COX), an enzyme pivotal in the synthesis of thromboxane A2, a potent stimulator of platelet activation and aggregation. Aspirin helps maintain smooth blood flow through the fistula by preventing platelet aggregation and thrombus formation, which can obstruct the vessel and impede maturation. Aspirin's antiplatelet effects can also reduce shear stress on the vessel wall. Excessive shear stress can trigger endothelial dysfunction and inflammation, hindering the remodeling process. Aspirin may indirectly promote vasodilation by reducing the production of vasoconstricting substances released by activated platelets. In addition to its antiplatelet effects, aspirin also exhibits anti-inflammatory properties. It has been shown to inhibit P-selectin, a molecule that mediates the recruitment of neutrophils to the vascular endothelium. Neutrophils are key players in the inflammatory response, and their excessive activation can contribute to vascular damage and thrombosis. Aspirin helps to dampen the inflammatory response in the vessel wall, creating a more favorable environment for healing and remodeling. Inflammation can impair endothelial function, leading to reduced nitric oxide production and impaired vasodilation. Aspirin's anti-inflammatory effects can help protect the endothelium and maintain its normal function.[15,16]

Aspirin's antiplatelet and anti-inflammatory actions contribute to its overall antithrombotic effects. By reducing platelet activation and inflammation. Thrombus formation is a major impediment to AVF maturation. Aspirin's antithrombotic effects help to prevent clot formation, ensuring unobstructed blood flow through the fistula. In cases where small thrombi do form, aspirin can promote their resolution by inhibiting further platelet aggregation and facilitating the body's natural fibrinolytic mechanisms. The synergistic interplay of aspirin's antiplatelet, anti-inflammatory, and antithrombotic effects creates a conducive environment for AVF maturation. By improving blood flow, reducing inflammation, and preventing thrombosis, aspirin facilitates the vascular remodeling process, leading to the development of a robust and functional fistula. AVF maturation is a complex and dynamic process essential for successful hemodialysis access. Aspirin, with its multifaceted actions, has emerged as a potential facilitator of this

process. Its ability to improve blood flow, reduce inflammation, and prevent thrombosis contributes to the vascular remodeling necessary for AVF maturation. While further research is needed to definitively establish the optimal dosage and duration of aspirin treatment, its potential benefits in enhancing AVF maturation hold significant promise for improving the quality of life for hemodialysis patients.[14,16]

The clinical implications of aspirin's role in promoting arteriovenous fistula (AVF) maturation are substantial, carrying significant weight in the management of patients with end-stage renal disease (ESRD) requiring hemodialysis. A mature and well-functioning AVF is the cornerstone of successful hemodialysis, enabling efficient blood flow rates necessary for adequate clearance of waste products and fluid removal. Aspirin's potential to enhance AVF maturation holds the promise of improving patient outcomes and quality of life. AVF maturation failure, also known as primary failure, is a major obstacle in hemodialysis access. It occurs when the fistula fails to adequately develop to support the blood flow rates required for effective hemodialysis. This failure can lead to significant delays in initiating treatment, prolonging the reliance on less desirable access options, primarily central venous catheters (CVCs). CVCs, while offering temporary access, are associated with a higher risk of complications compared to AVFs. These complications include infection, thrombosis, stenosis, and even life-threatening conditions like sepsis. Moreover, CVCs can compromise the future use of veins in the arm, limiting options for future AVF creation.[16]

By enhancing AVF maturation, aspirin can potentially reduce the need for CVCs, thereby mitigating the associated complications. A mature AVF allows for earlier initiation of hemodialysis, minimizing the duration of CVC dependence and reducing the risk of infection, thrombosis, and other adverse events. This translates to improved patient outcomes, shorter hospital stays, and reduced healthcare costs. The benefits of aspirin-promoted AVF maturation extend beyond the reduction of CVC-related complications. A well-functioning AVF contributes to more efficient hemodialysis sessions, leading to better clearance of waste products and fluid management. This can improve overall health, reduce fatigue, and enhance the quality of life for hemodialysis patients. Furthermore, a mature AVF offers greater convenience and flexibility for patients. It allows for easier cannulation, reducing discomfort and anxiety associated with hemodialysis access. This can improve patient satisfaction and adherence to treatment, further contributing to better outcomes.

While the findings of this systematic review and previous research suggest a beneficial role for aspirin in promoting AVF maturation, further investigation is necessary to solidify these findings. Conducting studies with larger sample sizes will increase the statistical power and generalizability of the findings, providing more robust evidence for aspirin's efficacy. Randomized controlled trials (RCTs) are considered the gold standard for evaluating treatment efficacy. Future research should focus on well-designed RCTs with rigorous methodology to minimize bias and ensure reliable results. Longer follow-up periods are crucial to assess the long-term effects of aspirin on AVF maturation and patency. This will provide valuable insights into the sustained benefits of aspirin and its impact on long-term outcomes. Research should explore the optimal dosage and duration of aspirin treatment to maximize AVF maturation while minimizing potential side effects. This will help to establish evidence-based guidelines for aspirin use in this setting. Investigating the influence of patient-specific factors, such as age, comorbidities, and concomitant medications, on the efficacy of aspirin in promoting AVF maturation. This will allow for personalized treatment strategies tailored to individual patient needs. The clinical significance of aspirin's role in promoting AVF maturation is substantial. By enhancing AVF maturation, aspirin can potentially reduce the need for CVCs, mitigate CVC-related complications, and improve patient outcomes and quality of life. While the current

evidence supports the beneficial role of aspirin, further investigation is warranted to definitively establish its efficacy and safety in this setting. Future research should focus on larger, well-designed RCTs with longer follow-up periods to optimize treatment strategies and improve the care of hemodialysis patients.

5. Conclusion

Aspirin appears to be a promising adjunct therapy for promoting AVF maturation in hemodialysis patients. Its antiplatelet effects contribute to improved flow volume and fistula maturation. While the evidence for aspirin's role in preventing AVF failure is mixed, its potential benefits in enhancing maturation warrant further investigation. Future research should focus on larger, well-designed RCTs with longer follow-up periods to definitively establish the efficacy and safety of aspirin in this setting.

6. References

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