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"ANTITHROMBOTIC THERAPY IN DIALYSIS PATIENTS UNDERGOING AV GRAFT PLACEMENT – PATENCY AND BLEEDING COMPLICATIONS"

by

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To my father

To my mother

And of course to my brother, Filippos

For they have been everything I could ever ask

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1. ABSTRACT

Introduction: End-stage renal disease patients undergoing hemodialysis require long-term, durable vascular access for effective renal replacement therapy. Arteriovenous grafts (AVG) are often the only solution for patients unsuitable for arteriovenous fistula (AVF) creation. Currently, evidence is scarce regarding the use of antithrombotic therapies for AVG thrombosis prevention, as well as the associated bleeding risk. **Materials & Methods:** Following the PICO model and the PRISMA guidelines, a data search of the English literature in 3 large electronic databases (PubMed, SCOPUS, Central Cochrane) was conducted, until March 1st, 2023 (PROSPERO Protocol Number: CRD42023401785). Studies on human subjects with an AVG receiving any kind of antithrombotic medication, reporting on primary and secondary patency rates, as well as bleeding complications were included in the analysis. Due to the heterogeneity of the data, only a descriptive report of the outcomes was undertaken.

Results: A total of 12 studies, with 22.364 patients with ESRD and an AVG were included, with patient recruitment spanning over a 37-year time-period (1982-2019). Antithrombotic compounds evaluated included aspirin, clopidogrel, dipyridamole, warfarin, UFH, DOACs and fish oil. Ten studies included placebo/control groups of patients for comparison of interventions, while two studies did not. Eleven studies reported on primary patency rates, and two studies reported on secondary patency rates. Studies on antiplatelet medication presented contradictory results regarding primary and secondary patency rates, while studies on anticoagulant medication presented worse outcomes in both terms of primary and secondary patency rates, as well as increased bleeding risk.

Conclusions: Managing antithrombotic therapy in these patients requires careful consideration due to their heightened bleeding risks and variable responses to treatment. Individualized antithrombotic algorithms, tailored to each patient thrombotic and hemorrhagic risk, are crucial for better patient safety, due to the idiosyncrasy of ESRD patients, while randomized, controlled trials with cautious confounder control are essential for robust outcomes on AVG thrombosis and bleeding complications prevention.

Key words: arteriovenous graft, antithrombotic therapy, patency, bleeding, hemodialysis

2. ΠΕΡΙΛΗΨΗ

Εισαγωγή: Οι ασθενείς με νεφρική νόσο τελικού σταδίου που υπόκεινται σε αιμοκάθαρση χρειάζονται ανθεκτικές αγγειακές προσπελάσεις για αποτελεσματική θεραπεία υποκατάστασης της νεφρικής λειτουργίας. Τα μοσχεύματα αρτηριοφλεβικής επικοινωνίας συχνά αποτελούν τη μοναδική επιλογή για ασθενείς οι οποίοι δεν είναι κατάλληλοι υποψήφιοι για δημιουργία αυτόλογης αρτηριοφλεβικής επικοινωνίας. Στην παρούσα φάση, υπάρχει περιορισμένος αριθμός δεδομένων σχετικά με την χρήση των αντιθρομβωτικών φαρμάκων στην πρόληψη θρόμβωσης των αρτηριοφλεβικών μοσχευμάτων, καθώς και σχετικά με τον σχετιζόμενο αιμορραγικό κίνδυνο.

Μέθοδοι & Υλικά: Ακολουθώντας το μοντέλο PICO και τις οδηγίες PRISMA, πραγματοποιήθηκε μία συστηματική ανασκόπηση της Αγγλικής βιβλιογραφίας σε 3 μεγάλες επιστημονικές βάσεις δεδομένων (PubMed, SCOPUS, Central-Cochrane) με καταληκτικό σημείο αναζήτησης την 1η Μαρτίου, 2023. Συμπεριελήφθησαν μελέτες σε ασθενείς με αρτηριοφλεβικά μοσχεύματα και οι οποίοι λαμβάνουν οποιαδήποτε αντιθρομβωτική αγωγή. Δεδομένης της ετερογένειας των αποτελεσμάτων, πραγματοποιήθηκε μόνο περιγραφική απόδοση των αποτελεσμάτων, καθότι ήταν αδύνατη η στατιστική ανάλυση.

Αποτελέσματα: Συμπεριελήφθησαν συνολικά 12 μελέτες, με 22.364 ασθενείς με μοσχεύματα αρτηριοφλεβικής επικοινωνίας, με την εισαγωγή των ασθενών στις μελέτες να πραγματοποιείται εντός διαστήματος 37 ετών (1982-2019). Οι αντιθρομβωτικές ουσίες οι οποίες εκτιμήθηκαν ήταν το ακετυλοσαλυκιλικό οξύ, η κλοπιδογρέλη, η διπυριδαμόλη, η βαρφαρίνη, η μη κλασμοποιημένη ηπαρίνη, τα από-του-στόματος αντιπηκτικά και τα ω-3 λιπαρά οξέα. Δέκα μελέτες συμπεριελάμβαναν ομάδες ασθενών placebo για σύγκριση των αποτελεσμάτων. Έντεκα μελέτες εκτίμησαν

την πρωτογενή βατότητα μοσχεύματος, ενώ δύο μελέτες εκτίμησαν την δευτερογενή βατότητα του μοσχεύματος. Τα δεδομένα από μελέτες όπου εκτιμήθηκε η δράση των αντιαιμοπεταλιακών φαρμάκων ήταν διφορούμενα, χωρίς σαφή αποτελέσματα υπέρ ή κατά της χρήσης τους, από το σύνολο των μελετών σχετικά με την πρωτογενή και δευτερογενή βατότητα. Δεδομένα από τις μελέτες όπου εκτιμήθηκε η δράση των αντιπηκτικών φαρμάκων αναφέρουν δυσμενέστερα αποτελέσματα τόσο σχετικά με την πρωτογενή και δευτερογενή βατότητα, όσο και σχετικά με τις αιμορραγικές επιπλοκές.

Σύνοψη: Η διαχείριση της αντιθρομβωτικής αγωγής σε ασθενείς με νεφρική νόσο τελικού σταδίου είναι ιδιαίτερη και απαιτεί προσοχή, λόγω του αυξημένου αιμορραγικού κινδύνου και των πιθανών απαντήσεων στην θεραπεία. Τα εξατομικευμένα θεραπευτικά πρωτόκολλα είναι απαραίτητα για την ασφάλεια των ασθενών, λαμβάνοντας υπόψιν την ιδιοσυγκρασία τους. Είναι απαραίτητα μακροπρόθεσμα δεδομένα από τυχαιοποιημένες μελλοντικές μελέτες όπου θα έχει πραγματοποιηθεί προσεκτικός έλεγχος των παραγόντων συστηματικών σφαλμάτων, προς την παραγωγή ισχυρών δεδομένων σχετικά με την επίδραση των αντιθρομβωτικών φαρμάκων στην πρόληψη της θρόμβωσης των μοσχευμάτων αρτηριοφλεβικής επικοινωνίας και των αιμορραγικών επιπλοκών.

3. ABBREVIATIONS

*In order of appearance

CKD; Chronic Kidney Disease

eGFR; estimated Glomerular Filtration Rate

KDIGO; Kidney Disease: Improving Global Outcomes

ACR: Albumin-to-Creatine ratio

ESRD; End-Stage Renal Disease

RRT; Renal Replacement Therapy

KT: Kidney Transplantation

HD: Hemodialysis

PD: Peritoneal Dialysis

AVF; Arteriovenous Fistula

AVG; Arteriovenous Graft

VA: Vascular Access

ePTFE: expanded polytetrafluoroethylene

CVC: Central Venous Catheter

DOAC: Direct Oral Anticoagulant

ESVS: European Society of Vascular Surgery

ISN: International Society of Nephrology

NICE: National Institute for Health and Care Excellence

4.1 Epidemiology & Natural History of End-Stage Renal Disease (ESRD)

Chronic kidney disease (CKD) is a multifactorial clinical entity which has a massive impact on patients' quality of life, morbidity, and mortality. Both the renal structure and function are often impacted, leading to clinical manifestations of various severity. Estimated glomerular filtration rate (eGFR) is accepted as the most used index for renal function, measured in ml/min/1.73m^2, while urine albumin to creatine ratio is also utilized as a marker for renal impairment and tubular injury. Based on the KDIGO 2012 Guidelines, CKD can be classified into five stages, taking into consideration the eGFR and the albumin to creatine ratio (ACR), highlighting the increased risk of complications in patients with later stages of CKD and finally ESRD. (**Figure I**).

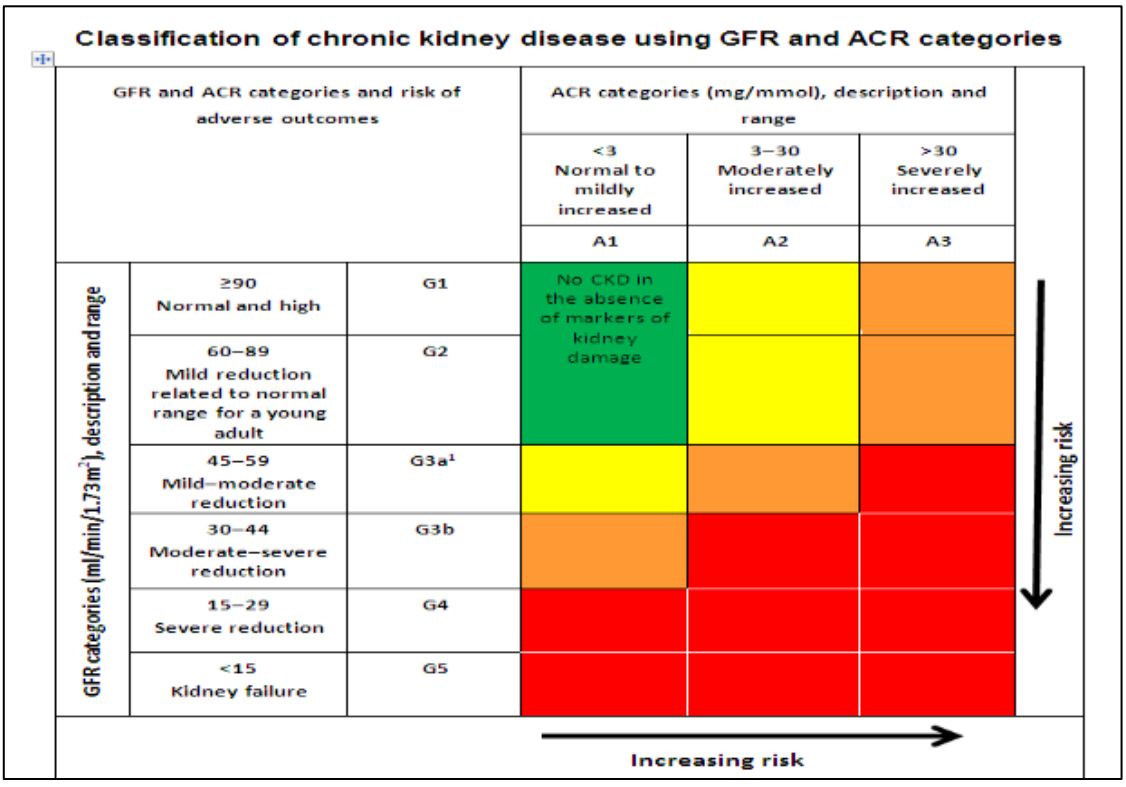

Figure I. CKD Classification (adapted with permission from Kidney Disease: Improving Global Outcomes Work Group (2013), KDIGO Clinical Practice Guidelines)[1]

The etiology of CKD includes a myriad of possible underlying conditions and mechanisms of kidney damage, while recent data involving over 34 thousand patients suggest that the three most common causes are diabetes mellitus, hypertension, and glomerulonephritis, with respective prevalences of 27.7%, 27.6% and 6.4%.[2] Preventative measures for the timely diagnosis and treatment of these underlying conditions are crucial for preemptive management of renal structural and functional damage. Importantly, CKD is indissolubly associated with increased cardiovascular risk, while a number of factors have been linked to increased rates of CKD progression to ESRD, including older age, male sex, diagnosis of diabetic nephropathy and nephrosclerosis.[3]

The debilitating nature of the disease has prompted the global medical community to take actions towards prompt diagnosis, progression, and holistic management efforts, aiming for the inclusion of several medical specialties for suffice treatment. Data from the last two decades suggest that over 9% of the global population live with CKD (between 700 million and one billion people)[4,5], with increasing associated complications and financial costs related to patient management. Reports for more than 500.000 people suffering from CKD at the United State of America underline the impact of the disease in countries with highly developed health care systems.[6] The financial burden associated with CKD is loosely estimated at around 1.3% of total healthcare cost, deriving data from healthcare systems in European countries, while ESRD only affects about 1% of CKD patients.[7,8] Analyses from the Medicare Health System report that over $ 20 billion are spent on annual dialysis costs.[9]

4.2 Renal Replacement Therapy (RRT) Types

Patients suffering from ESRD are bound to undergo RRT, the primary aim of which remains the prolongation of life in patients, especially in those eligible for renal transplantation. RRT therapies include allograft kidney transplantation, hemodialysis (HD) and peritoneal dialysis (PD). Allograft kidney transplantation (KT) is the preferred method of RRT, which is inadvertently complicated due to confined available and eligible organ donations. Non-absolute ineligibility for KT includes patients with limited life prognosis or multiple comorbidities, defined as high-risk for transplantation surgery with its associated risks and inadvertent immunosuppression.[9] Hemodialysis is the most common type of RRT, accounting for approximately 86% of ESRD patients.[10] During HD, metabolic, toxic byproducts, excreted normally by the kidneys, are removed from the systemic circulation through their passing by a semi-permeable membrane (hemodialysis machine). Hemodialysis requires vascular access to the systemic circulation, allowing for brisk blood flow inside and outside of the HD machine. Vascular access remains the "Achilles Heel" of ESRD patients undergoing HD and can be achieved through a variety of options (See 2.3. Vascular Access Options).[10] Peritoneal dialysis includes the catharsis of metabolic byproducts through the administration of a dialysis solution through a peritoneal catheter, filtering of accumulated byproducts through the peritoneal membrane and then discarding the fluid. Two types of PD are currently available, continuous ambulatory peritoneal dialysis and automated peritoneal dialysis, with the main difference regarding the ability to perform the fluid administration and dialysis at home or at a health facility by a machine.[11]

4.3. Vascular Access (VA) Options & Nomenclature

Hemodialysis vascular access remains one of the most troublesome aspects of ESRD patients' management, associated with various complications and reducing quality of life. Vascular access can be achieved through either creation of autogenous arteriovenous fistula (AVF), placement of a nonautogenous arteriovenous bridging graft (AVG) or through the insertion of a large bore, double lumen, central venous catheter, either temporary or permanent.[12] Each option bears advantages and disadvantages. Basic characteristics of each vascular access option include conduit type (autogenous, non-autogenous), location, configuration (translocation, transposition, looped, straight). Moreover, main outcomes associated with the technical success of vascular access include primary, assisted primary and secondary patency, as well as complications, including mainly thrombosis, infection and distal ischemic lesions, among others.[13]

An autogenous conduit describes a native vein derived from the patient, either translocated, transposed, or used in-situ. Non-autogenous conduits can be split into two categories, including prosthetic grafts, most common Dacron (polyester – **Figure II**) or expanded polytetrafluoroethylene (ePTFE - **Figure II**) and biografts, including human umbilical vein grafts or bovine heterografts. Regarding location, the arterial site of inflow is reported first, followed by the venous outflow site. The body location site of vascular access creation is also reported, while upper or lower extremity locations are further categorized based on specific site (eg. forearm, upper arm). Configuration types provide details in terms of the anastomotic connections, including transposition, translocation, looped or straight, referring to the conduit's course.[13]

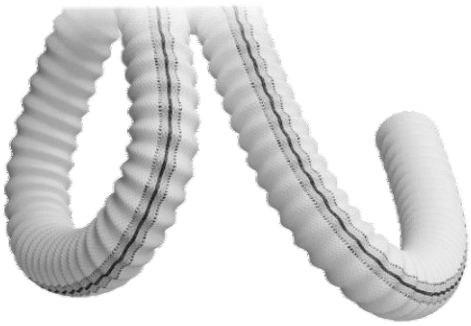

Figure II. Dacron (polyester) graft

Figure III. ePTFE graft

Central venous catheters (CVC) used for hemodialysis are a useful type of vascular access, bearing their own nomenclature in terms of duration of intended use, technical characteristics regarding the length and diameter as well as the vein of insertion. Regarding the catheter's intended duration of use, a temporary or a permanent one can be inserted, with temporary CVC utilized in short-term hemodialysis for acute kidney injury or until a permanent vascular access has been created and matured. Permanent CVC can be better described as tunneled, due to the creation of a subcutaneous tunnel through which the catheter traverses before being inserted into a large-lumen vein. Furthermore, tunneled CVC can be cuffed or noncuffed, with cuffed CVC being equipped with a cuff for promotion of further tissue ingrowth inside the subcutaneous tunnel.[14]

Current guidelines suggest an AV access (AVF or AVG) over the use of a CVC on most patients undergoing HD, due to the decreased risk of complications associated with this type of AV access, including patency related as well as infectious and non-infectious complications. However, a variety of parameters should be considered when deciding the type of AV access, as patient comorbidities, life-expectancy, patient preference and technical characteristics (vessel type and quality) all affect HD quality, patients' quality of life, morbidity and mortality.[15,16]

4.4 Arteriovenous Grafts

4.4.1. Types of Arteriovenous Grafts

Arteriovenous grafts pose as an attractive option for AV access. Advantages include earlier maturation when compared to AVF (2-3 weeks versus 6-8 weeks), lower early failure rates and easier cannulation. However, guidelines suggest that AVF should be considered the first AV access choice, as studies have suggested lower morbidity rates when compared to AVG.[15,16]

AVG ideally should be nonantigenic, equipped with a non-thrombogenic lumen, resistant to infection, provide timely healing of puncture sites and easy to access, either for initial puncture or in cases of thrombosis for graft thrombectomy.[13] Available AVG include biografts, such as bovine heterograft, cryopreserved saphenous vein, engineered human extracellular matrix compositions or human umbilical vein grafts and prosthetic grafts, including Dracron (polyester) and ePTFE grafts, as well as variants (trilaminate composition AVG, polyurethaneurea ("quick-cannulation" AVG) and siloxane additives, heparin bonding).[10] Currently, ePTFE AVG, firstly introduced over 40 years ago[17], are the most commonly implanted type of graft used for HD, due to its availability, high patency rates, ease of handling, quick puncture hole healing and nonantigenic properties, while bearing a higher risk of infection compared to biografts.[18] However, studies comparing ePTFE with Dacron or polyurethaneura AVG do not suggest the superiority of any type of AVG over the other in terms of patency and complication rates.[19,20]

4.4.2. Anatomic Location & Configuration of Arteriovenous Grafts

AVG can be implanted on the upper or lower extremities or on the chest or cervical region and can have a straight or looped configuration (**Figure IV**), depending on the distance and topography between the artery and vein to be used. Upper extremity AVG are most often opted for due to lower infection rates, quicker maturation duration and less frequent technical difficulties, while recent studies support the use of lower extremity AVG in patients where upper extremity vascular access cannot be established, with higher primary patency rates and lower postoperative complication rates.[21] Upper extremity vascular access most commonly includes radial artery to antecubital vein forearm (straight), brachial artery to antecubital vein forearm (looped), brachial artery to axillary vein upper arm (straight) and axillary artery to axillary vein upper arm (looped) access.[13] Lower extremity vascular access most commonly includes femoral artery to greater saphenous vein (loop) and popliteal artery to greater saphenous vein (straight). The effect of configuration type on AVG patency are scarce, relying on less modern studies, albeit in favor of loop configurations over straight AVG, reporting easier cannulation, higher patency rates and lower complication rates.[22,23]

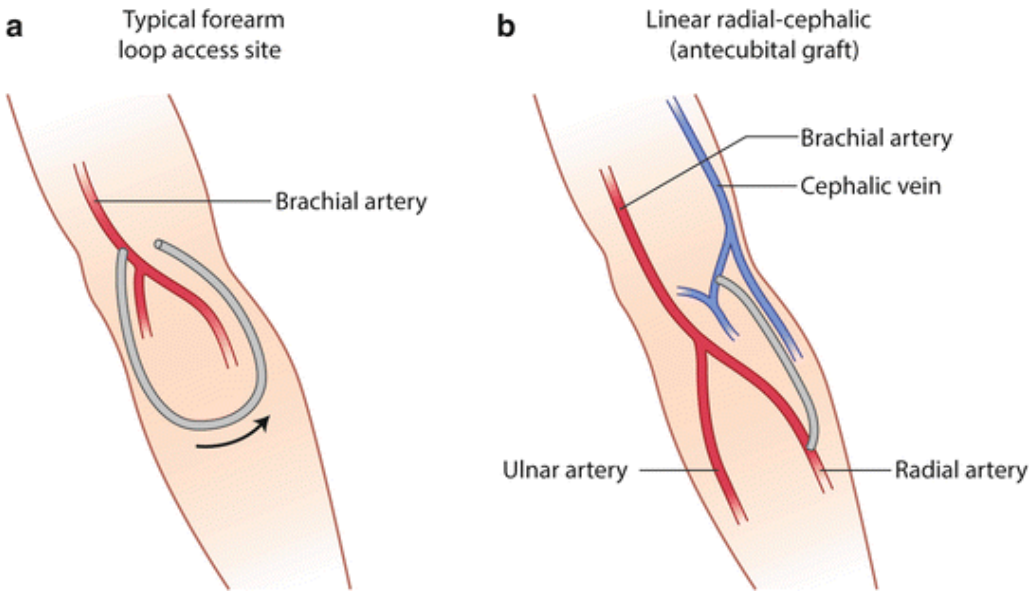

Figure IV. Looped (a) & Straight (b) AVG configuration

4.4.3. Primary & Secondary Patency of Arteriovenous Grafts

Primary AVG patency is defined as the time interval between AVG initial implantation until any open surgical or endovascular intervention designed for graft patency maintenance or re-establishment in case of graft thrombosis, or until AVG patency evaluation in case of absence of graft thrombosis.[14] Secondary AVG patency is defined as the time interval between open surgical or endovascular intervention for re-establishment of AVG patency until AVG abandonment due to thrombosis or other complications.[14] These represent the main outcomes through which AVG functionality is universally reported for improvement of perioperative patient outcomes.

Data on primary and secondary patency of AVG is available since the introduction of the modality. The lifelong effect of HD on the majority of CKD patients due to the very low frequency of renal transplantation availability, in addition to the increased life expectancy of these patients, ideally requires AVG with high primary and secondary patency rates. Primary patency rates are generally low, with decreasing rates over longer follow-up. Studies conducted during the last 15-years, including mainly ePTFE AVG with optimized antithrombotic technologies and engineering, report primary patency rates of 56%, 41%, 34% and 28% at 6, 12, 18 and 24-months of follow-up, respectively.[24] Reports from over 20-years ago suggest secondary patency rates following surgical or endovascular manipulations for re-establishment of patency at 76% and 55%, at 6 and 18-months of follow-up, respectively.[25] Unfortunately, most recent cumulative data derived from studies including solely newer generation of ePTFE AVG report secondary patency rates of 80%, 70%, 59% and 54% at 6, 12, 18 and 24-months of postoperative surveillance, respectively.[24] A meta-analysis including a variety of AVG (not solely reporting on ePTFE grafts) found primary and secondary patency rates of 40% and 60% at 24-months of follow-up, respectively.[26] Compared to

older studies, where reported secondary patency rates are ~33% at 18-months of follow-up, a trend towards better outcomes could be observed.[25] This observation could be the result of improvement of AVG technologies, including covalent heparin bonding at the luminal surface of ePTFE grafts as well as the gradual introduction of advanced endovascular means, including drug-coated and drug-eluting balloons and drug-coated covered stentgrafts, allowing for the timely treatment of thrombosed AVG with long-term, durable outcomes.[27,28] While re-establishing patency of a thrombosed AVG is generally associated with good immediate results, with technical success reported at 99%, durable solutions are needed.[29]

Data on the effect of antithrombotic therapy for primary and secondary patency of AVG, including mainly antiplatelet and anticoagulant medications, are contradictory. While some large cohort studies have supported that antiplatelet medication is associated with increased secondary patency rates, reporting an odds ratio of 0.81 (95% CI: 0.728 – 0.901, p = 0.0001) for longer secondary AVG patency,[30,31] randomized controlled trials on the effect of both antiplatelet and anticoagulant medication on AVG patency did not seem to have a positive effect on primary and secondary AVG patency, while increasing the risk for minor and major bleeding complications.[32,33]

4.4.4. Thrombosis & Infection of AVG

AVG Thrombosis: Thrombosis of an AVG should be managed in a timely fashion, aiming towards vascular access salvage. Several factors have been associated with AVG thrombosis, including hypotension, high hemoglobin target, hypercoagulability states, female sex, and diabetes mellitus.[34] AVG thrombosis can be treated by plain thrombectomy utilizing catheters specifically made for grafts, as well as by

endovascular means. Generally, thrombus accumulating in an AVG for a time period of over 5 days tends to require endovascular therapy for complete resolution and vascular access salvage. Randomized trials suggest comparable assisted primary patency outcomes between the two treatment modalities.[29] Pharmacological thrombolysis, pharmaco-mechanical thrombectomy and mechanical thrombectomy for AVG thrombosis provide better overall technical success rates compared to AVF thrombosis (99% versus 93%), albeit higher re-thrombosis occurrence in AVG.[35]

AVG Infection: Infection of an AVG is associated with high morbidity and mortality rates, possibly leading to sepsis alongside with suture line disruption and life-threatening bleeding in case of anastomoses rupture.[36] Routine HD is associated with higher rates of AVG infections, while transient bacteraemia from non-HD related infections is a known risk factor. Over 50% of AVG infections occur in the latter postoperative period, following AVG maturation.[16] The microorganisms most commonly involved in AVG, as in CVC, infections include Gram-positive cocci, with the most predominant being Staph. Aureus, Staph. Epidermitis, Strep. Viridans and Strep. Faecalis[37,38], while Gram-negative microorganism account for approximately 33% of AVG infections. Antimicrobial therapy alone is rarely sufficient for adequate infection control, with graft excision warranted for infection control.[36] Total excision insists of complete graft removal alongside artery repair, while subtotal or partial excision describe the partial removal of the AVG, leaving in place part of the graft, usually anastomosed with the inflow artery. Recent guidelines suggest broad-spectrum antibiotics for Gram-positive and Gram-negative bacteria and total excision in cases of AVG infections in patients with signs of sepsis, clinical signs of infection and presence of peri-graft fluid accumulated around the whole graft.[15,16] Partial excision of an AVG may be considered in infections with signs of well incorporated AVG, with no signs of

complete graft infection. However, literature strongly supports that total excision is associated with better outcomes regarding infection resolution, with a recurrence rate of 1.6% versus 19% for total and subtotal excision, respectively.[39,40] Insertion of a CVC is almost always warranted for HD until complete resolution of the infection and creation of a permanent vascular access solution is given.

5. MATERIALS & METHODS

5.1. Study Aim

The aim of the current study was to concentrate, upon systematic research, the current evidence on primary and secondary patency rates, as well as bleeding complications, on patients with an AVG for HD on any kind of antithrombotic medication and evaluate whether any antithrombotic regimen provides a positive or a negative effect on these outcomes. Main outcomes are primary and secondary patency rates, while bleeding complications are secondary outcomes.

5.2. Study Protocol

The study protocol of the current systematic review has been registered to PROSPERO (CRD42023401785). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 2020 Guidelines for Systematic Reviews and Meta-analyses were followed.[41] Randomized and non-randomized observational studies reporting outcomes on patients undergoing vascular access creation via AVG with or without concomitant antithrombotic (antiplatelet, anticoagulant) medication at the time of AVG placement for any indication were included in the analysis. Case reports, case series, studies on any language besides English, studies on deceased subjects, as well as studies reporting on experimental diagnostic models were rejected. Studies reporting on vascular access outcomes without separate data on AVG were excluded. Scientific Council approval was not acquired due to the nature of the study. Systematic literature search was executed by two investigators (K.T.D., P.N.) as per the Cochrane Handbook for Systematic Reviews and Interventions guidelines. Following extensive scrutiny of initial search results, a third investigator (G.K.) crosschecked the results. Data

extraction and methodological assessment was executed by two investigators (K.T.D., P.N.). Any discrepancies were resolved by a third (G.K.) investigator. A full-text review of all the included studies was conducted based on respective inclusion and exclusion criteria.

A data search of the English medical literature was executed, with an endpoint set for March 1st, 2023. The scientific databases PubMed (MEDLINE), SCOPUS and CENTRAL (Cochrane Database) were searched following clinically based questions, predefined as per protocol. The P.I.C.O. (patient; intervention; comparator; outcome) model was applied for providing a clinically guided, specific searching strategy.[42] The P.I.C.O. model guided questions based on which the systematic search of the databases was carried out is shown on **Table I**.

Table I. P.I.C.O Model

P	Patient, population or problem	Patients with chronic kidney failure requiring dialysis who underwent AV graft placement surgery.
I	Intervention, prognostic factor or exposure	Antithrombotic therapy administration (single antiplatelet, dual antiplatelet, anticoagulant)
C	Comparison of intervention	No antithrombotic therapy or Single antiplatelet therapy
O	Outcome you would like to measure or achieve	AV graft primary patency, Vascular Access Hemorrhage (VAH)
	What type of question are you asking?	Do dialysis patients who undergo AV graft placement and receive antithrombotic therapy have increased primary patency rates versus patients who do not receive antithrombotic therapy? Do dialysis patients who undergo AV graft placement and receive antithrombotic therapy have increased bleeding complications and bleeding-related AV graft failure? Is single antiplatelet therapy associated with lower AV graft primary patency rates compared to dual antiplatelet therapy? Is anticoagulant therapy associated with higher AV graft primary patency rates compared to single or dual antiplatelet therapy?

		Is anticoagulant and dual antiplatelet therapy associated with higher risk for VAH compared to single antiplatelet therapy?
	Type of study you want to find	Observational studies (Randomized, Non-randomized)

Footnote: P.I.C.O. (patient; intervention; comparison; outcome) model was used to define the clinical questions and clinically relevant evidence in the literature, VAH; Vascular Access Hemorrhage, AV; Arteriovenous

5.3. Search Strategy

The terms "chronic kidney failure", "dialysis", "hemodialysis", "arteriovenous graft", "AV graft", "antiplatelet therapy", "single antiplatelet therapy", "dual antiplatelet therapy", "SAPT", "DAPT", "anticoagulant therapy", "primary patency", "primary AV graft patency", "primary graft patency", "primary arteriovenous graft patency", "vascular access hemorrhage" and "AV graft bleeding" were used in various combinations, both as specific items as well as in MeSH Terms, as proposed by the Cochrane Handbook for Systematic Review and Interventions.[43] The complete search strategy and combinations of terms used based on each database's structured format is shown on Table II.

Table II. Search items per database.

PUBMED	(((((((chronic kidney failure) OR (chronic kidney failure[MeSH Terms])) OR ((dialysis) OR (dialysis[MeSH Terms]))) OR ((hemodialysis) OR (hemodialysis[MeSH Terms]))) OR ((arteriovenous graft) OR (arteriovenous graft[MeSH Terms]))) OR ((AV graft) OR (AV graft[MeSH Terms]))) AND (((((((antiplatelet therapy) OR (antiplatelet therapy[MeSH Terms])) OR ((single antiplatelet therapy) OR

	(single antiplatelet therapy[MeSH Terms])) OR ((dual antiplatelet therapy) OR (dual antiplatelet therapy[MeSH Terms])) OR ((SAPT) OR (SAPT[MeSH Terms])) OR ((DAPT) OR (DAPT[MeSH Terms])) OR ((anticoagulant therapy[Author]) OR (anticoagulant therapy[MeSH Terms]))) AND (((((((primary patency) OR (primary patency[MeSH Terms])) OR ((primary AV graft patency) OR (primary AV graft patency[MeSH Terms])) OR ((primary graft patency) OR (primary graft patency[MeSH Terms])) OR ((primary arteriovenous graft patency) OR (primary arteriovenous graft patency[MeSH Terms])) OR ((vascular access hemorrhage) OR (vascular access hemorrhage[MeSH Terms])) OR ((AV graft bleeding) OR (AV graft bleeding[MeSH Terms]))
SCOPUS	("chronic kidney failure" OR "dialysis" OR "hemodialysis" OR "arteriovenous graft" OR "AV graft") AND ("antiplatelet therapy" OR "single antiplatelet therapy" OR "dual antiplatelet therapy" OR "SAPT" OR "DAPT" OR "anticoagulant therapy") AND ("primary patency" OR "primary AV graft patency" OR "primary arteriovenous graft patency" OR "vascular access hemorrhage" OR "AV graft bleeding")
CENTRAL	#1 chronic kidney failure #2 [mh "chronic kidney failure"] #3 dialysis #4 [mh "dialysis"] #5 hemodialysis #6 [mh "hemodialysis"] #7 arteriovenous graft #8 [mh "arteriovenous graft"] #9 AV graft #10 [mh "AV graft"] #11 antiplatelet therapy #12 [mh "antiplatelet therapy"] #13 single antiplatelet therapy #14 [mh "single antiplatelet therapy"] #15 dual antiplatelet therapy

	#16 [mh "dual antiplatelet therapy"] #17 SAPT #18 [mh "SAPT"] #19 DAPT #20 [mh "DAPT"] #21 anticoagulant therapy #22 [mh "anticoagulant therapy"] #23 primary patency #24 [mh "primary patency"] #25 primary AV graft patency #26 [mh "primary AV graft patency"] #27 primary arteriovenous graft patency #28 [mh "primary arteriovenous graft patency"] #29 vascular access hemorrhage #30 [mh "vascular access hemorrhage"] #31 AV graft bleeding #32 [mh "AV graft bleeding"] #33 {OR #1-#10} #34 {OR #11-#22} #35 {OR #23-#32} #36 {AND #33-#35}

Footnote: DAPT; dual antiplatelet therapy, SAPT; single antiplatelet therapy, AV; arteriovenous.

Duplication screening was executed via automated tools (EndNote 20.2.1 X9, Clarivate), followed by two investigators independently (K.T.D., P.N.). Selection of included studies for final data extraction, based on data presented on manuscript full text as well as tables and figures, was undertaken as a final, secondary investigation.

5.4. Data Extraction

Data extraction and retention was undertaken on a standard Microsoft Excel spreadsheet. Included data were general study information (primary and secondary authors, study title, journal of publication, year of publication, study type, number of included centers, study aim, definition of reported outcomes). Additionally, patient

demographic data and clinical information [age, sex, comorbidities, type of AVG placed, anatomic region of AVG placement, type of antithrombotic medication administered, primary patency, secondary patency, AVG complications (stenosis, thrombosis,)] were also extracted.

5.5. Data Analysis

In case of available, hard data on either main or secondary outcomes, an appropriate statistical analysis will be undertaken. In case of heterogeneity between the included studies, bearing a statistical analysis impossible, a descriptive report of the outcomes will be undertaken.

5.6. Quality Assessment

All included studies underwent quality assessment utilizing the ROBINS-I[44] tool for non-randomized, observational studies or the ROB-II[45] tool for randomized, controlled clinical trials. Both evaluation models are suggested Cochrane tools for risk of bias judgement of studies included in systematic reviews and meta-analyses. Risk of bias is achieved through a series of signaling questions on trial design, conduct as well as reporting of outcomes and possible cofounders. The ROBINS-I tool is a quality assessment tool which applies a 7-domain evaluation model, providing a score of "low", "moderate", "serious" or "critical" risk of bias. Each domain addresses sections of possible bias, providing a "low", "moderate", "serious" or "critical" risk of bias score. The ROB-II tool assesses possible risk of bias via 5 domains, including selection,

performance, attrition, reporting and other possible factors, finally providing a “high”, “some concerns” or “low” risk of bias.

5.7. Definitions

Loss of patency was defined as the absence of thrill or bruit of the respective AVG, confirmed through imaging modalities such as duplex ultrasound or angiography, leading to the inability of normal HD. Major, intermediate or minor bleeding events were determined based on the description of each study.

6. RESULTS

The initial search yielded 506 studies, across the three electronic databases used. Following duplicate removal, conducted using automation tools (EndNote 20.2.1 X9, Clarivate) and by-hand, 59 studies were excluded. Title screening on the 447 studies led to the exclusion of 337 studies. Abstract screening included 110 studies, excluding 82 studies. Full-text screening was carried out, with 28 studies being evaluated for data extraction, while one study could not be retrieved from the electronic databases. A total of 19 studies were excluded. The reasons for exclusion were no reference on antithrombotic management on AVG (9 studies), no separate data on AVG outcomes (4 studies), report only on native AVF (4 studies), evaluation of post-mortem deceased subjects (1 study) and not available English draft (1 study). Full-text evaluation of the final 8 studies included appraisal of the included references for further publications missed during the initial search. Four studies that were initially missed were included, for a total of 12[30-33,46-53] studies included in the final analysis for data extraction. The screening process can be appreciated on **Figure V**.

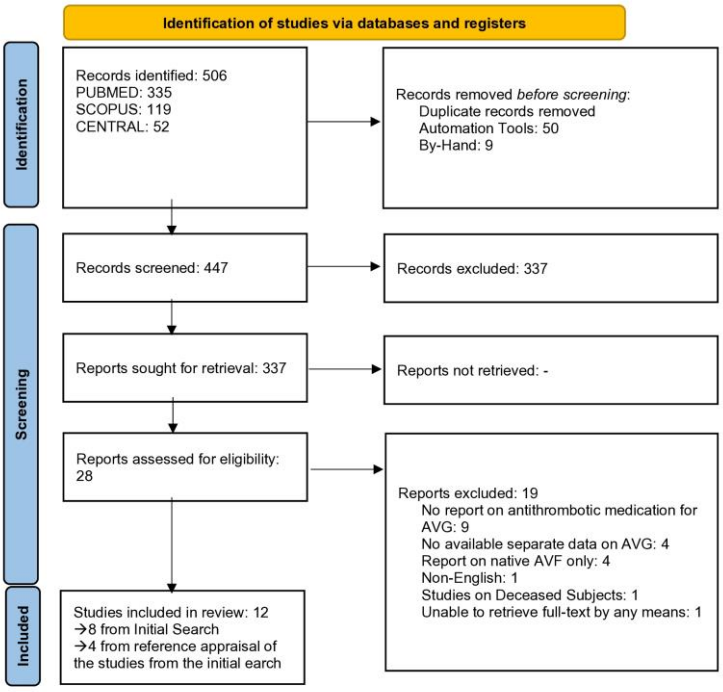

Figure V. PRISMA 2020 Flow Diagram for Systematic Reviews and Registries[41]

Types of studies – Time Span – AVG anatomic location

The final 12 studies included in were published during a 28 year time period, from 1994 to 2022. Patient recruitment into the trials/studies occurred during a 37 year time period, spanning from 1982 unti 2019. Seven[32,33,46,47,49-51] studies were randomized, single or double blind trials, while five[30,31,48,52,53] studies were non-randomized, observational, with either prospective or retrospective data collection. Six studies were multicenter[30-33,48,53] and six studies were single center[46,4749-52]. Eleven[30-33,46-52] studies reported on PTFE or ePTFE AVG, while one study[53] reported on both Dacron and ePTFE AVG placed. All the included studies reported on patients with AVG placement on the upper limb, either in the forearm or in the upper arm **(Table III)**.

Table III. Study characteristics, AVG type & anatomic location.

Author	Year	Journal	Study Type	Study Period	Center (Number of Centers)	Graft Type	AVG Location
Sreedhara, R, et al[46]	1994	Kidney Int	Randomized, Double Blind	1982-1988	Single	ePTFE	Upper limb
Schmitz PG, et al[47]	2002	JASN	Randomized, Double Blind	1996-1998	Single	ePTFE	Upper limb
Crowther MA, et al[32]	2002	JASN	Randomized, Double Blind	1997-2000	Multicenter (3)	PTFE	Upper limb
Saran R, et al.[48]	2002	Am J Kidney Dis	Observational, Prospective	1996-2001	Multicenter (133)	PTFE	Upper limb
Kaufman JS, et al[33]	2003	JASN	Randomized, Double Blind	1998-1999	Multicenter (30)	PTFE	Upper limb
D'Ayala M, et al[49]	2008	Ann Vasc Surg	Randomized, Single Blind	2004-2006	Single	PTFE	Upper limb
Yeh CH, et al[50]	2017	JVA	Randomized, Single Blind	2006-2009	Single	PTFE	Upper limb
Tayebi P, et al[51]	2018	Electron Physician	Randomized, Double Blind	2014-2014	Single	ePTFE	Upper limb
Locham S, et al[31]	2018	J Nephrol	Observational, Retrospective	2011-2017	Multi (NA)	ePTFE	Upper limb
Hsu YH, et al[30]	2018	PLoS ONE	Observational, Retrospective	2002-2012	Multi (NA)	ePTFE	Upper limb
Kim CH, et al[52]	2019	JCM	Observational, Prospective	2009-2014	Single	ePTFE	Upper limb
Kumpfbeck, et al[53]	2022	AVS	Observational, Retrospective	2011-2019	Multi (NA)	Dacron, ePTFE	Upper limb

Footnote; ePTFE; expanded Polytetrafluoroethylene, NA; not available

Aim of Studies – Antithrombotic Regimens – Primary & Secondary Patency Rates

Seven studies[30-32,47,49,51,52] reported solely on primary patency rates, one study[50] reported solely on secondary patency rates, while four studies[33,46,48,53] presented outcomes on both primary and secondary patency rates. All studies included reported on the definition of primary or secondary patency loss diagnosis, including clinical examination with absence of thrill or bruit as well as imaging detection of AVG thrombosis via either ultrasound or angiographic methods, without determining the number and experience of clinicians associated with the diagnosis **(Table IV)**.

Aspirin (acetylsalicylic acid) was the most commonly evaluated antithrombotic medication, in a total of eight studies[30,31,33,46,48,50-52], either alone or in combination with other antithrombotic medication. Clopidogrel was evaluated in four studies[30,31,33,50], warfarin was evaluated in three studies[32,48,53], dipyridamole was evaluated in three studies[30,46,51], while unfractioned heparin (iv)[49], DOACs (dabigatran, rivaroxaban)[53], and fish-oil[47] was evaluated in one study, respectively. All antithrombotic regimens evaluated were administered in various doses pre each study protocol. Ten studies[31-33,36,47,49-53] included placebo/control groups of patients for comparison of interventions, while two studies[30,48] did not. Antithrombotic regimens, dosages and patient cohorts based on receiving intervention can be appreciated on **Table V**.

Table IV. Study Aim & Type of Patency evaluated

Author	Aim (AVG specific)	Patency Rate evaluated
Sreedhara, R, et al[46]	Effect of dipyridamole and/or aspirin on AVG primary and secondary patency rates	Primary, Secondary
Schmitz PG, et al[47]	Effect of fish-oil (80% ω-3) on primary AVG patency rates	Primary
Crowther MA, et al[32]	Effect of low-dose warfarin (max. 4mg) on primary AVG patency rates	Primary
Saran R, et al.[48]	Effect of aspirin and warfarin on primary and secondary AVG patency rates	Primary, Secondary
Kaufman JS, et al[33]	Effect of combined aspirin and clopidogrel on primary and secondary patency rates.	Primary, Secondary
D'Ayala M, et al[49]	Effect of intravenous UFH on vascular access primary patency	Primary
Yeh CH, et al[50]	Effect of aspirin and clopidogrel on secondary AVG patency rate	Secondary
Tayebi P, et al[51]	Effect of aspirin and dipyridamole on primary AVG patency rate	Primary
Locham S, et al[31]	Effect of aspirin and clopidogrel on primary AVG patency rate	Primary
Hsu YH, et al[30]	Effect of antiplatelets (aspirin, clopidogrel, dipyridamole) or anticoagulants on primary AVG patency rate	Primary
Kim CH, et al[52]	Effect of aspirin on AVG primary patency rate	Primary
Kumpfbeck, et al[53]	Effect of anticoagulants (warfarin, dabigatran, rivaroxaban) on AVG patency and wound complication rates	Primary, Secondary

Footnote; AVG; arteriovenous graft, UFH; unfractioned heparin,

Table V. Type of antithrombotic treatment & dose

Author	Intervention	Dose	Placebo/ Control	Antithrombotic Medication Regimen
Sreedhara, R, et al[46]	Dipyridamole, Aspirin	Dipyridamole: 225mg (75 tid), Aspirin 325mg (qd)	Yes	1. Dipyridamole, 2. Aspirin, 3. Dipyridamole + Aspirin, 4. Placebo
Schmitz PG, et al[47]	Fish-Oil(44% eicosapentaenoic acid, 24% docosahexaenoic acid, and 10 to 12% other oils),	4000mg (4x1000mg, qd)	Yes	1. Fish Oil 2. Placebo
Crowther MA, et al[32]	Warfarin	4mg (qd) for an INR of 1.4-1.9	Yes	1. Low-Dose Warfarin 2. Placebo
Saran R, et al.[48]	Aspirin, Warfarin	Aspirin: Na, Warfarin: NA	No	1. Aspirin 2. Warfarin
Kaufman JS, et al[33]	Aspirin, Clopidogrel	Aspirin: 325mg (qd), Clopidogrel 75mg (qd)	Yes	1. Aspiring + Clopidogrel 2. Placebo

Table V. (continued)

D'Ayala M, et al[49]	UFH	5.000 U (qd - during Vascular Access surgery)	Yes	1. UFH (iv) 2. Placebo
Yeh CH, et al[50]	Aspirin, Clopidogrel	Aspirin: 100mg (qd), Clopidogrel: 75mg (qd)	Yes	1. Aspirin or Clopidogrel 2. Control
Tayebi P, et al[51]	Aspirin, Dipyridamole	Aspirin: 80mg (qd), Dipyridamole: 75mg (qd)	Yes	1. Aspiring 2.Aspirin + Dipyridamol 3. Placebo
Locham S, et al[31]	Aspirin, Clopidogrel	Aspirin: NA, Clopidogrel: NA	Yes	1. Aspirin, 2. Clopidogrel 3. Control
Hsu YH, et al[30]	Antiplatelet, Anticoagulants	Antiplatelets: NA, Dipyridamole: NA Anticoagulant: NA	No	1. Antiplatelet, 2. Dipyridamole 3. Anticoagulant
Kim CH, et al[52]	Aspirin	Aspirin: NA	Yes	1. Aspirin 2. Control
Kumpfbeck, et al[53]	Anticoagulants (warfarin, dabigatran, rivaroxaban)	NA	Yes	1. Anticoagulants 2. Control

Footnote: qd; once daily, bd; bi-daily, tid; thrice-daily, U; units, NA; not available, UFH; unfractioned heparin, iv; intravenous

Patients' Cohort Characteristics

A total of 90.165 ESRD patients requiring HD on a permanent basis were included in sum of studies. Of those, at least 22.364 were patients with new AVG placement or prior AVG placement (one study[52] did not provide data on the exact number of patients undergoing HD by an AVG). Follow-up duration spanned from one to 12 months, or until complete loss of AVG patency. Inclusion criteria in the majority of the included studies were patients on permanent HD, over 18 years of age, who agreed to the participation in each respective study, regarding the randomized trials. Specific data on the inclusion and exclusion criteria for each study can be found in **Supplementary Table I**. Available characteristics in regard to patient age, sex, HD via new or prior AVG, and duration of follow-up, when available, are presented on **Table VI**.

Table VI. Patient Characteristics, AVG and duration of FU

Author	Total Number (Patients)	AVG Number	Mean Age	Males	New AVG	Prior AVG	Follow-Up (months)
Sreedhara, R, et al[46]	96	96	54.5 (19-84)	45	85	11	18 or until AVG loss of patency
Schmitz PG, et al[47]	24	24	53±4	11	24	0	12 or until AVG loss of patency
Crowther MA, et al[32]	107	107	65.6 (24-86)	61	107	0	42 months or until AVG loss of patency, study closure or death
Saran R, et al.[48]	1511	1944	61.9±14.9	772	NA	NA	NA
Kaufman JS, et al[33]	200	200	61±12	195	96	104	6
D'Ayala M, et al[49]	112	31	NA	NA	31	0	3
Yeh CH, et al[50]	216	216	65.5±11	99	0	216	72 or until AVG loss of patency
Tayebi P, et al[51]	60	60	55.69±13.9	33	60	0	>36
Locham S, et al[31]	24847	5385	63	2362	1182	4203	9.85 ± 8.2
Hsu YH, et al[30]	34354	8421	NA	3248	8421	0	>12 (up-to120)
Kim CH, et al[52]	881	NA	57.9±13.4	NA	NA	NA	30
Kumpfbeck, et al[53]	27757	5880	NA	NA	5880	NA	6

Footnote; AVG; arteriovenous graft, FU; follow-up, NA; not available

Primary & Secondary Patency Rates (PPR, SPR)

Aspirin

Five[31,46,48,51,52] evaluated the effect of aspirin alone on primary and/or secondary patency rates. Regarding PPR, one study[31] found improved PPR for aspirin users (47% vs 41%, p=0.08), two studies[46,51] found worse PPR for aspirin users, without statistical significance, while two studies[33,52] examined the outcome as a Hazard Ratio and found no significant differences between patients receiving and not receiving aspirin. Regarding SPR, one study [48] reported results in favor of aspirin in terms of AVG thrombosis (RR:0.7, p<0.001). In terms of adjunctive administration of aspirin and other antiplatelet medication, one study[33] reported on a trend towards improved SPR for aspirin and clopidogrel users, without statistical significance, and one study[46] reported improved PPR for patients receiving aspirin and dipyridamole versus patients not receiving any antiplatelet therapy (75±11% vs 58±13%). **(Table VII)**

Clopidogrel

Four studies[30,31,33,50] reported on the effect of clopidogrel on PPR and SPR, either alone or in conjunction with other antithrombotic regimens. Regarding PPR, two studies[30,31] reported favorable outcomes in patients receiving versus not receiving clopidogrel, out of which one[31] examined solely clopidogrel and one[30] among other antiplatelet medication (51% vs 41%, p=0.08[31], adjusted Odds Ratio (OR):0.81, p<0,05[30]), while one study[33] showed no difference between patients receiving aspirin and clopidogrel versus the control cohort. Regarding SPR, one study[50] showed statistically significant worse outcomes for patients receiving aspiring or clopidogrel (HR: 2.13, p=0.025).

Dipyridamole

Three studies[30,46,51] examined PPR of patients receiving dipyridamole. Two[30,46] of the included studies reported outcomes in favor of dipyridamole, either being administered alone or in conjunction with aspiring (79±9% vs 58±13%, p=0.062[46], adjusted OR:0.78, p=0.36). One study[51] did not report differences between patient cohorts. **(Table VII)**

Warfarin

Three studies[32,48,53] examined the effect of warfarin on PPR. Two studies reported not statistically significant, yet unfavorable outcomes for patients receiving warfarin (27% vs 39%[32], 81.2% vs 83%[53]), while one study[48] reported statistically significant worse outcomes for the cohort receiving warfarin, describing an increased risk for loss of patency (RR:1.33, p=0.009). **(Table VII)**

Unfractioned Heparin (UFH)

One study[49] examined the effect of intravenous UFH infusion during AVG placement on short-term (1 month) PPR and reported on worse PPR rates for patients receiving the intervention (84% vs 100%, p=0.99). **(Table VII)**

DOAC (dabigatran, rivaroxaban)

DOACs were evaluated for their effect on PPR in conjunction with warfarin in one study[53] without clear separation on patient cohort receiving either warfarin or DOACs

(dabigatran, rivaroxaban). The respective study showed unfavorable outcomes for patients on anticoagulant therapy, without statistical significance. **(Table VII)**

Fish Oil

One study[47] reported on the effect of fish oil administration on PPR, showing statistically significant improved PPR of patients receiving fish-oil versus those not receiving (75.6% vs 14.9%, $p<0.05$). **(Table VII)**

Major Bleeding Complications

A total of nine studies[31,33,46,49,50,51,53] evaluated the risk of major bleeding on patients receiving antithrombotic medication. Two studies, one examining the effect of aspirin and dipyridamole[46] and one the effect of aspirin and clopidogrel[50] found no statistically significant increase in risk of bleeding events between patients receiving and not receiving the intervention. From the remaining seven studies, one[33] found a negative impact of aspiring plus clopidogrel on major bleeding events (HR: 1.98 (95% CI 1.19-3.28, p=0.07), one[51] found a negative impact of aspiring plus dipyridamole (10% vs 0%, p=0.33), while one study[31] found similar major bleeding rates (2.3% vs 2%, $p<0.05$) for patients receiving either aspirin or clopidogrel. Both warfarin[32] (6 vs 0 major bleeding events, p=0.03) and UFH[49] (14 vs 0 major bleeding events, p=0.08) were associated with increased risk for major bleeding. Finally, one study[53] reported on increased risk for wound infection on patients receiving any kind of anticoagulant (warfarin, dabigatran, rivaroxaban), with an OR: 3.01 (95% CI, 2.4-3.7%, $p<0.001$).

Table VII. Primary & Secondary AVG Patency Rates

Author	Antithrombotic Medication Regimen	PPR (Intervention Group)	PPR (Placebo/Control Group)	SPR (Intervention Group)	SPR (Placebo/Control Group)
Sreedhara, R, et al[46]	1. Dipyridamole 2. Aspirin 3. Dipyridamole + Aspirin 4. Placebo	1. 79±9% (p=0.062) 2. 20±12 % (p=0.34) 3. 75±11%	4. 58±13%	-	-
Schmitz PG, et al[47]	1. Fish Oil 2. Placebo	1. 75.6% (p<0.05)	2. 14.9% (p<0.05)	-	-
Crowther MA, et al[32]	1. Low-Dose Warfarin 2. Placebo	1. 27% (p=0.74)	2. 39% (p=0.74)	-	-
Saran R, et al.[48]	1. Aspirin (among others) 2. Warfarin (among others)	2. RR: 1.33 (p=0.009)	-	1. RR: 0.7 (p<0.001)	-
Kaufman JS, et al[33]	1. Aspiring + Clopidogrel 2. Placebo	1. HR: 0.81 (95% CI, 0.47-1.4)	-	1. HR: 0.52 (95% CI, 0.22-1.26)	-
D'Ayala M, et al[49]	1. UFH (iv) 2. Placebo	84%	100% (p=0.99)		
Yeh CH, et al[50]	1. Aspirin or Clopidogrel 2. Control	-	-	78.8% (p=0.11)	69% (p=0.11)
Tayebi P, et al[51]	1. Aspirin 2.Aspirin + Dipyridamol 3. Placebo	1. 50% 2. 85% (p=NA)	3. 85% (p=NA)		

Table VII. (continued)

Locham S, et al[31]	1. Aspirin 2. Clopidogrel 3. Control	1. 47% (p=0.08) 2. 51% (p=0.08)	3. 41% (p=0.08)	-	-
Hsu YH, et al[30]	1. Antiplatelet, 2.Dipyridamole 3. Anticoagulant	1. aOR: 0.81 (p<0.05), 2. aOR: 0.78 (p=0.36), 3. aOR: 1.44 (p=0.13)	-	-	-
Kim CH, et al[52]	1. Aspirin 2. Control	HR: 1.11 (0.59-2.08) (p=0.75)	-	-	-
Kumpfbeck, et al[53]	1. Anticoagulants (warfarin, dabigatran, rivaroxaban) 2. Control	1. 81.2% 2. 83% (p=0.106)	-	-	-

Footnote: PPR; Primary Patency Rate, SPR; Secondary Patency Rate, HR; Hazard Ratio, RR; Relative Risk, aOR; adjusted Odds Ratio, CI; Confidence Interval

Risk of Bias

Randomized Controlled Trials

Seven[32,33,46,47,49-51] out of the 12[30-33,46-53] included studies were prospective, randomized trials, while the remaining five[30,31,48,52,53] were observational, prospective or retrospective. Regarding the randomized controlled trials, based on the evaluation applying the ROB-II tool, two had a score of "Low" risk of bias, four had a score of "Some concerns" risk of bias, while one study had a score of "High" risk of bias. Studies evaluated with a "Some concerns" risk of bias were done so due possible confounding in regards either to the randomization process not clearly stated and explained, or due to deviation from the intended intervention. The one study evaluated with a "High" risk of bias score had unclear report of outcomes (**Figure VI**).

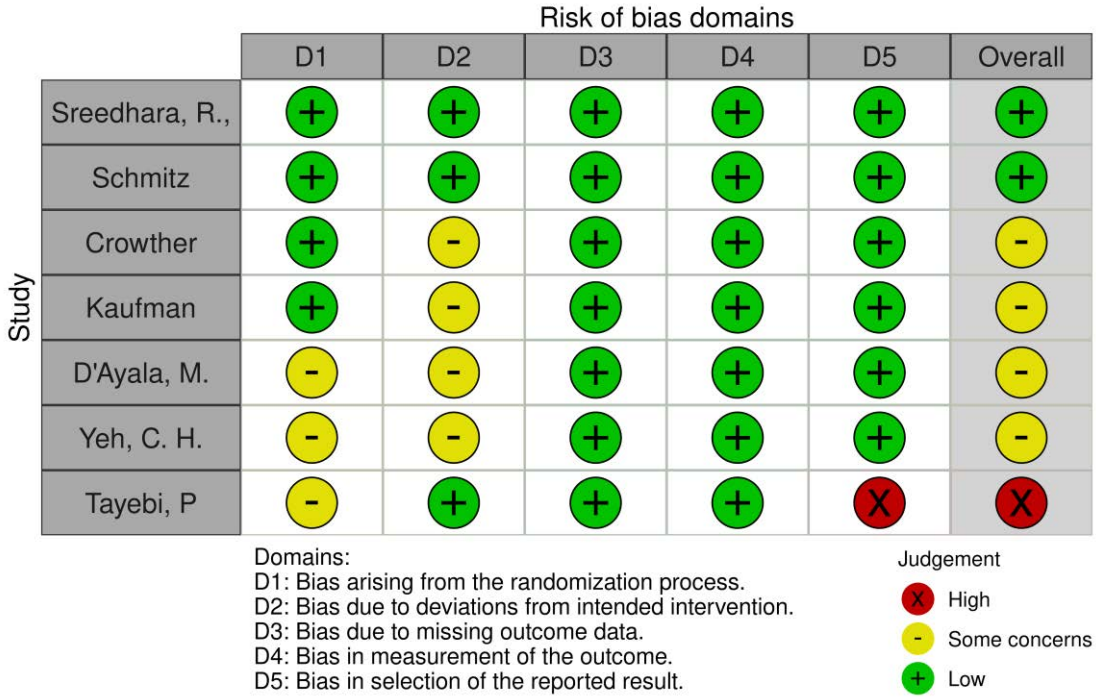

Figure VI. ROB-II evaluation for randomized, controlled trials.

Observational Studies

Regarding the five[30,31,48,52,53] observational studies, four of them were evaluated to bear a "Serious" risk of bias, while one of them was accredited a "Critical" risk of bias. The main reasons for these evaluations were increased risk of bias in confounding factors

such as report on timing and type of AVG placed, number and experience of surgeons operating on the patients, initiation and discontinuation of antithrombotic medications and details on the hemodialysis conditions and details. Additionally, bias in the selection of the participants, without clear report on possible excluded patients, critical missing data regarding need for AVG thrombosis diagnosis as well as the selection of the reported results, led to "Serious" and "Critical" risk of bias score assessment (**Figure VII**).

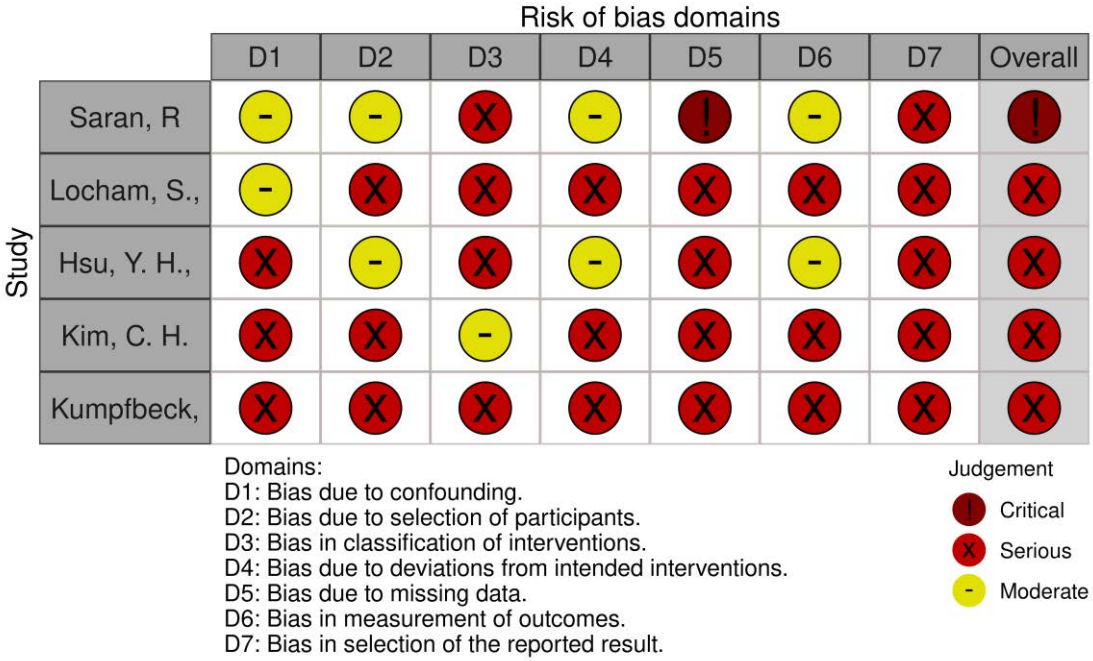

Figure VII. ROBINS-I evaluation for observational studies.

7. DISCUSSION

Both thrombosis and bleeding complications pose potentially clinically significant events for patients with AVG undergoing hemodialysis.[54] AVG thrombosis is primarily associated with neointimal hyperplasia leading to graft lumen narrowing and alongside other pathophysiological mechanisms, including platelet activation and aggregation, endothelial injury, turbulent blood flow as well as coagulation cascade activation, leads to vascular access failure.[55] Bleeding complications are often attributed to a variety of mechanisms, including intraoperative and perioperative factors, pseudoaneurysm (arterial, vein) formation, antithrombotic medication, infectious erosion of vessel wall, as well as technique related hemorrhage, due to inappropriate needle puncture.[56] The widespread use of antithrombotic medication for any kind of associated indication, in addition to the contradictory state of hypercoagulability and high hemorrhagic risk of ESRD patients demand extreme cautiousness in the management of such regimens in this patient population. Personalized risk assessment is of critical importance, something highlighted in recent guidelines by both the KDOQI as well as the ESVS.[15,16]

Regarding the use of antiplatelet medication, results from our review found contradictory evidence. Four studies[30,31,33,46] reporting favorable outcomes regarding either PPR[30,31,33] for patients who received aspirin, clopidogrel or dipyridamole (alone or in a combination), or SPR[46] for patients receiving aspirin or dipyridamole. Three studies[48,51,52] presented data with no difference between patient cohorts receiving and not receiving antiplatelet medication in terms of PPR, while one study[50] suggested worse SPR for patients on aspirin or clopidogrel. This heterogeneity in outcomes could most likely be attributed to a variety of factors, including patient heterogeneity, study design (randomized – observational, single-double blind, prospective – retrospective),

duration of exposure to the intervention, as well as anecdotal evidence on AVG management during HD. Moreover, the variable efficacy of antiplatelet medication could be associated with patient comorbidities as well as graft type used, given that the time span of the included studies is over 30 years, with notable differences in surgical techniques and dialysis specific factors.

The risk of serious major bleeding complications in patients receiving antiplatelet medication has also been examined in five studies in the present analysis[31,33,46,50,51] Results are also contradictory, with three[31,46,50] studies reporting no differences in major bleeding events and two studies reporting on higher bleeding rates amongst patients receiving aspirin, clopidogrel of dipyridamole (especially in a combination)[33,51]. As is the case in PPR and SPR, a variety of factors can possible contribute to the heterogeneity of the outcomes. Differences in study design, patient individualized risk profile, variability in bleeding complications, duration of follow-up postoperative surveillance could affect the reported outcomes. Additionally, study populations characteristics, such as geographic variability, access to healthcare during a bleeding complication, as well as traditional demographic characteristics including age and sex could partially account for such differences in produced outcomes. Finally, antiplatelet medication, specifically in ESRD patients possible receiving other medication, could result in interactions unaccounted for, ultimately leading to diverse outcomes.

Anticoagulant medication could theoretically pose a preventative measure for AVG thrombosis, given the mechanisms of action on the intrinsic, extrinsic and common pathways on the coagulation cascade, in addition to their effect on platelet aggregation.[59] Results from the included studies[32,49,53] however suggest that warfarin, while under close INR surveillance, UFH and DOACs (dabigatran, rivaroxaban), administered under a randomized controlled trial setting, did not improve PPR or SPR.

Contrariwise, the administration of anticoagulants was associated with increase major bleeding events, in both the cases of intravenous use of UFH[49] and in a low-dose warfarin administration setting[32]. Interestingly, almost 10% of patients receiving low-dose warfarin developed major hemorrhagic events, despite close INR monitoring[32]. Unless patients are receiving anticoagulant medication for other absolute indications, no basis exists for their prescription on the ground of prevention of AVG thrombosis, as is depicted in available guidelines[15,16,57,58].

Fish-oil, mainly due to its omega-3 fatty acid composure and its anti-proliferative, antioxidant, and vasodilatory effects, has been investigated as a possible preventative measure for AVG thrombosis.[47] Two randomized controlled trials have examined the use of fish-oil on PPR of patients with AVG, presenting results either in favor[47], or neutral[60] regarding its effect. Similar studies on patients with AVF or under the need for CVC placement showed no significant differences between intervention (fish-oil) and placebo patient cohorts[61]. The available literature provides insufficient evidence for the strong recommendation of fish-oil as a routine preventative measure for AVG primary and secondary patency maintenance.

Available guidelines by several scientific societies have presented recommendations on the use of antiplatelet or anticoagulant medication for both primary as well as secondary patency. Guidelines by the ESVS, the International Society for Nephrology (ISN), the National Institute for Health and Care Excellence (NICE) as well as the KDOQI guidelines, regarding the use of antiplatelet therapy, suggest that such medication, focusing on aspirin, could provide some benefits.[15,16,57,58] However, the current available evidence are not enough to support the routine prescription and administration of such medication, as the risk of bleeding to benefit in patency conservation ratio is unbalanced. Moreover, all the abovementioned societies are unequivocally against the

use of anticoagulants, such as warfarin and DOACs for the prevention of AVG thrombosis.

8. CONCLUSION

Thrombosis and bleeding complications are significant concerns for patients with arteriovenous grafts (AVGs) undergoing hemodialysis. Managing antithrombotic therapy in these patients requires careful consideration due to their heightened bleeding risks and variable responses to treatment. Individualized antithrombotic algorithms, tailored to each patient thrombotic and hemorrhagic risk, are crucial for better patient safety, due to the idiosyncrasy of ESRD patients, while randomized, controlled trials with cautious confounder control are essential for robust outcomes on AVG thrombosis and bleeding complications prevention.

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10. SUPPLEMENTARY MATERIAL

Supplementary Table I. Inclusion & Exclusion Criteria

Author	Inclusion Criteria (AVG specific)	Exclusion Criteria
Sreedhara, R, et al[46]	ESRD - AVG with either new ePTFE AVG or prior ePTFE AVG thrombosis	Uncontrolled hypertension, gastrointestinal ulcer, hemophilia, von Willebrands disease, other bleeding disorder or cancer, aspirin or dipyridamole hypersensitivity
Schmitz PG, et al[47]	ESRD - AVG with new ePTFE	Gastrointestinal bleeding, Chronic anticoagulation (warfarin), pregnancy, terminal illness, life-threatening disease
Crowther MA, et al[32]	ESRD - AVG with new PTFE	Recent major hemorrhage (within the previous 6 months); defined as bleeding requiring transfusion, bleeding in a critical site (retroperitoneal or intracranial), bleeding associated with hypovolemia or requiring admission to hospital, or bleeding resulting in 20 g/L (2 g/dl) drop in the hemoglobin., allergy to warfarin, persistent thrombocytopenia (<50.000 mm3), inability to take oral medications, on warfarin for other indication, expectation for renal recovery or life expectancy <2 months, lack of informed consent or inability to give consent
Saran R, et al.[48]	ESRD - AVG with either new PTFE or prior PTFE under aspirin or warfarin for other indications	NA
Kaufman JS, et al[33]	At least 21 years old, thrice-weekly hemodialysis, PTFE on upper limb	Blood loss requiring either hospitalization or transfusion in the previous 3 months, advanced proliferative diabetic retinopathy, life expectancy <24months, uncontrolled hypertension, platelet count <100.000 mm3, INR>1.3, On antithrombotic medication for other indications,
D'Ayala M, et al[49]	ESRD - AVG with new PTFE	AVG revision surgery (initial loss of primary access)
Yeh CH, et al[50]	ESRD - Prior AVG with loss of patency undergoing salvage surgery	Prior antiplatelet medication, unsuccessful initial salvage surgery
Tayebi P, et al[51]	ESRD - New AVG placement	<20 years old, pregnancy, antiplatelet medication contraindications
Locham S, et al[31]	ESRD - AVG without prior salvage surgery	NA
Hsu YH, et al[30]	ESRD - New AVG placement	VA failure <3 months, renal transplant, peritoneal dialysis, unclear sex data, <20 years old, HD<90 days)
Kim CH, et al[52]	ESRD - New AVG placement, >18 years old	ESRD not supplying consent, death <30 days of study, salvage procedure for AVG, not using AVG 3 months into commencement of HD
Kumpfbeck, et al[53]	ESRD – New or prior AVG placement	NA

Footnote: ESRD; end-stage renal disease, AVG; arteriovenous graft, PTFE; Polytetrafluoroethylene, HD; hemodialysis