Efficacy and Safety of Clopidogrel in the Prevention of Primary Failure of Arteriovenous Fistula in Patients with End-Stage Renal Disease: A Systematic Review

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ABSTRACT

Background: *Arteriovenous fistula (FAV) is the most widely used vascular access for end-stage renal disease (ESRD) patients undergoing routine hemodialysis in Indonesia. However, FAV can become dysfunctional before it is used for the initiation of hemodialysis, a condition known as primary failure. Clopidogrel is an anti-platelet aggregation that has been reported to reduce the incidence of primary failure in FAV compared to other anti-platelet aggregation agents. Through this systematic review, we aimed to assess the role of clopidogrel to the incidence of primary FAV failure and the risk of bleeding in ESRD patients.* ***Methods:*** *A literature search was carried out to obtain randomized Control Trial studies conducted since 1987 from Medline / Pubmed, EbscoHost, Embase, Proquest, Scopus, and Cochrane Central without language restrictions. Risk of bias assessment was performed with the Cochrane Risk of Bias 2 application.* ***Results:*** *All of the three studies involved indicated the benefit of clopidogrel for the prevention of AVF primary failure. However, all of the studies have substantial differences. Abacilar's study included only participants with diabetes mellitus. This study also administered a combination of clopidogrel 75 mg and prostacyclin 200 mg/day, while Dember's study gave an initial dose of clopidogrel 300 mg followed by daily dose 75 mg and Ghorbani's study only gave clopidogrel 75 mg/day. Ghorbani and Abacilar started the intervention 7-10 days before AVF creation, while Dember started 1 day after VAF creation. Dember gave treatment for 6 weeks with an assessment of primary failure at the end of week 6, Ghorbani's treatment lasted for 6 weeks with an assessment at week 8, while Abacilar gave treatment for one year with an assessment at weeks 4 after AVF creation. In addition, the prevalence of bleeding did not differ*

between the treatment and control groups. ***Conclusion:*** *Clopidogrel can reduce the incidence of primary FAV failure without significant increase of bleeding events.*

Keywords*: arteriovenous fistula, primary failure, clopidogrel, end-stage renal disease, systematic review.*

INTRODUCTION

Arteriovenous fistula (FAV) is the most widely used vascular access by 75% of End Stage Renal Disease patients undergoing routine hemodialysis in Indonesia.[1] It is often used due to the lower risk of dysfunction and infection with long-term use compared to other vascular accesses.[2] However, newly created FAV cannot be used immediately and might become dysfunctional before the initiation of hemodialysis. This condition also known as primary failure is a major problem in ESRD patients undergoing FAV creation. The incidence of thrombosis is found in 65-85% of FAV, hence, it is estimated that thrombosis plays a major role in the incidence of primary failure.[3] The administration of heparin or aspirin reportedly does not reduce the prevalence of primary failure. Meanwhile, clopidogrel is an anti-platelet anti-aggregation that has a pleiotropic effect and reduces FAV primary failure.[4–6] To date, there is no recommendation for the use of clopidogrel in preventing FAV primary failure. Patients with ESRD are also at high risk for bleeding due to disturbances in coagulation factors. Therefore, we aimed to assess the role of clopidogrel to the incidence of FAV primary failure and the risk of bleeding in ESRD patients undergoing FAV surgery.

METHODS

This is a systematic review conducted based on The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). We registered our protocol on The International Prospective Register of Systematic Reviews (PROSPERO) with ID CRD42022323934.

Inclusion and Exclusion Criteria

The inclusion criteria were Randomized Control Trials on subjects aged > 18 years, studies using clopidogrel for the treatment arm, with primary FAV failure as the primary outcome, and bleeding as the secondary outcome. The exclusion criteria were active bleeding, known coagulopathy, thrombocyte < 75.000/ mm^3 and pregnancy.

Search Strategy

A comprehensive literature search was conducted by authors (WA and LU) from January until August 2022 using the databases Medline/Pubmed, EbscoHost, Embase, Proquest, Scopus, and Cochrane Library databases as well as manual searches on studies published since 1987 without language restrictions. The search used Medical Subject Heading (MeSH) and a combination of keyword synonyms (Boolean mode) for FAV, primary failure, and clopidogrel. The FAV synonym used was Arteriovenous Fistula OR Arteriovenous Shunt OR Hemodialysis Access OR Dialysis Access, with MeSH namely "Arteriovenous Shunt, Surgical". Meanwhile, the synonym used for clopidogrel was Clopidogrel OR P2Y12 inhibitor OR P2Y12 antagonist OR antiplatelet OR antithrombotic OR anti-aggregation OR antiaggregant, where MeSH is "Clopidogrel". The synonym for primary failure was Patency OR Maturation OR Immature OR Stenosis OR Thrombosis OR Fail, while the MeSH used was "Vascular Patency".

Extraction Data

Data extracted by authors (WA and LU) from the studies included the name of the first author, year of publication, the number of samples, average age, gender, type and dose of treatment given, time of assessment of primary failure, the proportion of primary failure, degree of bleeding and its proportion in each group, mortality, as well as the bleeding time before and after treatment, the data were then summarized in a tabular form.

Risk Assessment Bias

The assessment of the risk of bias was carried out using the Cochrane Risk of Bias 2

Table 1. Keywords for searching the database.

Database	Keywords	Filter	Number of Literature
Pubmed	"Arteriovenous Shunt, Surgical"[Mesh] OR "arteriovenous fistula*"[tiab] OR "arteriovenous shunt"[tiab] OR "hemodialysis access"[tiab] OR "dialysis access"[tiab] AND "Clopidogrel"[Mesh] OR clopidogrel[tw] OR "P2Y12 inhibitor*"[tiab] OR "P2Y12 antagonist*"[tiab] OR "antiplatelet"[tiab] OR "antithrombotic"[tiab] OR "antiaggregation"[tiab] OR "antiaggregant"[tiab] AND "Vascular Patency"[Mesh] OR "patency"[tiab] OR maturation[tiab] OR immature[tiab] OR stenosis[tiab] OR thrombosis[tiab] OR "fail*"[tiab]	Human, age ≥ 19 years old	79
EBSCOhost	(MM "Arteriovenous Shunt, Surgical") OR arteriovenous fistula(ab) OR arteriovenous shunt(ab) OR hemodialysis access(ab) OR dialysis access(ab) AND (MM "Clopidogrel") OR clopidogrel[text] OR P2Y12 inhibitor (ab) OR P2Y12 antagonist(ab) OR antiplatelet(ab) OR antithrombotic(ab) OR antiaggregation(ab) OR antiaggregant(ab) AND (MM "Vascular Patency") OR patency(ab) OR maturation(ab) OR immature(ab) OR stenosis(ab) OR thrombosis (ab)OR failure(ab)"	Human, age ≥ 19 years old	116
ProQuest	(MESH.EXACT("Arteriovenous Shunt, Surgical") OR ab("arteriovenous fistula") OR ab("arteriovenous shunt") OR ab("hemodialysis access") OR ab("dialysis access")) AND (MESH.EXACT("Clopidogrel") OR ft(clopidogrel) OR ab("p2y12 inhibitor") OR ab("p2y12 antagonist") OR ab(antiplatelet) OR ab(antithrombotic) OR ab(antiaggregation) OR ab(antiaggregant)) AND (MESH.EXACT("Vascular Patency") OR ab(patency) OR ab(maturation) OR ab(immature) OR ab(stenosis) OR ab(thrombosis) OR ab(fail*))	Human, article	151
Embase	'arteriovenous shunt, surgical'/exp OR 'arteriovenous fistula':ab OR 'arteriovenous shunt':ab OR 'hemodialysis access':ab OR 'dialysis access':ab AND 'clopidogrel'/exp OR clopidogrel OR 'p2y12 inhibitor':ab OR 'p2y12 antagonist':ab OR antiplatelet:ab OR antithrombotic:ab OR antiaggregation:ab OR antiaggregant:ab AND "Vascular Patency"/exp OR patency OR maturation OR immature OR stenosis OR thrombosis OR fail*	('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'cohort') AND (humans)/lim	48
Scopus	"arteriovenous fistula" OR "arteriovenous shunt" OR "hemodialysis access" OR "dialysis access" AND clopidogrel OR "P2Y12 inhibitor" OR "P2Y12 antagonist" OR antiplatelet OR antithrombotic OR anti-aggregation OR antiaggregant AND "Vascular Patency" OR patency OR maturation OR immature OR stenosis OR thrombosis OR fail	"Randomized controlled trial" OR " Clinical trial" OR "Cohort"	171
Cochrane	(MeSH descriptor: [Arteriovenous Shunt, Surgical] explode all trees OR "arteriovenous fistula", "arteriovenous shunt", "hemodialysis access", "dialysis access") AND (MeSH descriptor: [Clopidogrel] explode all trees OR clopidogrel, "P2Y12 inhibitor", "antiplatelet drug", "antiplatelet agent", "antiaggregation agent", "antiaggregation drug") AND (MeSH descriptor: [Vascular Patency] explode all trees OR patency OR maturation OR immature OR stenosis OR thrombosis OR failure)	Trials	305

application. Differences between the authors (WA and LU) were discussed until an agreement was reached or consultation with the third author (IR). Publication bias was analyzed by the Rank correlation test and the Egger regression test.

RESULTS

The search on 6 databases generated 496 literatures. 147 duplicate literatures were removed. There were 348 irrelevant articles based on title and abstracts were removed. Assessment for eligibility based on full text literatures, resulted in the exclusion of 9 articles, with 7 being non-RCT study reports, and 2 other articles did not include clopidogrel in the studies. Therefore, 3 articles remained and were reviewed further.. The literature search flow is shown according to the PRISMA flow chart. We did the last search on 13 July 2022.

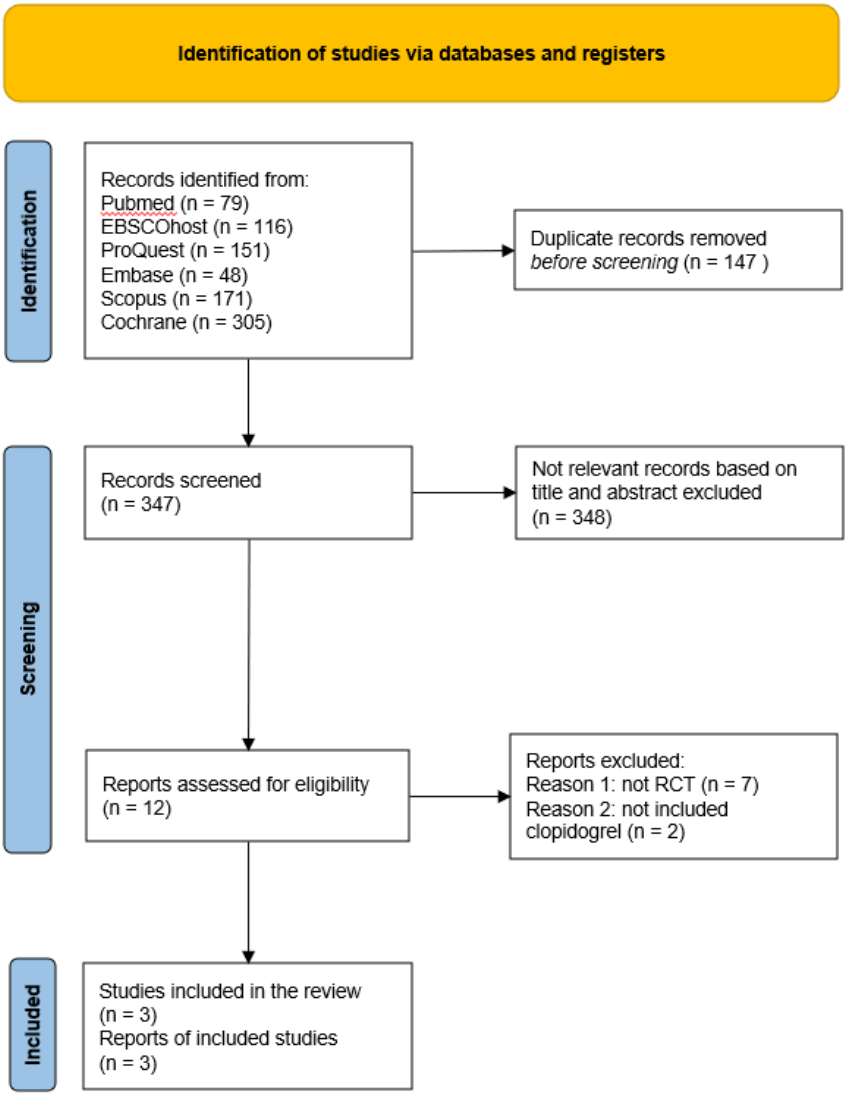

Figure 1. Study flow chart according to PRISMA.

Characteristics of Study

This systematic review involved 3 RCT studies with substantial differences. All participants in the Abacilar study were diabetes mellitus, in contrast to Dember and Ghorbani's study which involved less than 50% of participants with diabetes mellitus. Furthermore, Abacilar administered a combination of clopidogrel 75 mg and prostacyclin 200 mg/day, while Dember gave an initial dose of clopidogrel 300 mg followed by daily dose 75 mg and Ghorbani only gave clopidogrel 75 mg/day. Ghorbani and Abacilar started the intervention 7-10 days before AVF creation, while Dember started 1 day after AVF creation. There were also differences in the duration of intervention and the time for the assessment of AVF primary failure. Dember gave treatment for 6 weeks with an assessment of primary failure at the end of week 6, Ghorbani's treatment lasted for 6 weeks with an assessment at week 8, while Abacilar gave treatment for one year with an assessment at weeks 4 after AVF creation.[4–6]

Based on the three studies involved, the incidence of bleeding in the intervention group was similar to placebo group. The number of major bleeding events between the two groups was the same but the incidence of minor bleeding was slightly higher in the intervention group than in the control group. In Ghorbani's study, there was no significant difference between bleeding time before and after intervention. A similar result was found regarding mortality in both groups based on $p > 0.99$ (Dember) and $p = 0.47$ (Ghorbani).

Table 2. Characteristics of the study included in systematic review.

Study	Number of Participants		Average Age (years)		Male Gender		Diabetes mellitus		Type of Treatment (Duration)	Primary Failure Assessment	Primary Failure		
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control			Treatment	Control	P-value
Dember et al, 2008[4]	441	436	52,7 (±14.7)	54,5 (±14.4)	63.1%	61.9%	49.2%	47%	Clopidogrel 300 mg the first day, then 75 mg/day (42 days)	Day 42	12.2%	19.5%	0.18 (RR 0.63)
Ghorbani et al, 2009[5]	40	46	44,23 (±3.36)	45,8 (±2.84)	51.6%	51.6%	15.1%	11.8%	Clopidogrel 75 mg/day (42 days)	Day 56	5.2%	21.6%	0.03 (HR 0.72)
Abacilar et al, 2015[6]	50	46	54,23 (±2.6)	55,8 (±2.84)	68%	69.5%	100%	100%	Clopidogrel 75 mg and prostacyclin 200 mg daily (365 days)	Day 28	8%	30.4%	0.001 (HR 0.82)

Table 3. Comparison of bleeding events in the treatment and the control group.

No.	Study	Major Bleeding		Minor Bleeding		Mortality		Bleeding Time Before Treatment		Bleeding Time After Treatment	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
1.	Dember et al, 2008[4]	7 (1.6%)	7 (1.6%)	6 (1.4%)	5 (1.2%)	4 (0.9%)	4 (0.9%)	No data	No data	No data	No data
2.	Ghorbani et al, 2009[5]	0	0	7 (7.4%)	7 (7.5%)	2 (2.1%)	2 (2.1%)	8.1±0.3 minutes	8.4±0.6 minutes	8.5±0.4 minutes	8.6±0.3 minutes
3.	Abacilar et al, 2015[6]	0	0	9 (18%)	6 (13%)	0	0	No data	No data	No data	No data

Risk of Bias

Based on Cochrane's Risk of Bias 2 application, Ghorbani's research had a moderate risk of bias (some concerns) because it did not explain sequence generation process and concealment in detail. Ghorbani only provided a few variables on baseline characteristic that does not show comprehensive equality, and still shows p-value to express difference. Meanwhile, other studies had a low risk of bias.

Publication Bias

Assessment of publication bias of the three articles were done with Rank correlation tests and Egger regression tests. The results for each test were $p = 1.00$ and $p = 0.446$. A p-value < 0.05 in both tests indicates publication bias, and the results of the two tests were $p > 0.05$.[9]

Table 4. Assessment risk of bias based on Cochrane's Risk of Bias 2

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Dember	Clopidogrel	Placebo	AVF Primary Failure						
Ghorbani	Clopidogrel	Placebo	AVF Primary Failure						
Abacilar	Clopidogrel and prostacyclin	Placebo	AVF Primary Failure						

D1 : Randomization process
D2 : Deviations from the intended interventions
D3 : Missing outcome data
D4 : Measurement of the outcome
D5 : Selection of the reported result

Low risk
Some concerns
High risk

DISCUSSION

This systematic study involved three randomized controlled trials with a total of 1048 subjects with mean age being below 65 years. Based on the results, patients above 65 years and underwent FAV surgery have a higher risk of vascular access failure than those aged less than 65 years. This is associated with reduced blood flow and a smaller cross-section of blood vessels, especially in patients with comorbidities such as coronary heart and peripheral vascular disease, as well as diabetes mellitus.[10] Lok et al (2005), reported that patients aged 65 years or above are 1.7 times at risk of experiencing primary failure.[11] Most of the subjects in this systematic study were male, this is associated with a tendency for a larger cross-section of blood vessels in males compared to females.[12,13]

The average number of patients with diabetes mellitus in the Ghorbani, Dember, and Abacillar studies was 13.45%, 48.1%, and 100%, respectively.[4-6] According to Lin, diabetes alone does not predispose an individual to primary FAV failure. However, older adults with diabetes might have an increased risk of primary failure.[14] Afsar showed that diabetic patients with HbA1c less than 7 have a risk of primary failure with no significant difference from patients without diabetes, while diabetes mellitus patients with HbA1c more than 7 have a 2.8 times higher risk for primary failure.[15]

Administration of higher initial dose than the daily dose does not have a significant effect on primary FAV failure. The initial dose is usually given to speed up the onset of action and the time to achieve the maximum anti-aggregation effect. A single dose of 75 mg clopidogrel has an onset of 24 hours and reaches its maximum anti-aggregation effect in 4-7 days. Meanwhile, the administration of clopidogrel 300 mg has an onset of action of 2 hours and reaches its maximum anti-aggregation effect after 24 hours.[16] In Dember's study, administration of clopidogrel 300 mg 1 day after surgery followed by 75 mg/day did not provide a significant reduction in the incidence of primary FAV failure compared with the control group.[4] This can be attributed to the inflammatory process that occurred due to the vascular trauma during the FAV creation operation 1 day earlier.

The administration of clopidogrel 75 mg/day 7-10 days before FAV operation such as in the Ghorbani study culminated in a better reduction in the incidence of primary failure than in Dember. This can be attributed to the action of clopidogrel which has reached its maximum anti-aggregation effect at the time of the FAV preparation operation. Therefore, the incidence of thrombosis due to the postoperative inflammatory process is suppressed. Similar to Ghorbani's study, Abacillar who performed the treatment 7-10 days before FAV surgery also achieved significant results in decreasing primary FAV failure in the treatment group compared to the control. However, Abacilar added prostacyclin 200 mg/day, a derivative of arachidonic acid which is a vasodilator and also anti-platelet aggregation. As a vasodilator, prostacyclin can reduce the risk of primary failure by decreasing shear stress, which in turn reduces the risk of inward remodeling (stenosis).[6,17]

Previous reports suggested pleiotropic effect of clopidogrel as a vasodilator. Clopidogrel may also improve endothelial function as well as anti-inflammation caused by the release of NO and decreased levels of proinflammatory cytokines, including IL-1α, IL-2, IL-6, IL-13, TNF-α, and TNF-β thereby reducing vascular remodeling and the risk of vascular stenosis.[18–21]

There was no difference in the incidence of bleeding between the treatment and the control group presumably due to the mean age of the subjects in each study which was less than 65 years. Age over 65 years is a risk factor for bleeding due to the administration of anti-platelet aggregation.[22]

The limitation of this study is that it involved only three RCT studies and the differences in each study. However, the three studies above had a low risk of publication bias based on Rank correlation and Egger regression tests.

CONCLUSION

The administration of clopidogrel can reduce the incidence of primary FAV failure in patients with end-stage renal disease (ESRD). The incidence of bleeding in patients with ESRD who received clopidogrel was not different from

the control group. Further research is needed for application in daily clinical practice, especially to assess various factors (like age, gender and diabetes melitus) that can affect the risk of primary FAV failure and bleeding following clopidogrel administration. For example, clopidogrel daily dose 75 mg since 7-10 days before AVF creation until hemodialysis initiation.

CONFLICT OF INTEREST

The authors declare that this article has no conflict of interest

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