Systematic Review / Meta-analysis

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Comparison of efficacy and safety of sarpogrelate-based anti-platelet therapy with non-sarpogrelate-based anti-platelet therapy following arterial endovascular therapy: a systematic review

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Objective: Sarpogrelate is a selective serotonin/5-hydroxytryptamine 2A receptor antagonist used in the management of peripheral artery disease (PAD). The drug has emerged as a promising choice for medical management post-endovascular therapy (EVT) due to its anti-platelet aggregation, vasoconstriction, and anti-vascular smooth muscle proliferation properties. The aim of the meta-analysis is to evaluate the efficacy and safety of sarpogrelate-based APT following arterial EVTs in PAD.

Material and methods: PubMed, Google Scholar, Scopus, and the Cochrane were systematically searched from inception to December 2023. Any randomized controlled trial studies in English that evaluated the efficacy and safety of sarpogrelate-based APT after EVT in patients with PAD was included. Data on the restenosis rate, target lesion revascularization (TLR), and safety parameters were extracted and studied. The pooled differences in efficacy and safety parameters between sarpogrelate-based APT and non-sarpogrelate-based APT was calculated using the relative risk (RR) with a 95% CI.

Results: A total of three randomized controlled trials were included out of 354 articles obtained through a literature search. No significant differences were observed in the risk of restenosis (RR = 0.74, 95% CI = 0.55–1.00, $P = 0.954$) and TLR (RR = 0.76, 95% CI = 0.47–1.23 , $P = 0.476$) among patients being treated with sarpogrelate and non-sarpogrelate-based APT. Likewise, sarpogrelate-based APT had a similar safety profile as non-sarpogrelate-based APT.

Conclusion: Sarpogrelate-based APT can be considered an effective alternative to clopidogrel-based conventional APT after EVTs. However, there is a huge need for a larger multicenter, multinational, and multiethnic global trial with sufficient participants in order to produce generalizable findings.

Keywords: anti-platelets, clopidogrel, efficacy, peripheral artery disease, safety, sarpogrelate

Introduction

Peripheral artery disease (PAD) is characterized by the narrowing and/or blockade of arteries other than the coronary arteries. PAD can present in different patterns with the involvement of various upper and lower limb arteries, the aorta, carotid arteries, vertebral arteries, celiac and mesenteric arteries, and renal arteries[1]. PAD affects more than 200 million people worldwide[2]. PAD is also associated with coronary artery disease (CAD) and cerebrovascular disease due to the sharing of risk factors such as smoking, dyslipidemia, hypertension, hyperglycemia, etc[3]. As the burden of risk factors increased, the number of patients with PAD increased by up to 28.7% in low- and middle-income countries. When present, PAD first manifests as intermittent

HIGHLIGHTS

- Sarpogrelate-based APT has a similar restenosis rate as non-sarpogrelate-based APT after EVT in PAD.
- Sarpogrelate-based APT has a similar target lesion revascularization as non-sarpogrelate-based APT after EVT in PAD.
- The safety profile of sarpogrelate-based APT is comparable to non-sarpogrelate-based APT in PAD following EVT.
- A larger multicenter, multinational, and multiethnic global trial to demonstrate the efficacy and safety of sarpogrelate-based therapy is warranted.

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claudication, which progresses to rest pain, tissue loss, gangrene, and ultimately results in the amputation of extremities[3–6].

In order to prevent the loss of limbs and thus-arising disability and minimize the risk of acute cardiovascular thrombotic events in patients with PAD, various medical and surgical strategies are employed. One of such broad categories of interventions in PAD is endovascular therapy (EVT), which includes techniques such as stent insertion and balloon angioplasty. Following EVT, anti-platelet therapy (APT) is recommended to prevent early thrombosis, maintain the patency of the vessels, and also avert major adverse cardiovascular events in the future[1,7,8]. Commonly, aspirin- or clopidogrel-based monotherapy or double APT with both combined is commonly used for these purposes. According to the 2016 American Heart Association/American College of Cardiology (ACC/AHA) and the 2017 European Society of Cardiology (ESC)/European Society for Vascular Surgery (ESVS) guidelines, the use of aspirin and clopidogrel for 1–12 months, with a minimum of 1 month after EVTs, is recommended[9,10]. Despite this, the use of clopidogrel has produced some adverse events, such as the inability to prevent restenosis of lesions, increased bleeding propensity when combined with aspirin, and clopidogrel resistance[11,12]. Even with the APT, the risks of limb and cardiovascular events after the EVT remain considerable. Adverse limb events, including revascularization and acute limb ischemia, are the common reasons behind the hospitalization of PAD patients after EVT[13,14]. Therefore, the optimal antithrombotic agent for arterial EVTs remains undiscovered. A newer anti-platelet drug, sarpogrelate, a selective serotonin/5-hydroxytryptamine (5-HT) 2A receptor antagonist, is being increasingly used in the management of PAD. The drug has emerged in medical management post-EVT due to its anti-platelet aggregation, vasodilation, and anti-vascular smooth muscle proliferation properties[15,16]. Newer studies have assessed the efficacy and safety of sarpogrelate in improving the prognosis of PAD following EVT. Hence, we conducted a systematic review of the currently available literature to evaluate the efficacy and safety of sarpogrelate-based APT following arterial EVTs in PAD.

Methods

Registration of research, quality assessment and ethical compliance

The current systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Supplemental Digital Content 1, http://links.lww.com/MS9/A584) guidelines[17]. This review was found to be of moderate quality as per the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR2, Supplemental Digital Content 2, http://links.lww.com/MS9/A585) critical appraisal tool[18]. The review was registered in the PROSPERO register. Ethical approval and informed consent were not necessary because the study was a systematic review. However, all the primary studies included in the review were checked for ethical approval from the review committee and informed consent from the study participants.

Search strategy

We performed a systematic literature search of the PubMed, Google Scholar, Scopus, and Cochrane databases to identify relevant articles for review. Studies published in English from the inception to December 2023 were searched for using the following MeSH terms and keywords: "sarpogrelate", "endovascular therapy", "endovascular intervention", "arterial intervention", "peripheral arterial disease", "peripheral vascular disease", "anti-platelet therapy", "atherosclerosis", "aspirin", and "clopidogrel". The last search was conducted on January 1, 2024. The PubMed search and Embase search were conducted after the identification of corresponding appropriate MeSH terms and Emtree terms, respectively. Boolean operators "OR" and "AND" were used as required between the MeSH and Emtree terms to search for the articles in each database. The detailed search strategy is provided in the Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A586. We also sought the reference list of each of the included studies to identify other potential articles of interest.

Study selection criteria

The selection process involved an assessment of the abstracts and the content of the articles using the following inclusion criteria: (1) randomized controlled trial studies in English that evaluated the efficacy and safety of sarpogrelate-based APT after EVT in patients with PAD; (2) reported on at least one parameter of either efficacy or safety of sarpogrelate-based APT.

The exclusion criteria were: (1) studies of the use of sarpogrelate in patients with conditions other than PAD; (2) case series, letters, commentaries, and review articles, and; (3) missing or insufficient data on the outcomes, and full-text irretrievable articles.

The selection of the studies for systematic review was performed independently by two separate reviewers. Any disagreements in the study selection were resolved through the discussion among all the authors. Additionally, we used Endnote 20.0.1 Library to remove any duplicate articles.

Data extraction

A data extraction spreadsheet was created on Microsoft Excel version 2016 (Microsoft Corp.) to extract the data under different headings as follows: author, publication year, study country, study design, age, sample size, comparator/control drug, restenosis rate, target lesion revascularization (TLR), amputations, bleeding complications, overall mortality rates, and miscellaneous adverse drug reactions.

The parameters of the efficacy of sarpogrelate-based APT were restenosis rate and TLR. Restenosis was defined as greater than 50% luminal reduction of the initially treated PAD lesion on angiography or peak systolic velocity greater than 2.5 on duplex ultrasound at follow-up. TLR was defined as the need for subsequent intervention in the previously treated patient due to restenosis. Other endpoints of sarpogrelate-based therapy discussed in our review included frequency of amputations, bleeding complications, overall mortality rates, and miscellaneous adverse drug reactions in patients after EVT.

Risk of bias assessment

We used the Cochrane risk of bias tool in order to assess the quality of the RCTs included in our review. The tool comprises a total of seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective

reporting, and other biases. Each item was divided into low-risk, unknown, and high-risk[19]. The assessment of the included studies was calculated independently by two separate reviewers. Any dilemmas regarding the quality assessment were resolved with the discussion among the authors.

Data analysis and synthesis

We used STATA version 16.0 (StataCorp) for statistical analysis. We calculated the pooled difference in restenosis rate, TLR, rate of amputations, bleeding events, adverse drug reactions, and mortality between sarpogrelate-based APT and non-sarpogrelate-based APT using the relative risk (RR) with a 95% CI. We pooled data using either a random-effects or fixed-effects model. We evaluated the statistical heterogeneity across the selected studies using the I^2 index (0–40%: not important; 30–60%: moderate heterogeneity; 50–90%: substantial heterogeneity; 75–100%: considerable heterogeneity)[20]. When I^2 index was 50% or less, meta-analysis was performed using a fixed-effect model. We applied DerSimonian and Laird's random-effects model to conduct the analysis when I^2 was greater than 50%. We generated forest plots with 95% CIs to illustrate the overall weighted mean estimations. Additionally, we performed a sensitivity analysis by omitting each individual study sequentially to check the stability and robustness of the pooled outcomes.

Results

Study characteristics

Our literature search identified 354 articles, of which three[21–23] (569 participants) met the eligibility criteria and were included in the systematic review and meta-analysis. The results of the study selection are shown in Figure 1. Chen *et al.*[21] and Han *et al.*[22] compared the safety and efficacy of sarpogrelate-based APT with the conventional clopidogrel-based APT whereas Soga *et al.*[23] compared the sarpogrelate-based therapy with the non-sarpogrelate-based APT in PAD patients. All of the included studies consisted of subjects who underwent femoropopliteal EVT. All three studies were conducted in Asian population from South Korea, China, and Japan. The follow-up period of the study ranged from 6 months to a year. The characteristics of the included studies are briefly provided in Table 1.

Efficacy of sarpogrelate in PAD following EVT

All three studies included in this review measured the efficacy of sarpogrelate in PAD after EVT in terms of restenosis rate/patency rate, target lesion revascularization (TVR), and amputation events post-EVT. Primary patency was defined as the state of a treated vessel with no restenosis or repeat vascularization at follow-up. The frequency of restenosis in both groups was determined by subtracting the number of primary patent cases from the total number of cases.

Restenosis rate

All of the included studies have reported the restenosis rate as a parameter of the efficacy of the use of sarpogrelate after EVT. Two RCTs, each by Han *et al.*[22] and Chen *et al.*[21], compared the restenosis rate between sarpogrelate-based APT and conventional clopidogrel-based APT. On the other hand, an open-label RCT by Soga *et al.*[23] reported the primary patency as a primary measure of the efficacy of sarpogrelate-based APTs and compared it with the non-sarpogrelate-based APTs. The meta-analysis showed no significant differences in the risk of restenosis among patients being treated with sarpogrelate and non-sarpogrelate-based APT (RR = 0.74, 95% CI = 0.55–1.00 I^2 = 0%, $P = 0.954$) (Fig. 2).

Target lesion revascularization (TLR)

TLR is the next common parameter utilized by the studies to compare the efficacy of sarpogrelate-based APT with conventional APT. The incidence of TLR in femoropopliteal lesions was not statistically different between the experimental group and the control group, according to all three RCTs[21–23]. The meta-analysis showed no significant differences in the risk of TLR among patients being treated with sarpogrelate and non-sarpogrelate-based APT (RR = 0.76, 95% CI = 0.47–1.23 I^2 = 0%, $P = 0.476$) (Fig. 3).

Amputation and amputation-free survival

Three RCTs included in our review have also compared the occurrence of amputations between the experimental (sarpogrelate) group and the control (clopidogrel) group. None of the RCTs showed statistically significant differences in the rates of amputation between the two groups. Overall, the risk of amputation in patients taking sarpogrelate-based APT after EVT is minimal and comparable to that in patients taking clopidogrel-based APT (RR = 0.62, 95% CI = 0.10–3.77, I^2 = 24.9%, $P = 0.249$).

Safety of sarpogrelate in PAD following EVT

The safety of sarpogrelate-based APT has been assessed by all studies selected in this review. Studies have reported the safety of sarpogrelate in terms of bleeding, all-cause mortality, and miscellaneous serious adverse events.

Risk of bleeding

The risk of bleeding with the use of sarpogrelate is inconsistent in the literature. The first RCT by Soga *et al.*[23] observed a significantly higher incidence of serious bleeding in the sarpogrelate group compared to the clopidogrel group. The study recommended against using sarpogrelate as a first-line anti-platelet drug after EVT due to its potential to cause life-threatening bleeding. On the other hand, two subsequent RCTs by Chen *et al.*[21] and Han *et al.*[22], demonstrated that the risk of bleeding in sarpogrelate users is not different from the clopidogrel users. The pooled analysis also confirmed that there is no statistically significant differences in the risk of bleeding between sarpogrelate users and non-sarpogrelate users (RR = 0.64, 95% CI = 0.05–8.97, I^2 = 58%, $P = 0.098$). The forest plot of the pooled analysis is provided in the Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A586.

All-cause mortality

The all-cause mortality rate in patients taking sarpogrelate after EVT is minimal and comparable to that in patients taking conventional APT. Overall, pooled analysis demonstrated that all-cause mortality was similar between the experimental group and

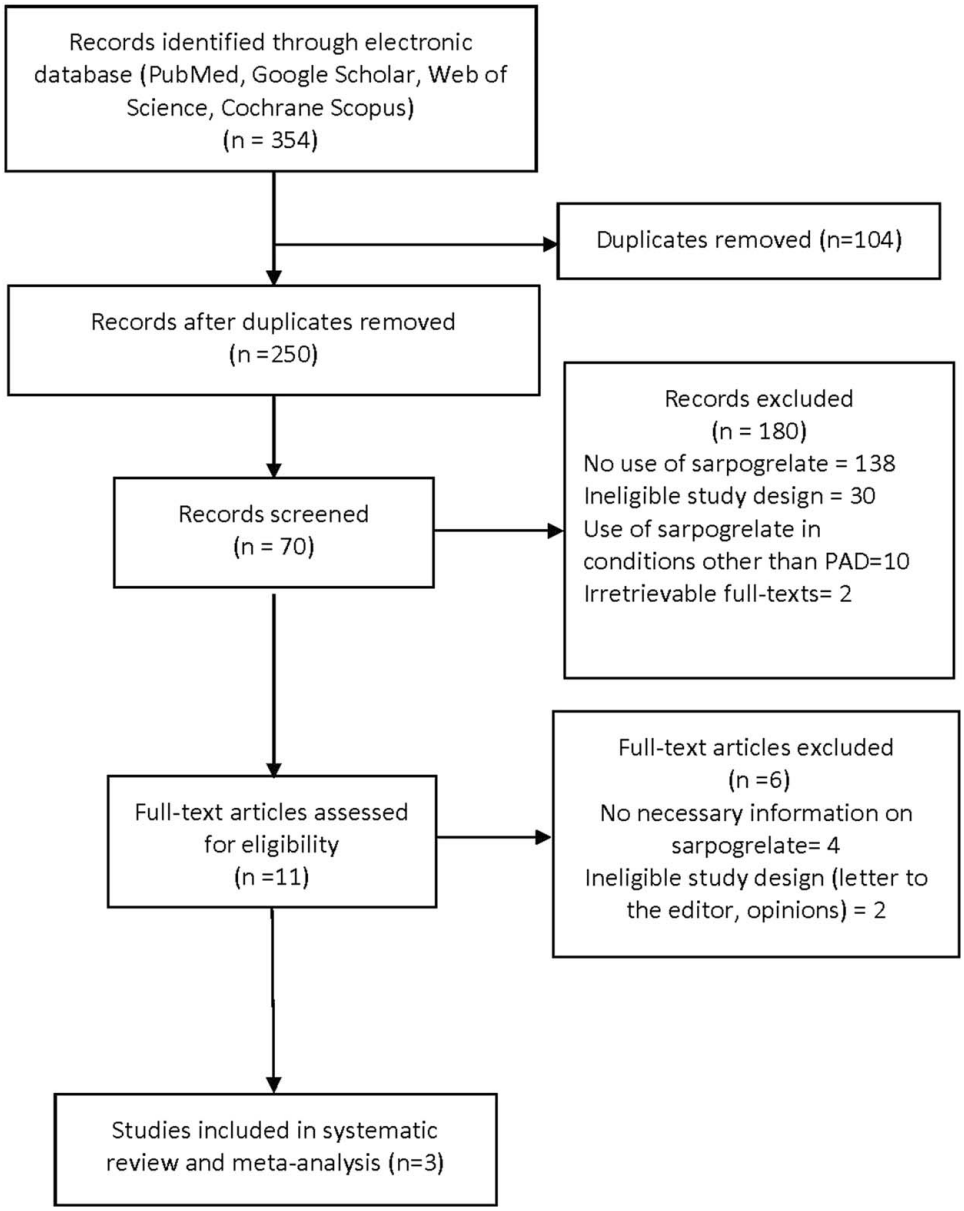

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

the control group in all three RCTs included in this review (RR = 1.52, 95% CI = 0.55–4.24, I^2 = 0%, P = 0.476). The forest plot of the pooled analysis is provided in the Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A586.

Miscellaneous adverse drug reactions to sarpogrelate

The data regarding adverse drug reactions to sarpogrelate in PAD patients after EVTs is trifling in the published literature. According to two trials that assessed adverse drug reactions to sarpogrelate-based APT, such reactions are rare[21,22]. Most of the adverse drug reactions were mild and did not require modification or discontinuation of the treatment. Chen *et al.*[21] reported a single case of severe gastrointestinal discomfort in the sarpogrelate group for which the drug had to be discontinued. Even though the rate of discontinuation of medication due to adverse reactions was lower in the sarpogrelate group than in the clopidogrel group, the difference was not significant. Another trial also reported a few instances of constipation, gastritis, and ileus in sarpogrelate users[22].

Risk of bias and sensitivity analysis

The selection bias was variable throughout the studies. The RCTS had low, high or unknown risk of selection bias. The risk of performance bias was found to be high in all three RCTS. However, the studies had relatively low detection and attrition bias. However, an unknown risk of reporting bias and other study biases existed in all included studies. The details of the risk of bias assessment are given in Appendix 2 of Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/

Table 1
Characteristics of included studies

Study	Study design	Study site	Sample size (Sarpogrelate/Non-sarpogrelate-based anti-platelet treatment)	Nature of intervention	Primary outcome	Secondary outcomes	Assessment/ follow-up period	Comparator drug
Han *et al.*, 2023[22]	RCT	South Korea	272 (134/138)	Femoropopliteal EVT	Restenosis rate	TLR, Amputation, Major Bleeding, All-cause mortality, serious adverse events	6 months	Clopidogrel
Chen *et al.*, 2015[21]	RCT	China	120 (63/57)	Femoropopliteal EVT	Restenosis rate, TLR	Amputation, Bleeding, All-cause mortality,	6 months	Clopidogrel
Soga *et al.*, 2016 (ESPAUER Trial)[23]	RCT	Japan	177 (89/88)	Femoropopliteal EVT	Primary patency/ Restenosis rate	All-cause mortality, Serious bleeding, Amputation	1 year	non-sapogrelate

EVT, endovascular therapy; RCT, randomized controlled trial; TLR, target lesion revascularization.

A586. The sensitivity analysis showed that the recalculated relative risk after removing each study by the leave-one-out method was similar, which indicates the stability of the analysis. The details of the sensitivity analysis are given in Appendix 3 of Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A586.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to evaluate the efficacy and safety of sarpogrelate-based APT in PAD after EVTs. The analysis showed that there are no statistically significant differences in all three major efficacy parameters; restenosis, TLR, and amputation events. In addition to this, the safety profile of sarpogrelate-based APT is comparable to that of non-sarpogrelate-based APT.

Sarpogrelate (Fig. 4) is a selective 5-hydroxytryptamine receptor subtype 2A (5-HT_{2A}) antagonist drug that was first described in 1990[15,24]. At higher concentrations, sarpogrelate can bind to 5-HT_1, alpha-, and beta-adrenergic receptors. 5-HT-mediated actions are prominent in platelet aggregation, vasoconstriction of arteries, and proliferation of aortic and coronary vascular smooth muscles in the body. Owing to its positive effect on platelet aggregation and vasoconstriction of collateral vessels, 5-HT is believed to play a role in the pathogenesis of PAD[15,25,26].

Platelets store serotonin, or 5-HT, which gets released upon their disruption. As a result, the released 5-HT acts on the platelets' 5-HT2A receptors to induce platelet aggregation. Sarpogrelate selectively antagonizes the receptor, which leads to inhibition of platelet aggregation. The anti-aggregation effect of the drug is complemented by simultaneous inhibition of the release of p-selectin from the platelets[15,16]. However, sarpogrelate has no effect on platelet adhesion, cAMP levels, or the production of thromboxane A_2. On the other hand, 5-HT_{2A} receptor-mediated vasoconstriction of vascular smooth muscle is an important step in thrombosis. Sarpogrelate, being a 5-HT_{2A} antagonist, is believed to have a role in PAD, owing to inhibition of both of these responses[15,27]. In experimental arterial thrombosis created in studies, sarpogrelate reduced thrombus formation and even prolonged the time required for occlusion of the arteries[28].

Apart from anti-platelet action, sarpogrelate has been shown to inhibit 5-HT-induced proliferation of aortic and coronary artery smooth muscle cells in animal studies. However, no effect on proliferative action mediated by platelet-derived growth factor, endothelin, or angiotensin-II was observed in the studies[26,29,30]. 5-HT also plays a role as a mitogen in stimulating the growth of collaterals following an acute thrombo-occlusive event. Other smooth muscle cells, like cardiomyocytes and mesangial cells, also showed a reduction in mitogenesis when sarpogrelate was used in cultured rat cells[31,32].

A gradual and progressive occlusion of major arteries in the lower extremities due to atherosclerosis entails the pathogenesis of PAD. The use of sarpogrelate as a part of medical therapy in PAD has been shown to improve peripheral perfusion and reduce the levels of IL-6 and hs-CRP, which are the molecular markers of atherosclerosis[33]. Sarpogrelate has shown a reduction in the progression of induced PAD lesions as well as suppression of thrombotic infarction in rat models[34]. Likewise, cholesterol-rich

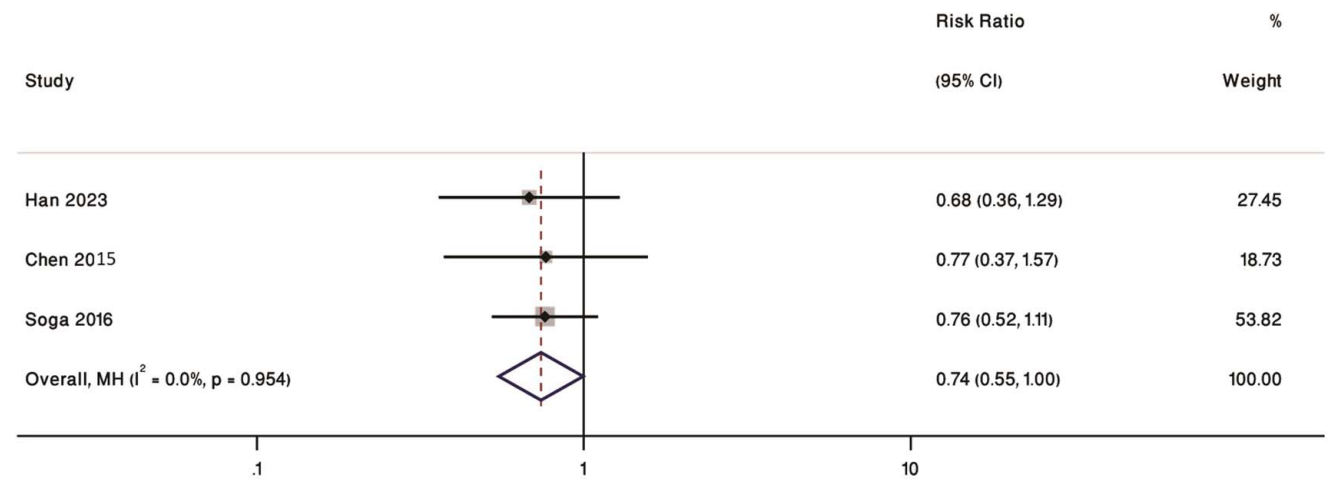

Figure 2. Meta-analysis of restenosis.

diet-induced atherosclerosis was reduced by treatment with a combination of vitamin E and sarpogrelate in rabbit models. Restenosis of lesions of PAD following EVT intervention in animal models was also reduced by the drug, and the reduction was greater in cholesterol-fed animal models[24,35].

The trials included in the systematic review were able to demonstrate sarpogrelate-based APT as a non-inferior alternative regimen to conventional APT in PAD after EVTs. In addition to this, Han *et al.*[22] undertook subgroup analysis to understand the effect of various sociodemographic, lifestyle, severity of PAD, and treatment factors on the restenosis rate. Most of the factors, such as sex, smoking, diabetes mellitus, use of statins and other APs, use of hemodialysis, diameter and length of stent, Rutherford classification of lesions, etc., had no influence on the occurrence of restenosis in the participants. However, patients with concomitant CAD had significantly higher restenosis rates when kept on sarpogrelate-based APT as compared to clopidogrel-based APT. The exact reason behind this intriguing outcome of this study is obscure, but a large-scale study is warranted to further explore this concept. The rates of primary patency of PAD patients on sarpogrelate-based APTs were higher than other APTs, but the difference was not statistically significant. This trial shows that the sarpogrelate-based APT is comparable in efficacy with conventionally used APT for patients who have undergone EVT. Guo *et al.*[36] also reported no significant differences in the restenosis rates between the patients treated with sarpogrelate and non-sarpogrelate-based APT for carotid stenosis after EVT.

Amputation of extremities is a life-saving therapeutic strategy for severe PAD, but it is also a marker of poor cardiovascular outcomes. Takahara *et al.*[37] are the first to study the risk of amputations and rates of amputation-free survival in patients taking sarpogrelate post-EVT for limb-threatening ischemia. The study demonstrated a significantly higher amputation-free survival rate in the sarpogrelate group than their matched controls.

Only Soga *et al.*[23] reported a higher risk of bleeding in the sarpogrelate-based APT group as compared to controls receiving conventional APT. The higher risk observed in their trial could be attributed to "too small" sample sizes that increase type II error. Additionally, Guo *et al.*[36] reported no cases of severe bleeding in patients taking sarpogrelate after EVT for carotid stenosis. The same study reported a few cases of general bleeding, which were numerically lower than the clopidogrel group but not statistically

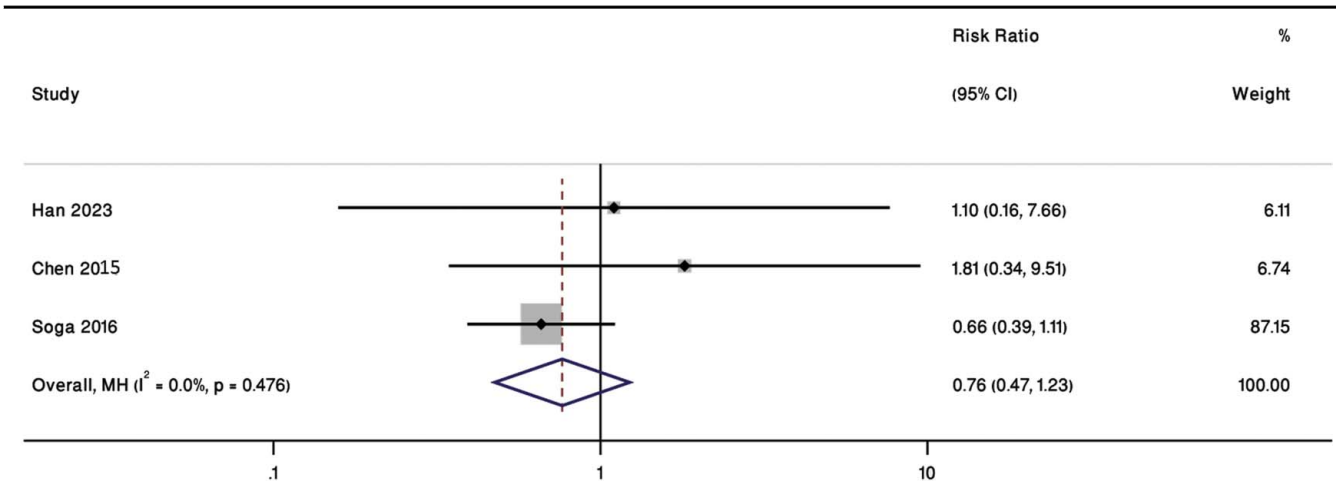

Figure 3. Meta-analysis of target lesion revascularization.

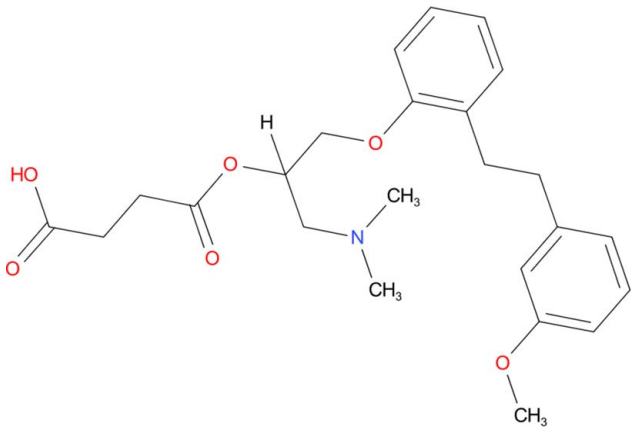

Figure 4. Sarpogrelate molecule.

different. Hence, it is safe to say from these studies that the risk of general or major bleeding in sarpogrelate users is either less or equal to that of clopidogrel users.

A newer sustained-release formulation of 300 mg sarpogrelate for once-daily usage can improve convenience and enhance medication adherence in patients. Additionally, the cost of sarpogrelate is lower in comparison to clopidogrel (USD 0.92 vs. USD 1.02 per tablet) in countries like Korea, where the FDA has approved its usage[38]. However, the data regarding the efficacy and safety of sarpogrelate is still limited. There are a few limitations to the current systematic review and meta-analysis. The major limitation is the limited availability of data to evaluate the efficacy and safety of sarpogrelate-based APT. The limited data also barred subgroup analysis and publication bias assessment of the data. The pooled results may not be generalizable and reliable since only three RCTs have been conducted on a small sample size in a specific population from three Asian countries.

Conclusion

Our review has shown that sarpogrelate-based APT is as efficacious and safe as conventional APT after EVTs in patients with PAD. However, there is a need for a larger multicenter, multinational, and multiethnic global trial with sufficient participants in order to produce generalizable findings.

Ethical approval

Ethics clearance was not necessary to obtain because of the nature of review article.

Consent

Since the systematic review doesn't involve first-hand data collection from the participants, the need of informed consent was waived. However, the primary studies included in the review had obtained informed consent prior to enrollment into their study.

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Author contribution

L.K.J., S.R., A.R., B.B.K., M.M.S., N.T.: study conception, data analysis, software, manuscript writing. L.K.J., S.R., M.M.S., N.T., H.T.: study conception, manuscript writing and editing. L.K.J., S.R., B.B.K., N.T., M.M.S., H.T.: manuscript writing and editing.

Conflicts of interest disclosure

The authors declare no conflict of interest.

Research registration unique identifying number (UIN)

Research Registration Database: PROSPERO Hyperlink to research protocol: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=532228&VersionID=2252629
Research Registration UIN: CRD42024532228.

Guarantor

Nandita Thapar.

Data availability statement

The data analyzed in this study shall be obtained from the primary authors upon request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Tran B. Assessment and management of peripheral arterial disease: what every cardiologist should know. Heart 2021;107:1835–43.
[2] Fowkes FG, Aboyans V, Fowkes FJ, *et al*. Peripheral artery disease: epidemiology and global perspectives. Nat Rev Cardiol 2017;14:156–70.
[3] Aday AW, Matsushita K. Epidemiology of peripheral artery disease and polyvascular disease. Circ Res 2021;128:1818–32.
[4] Wu A, Coresh J, Selvin E, *et al*. Lower extremity peripheral artery disease and quality of life among older individuals in the community. J Am Heart Assoc 2017;6:e004519.
[5] Abaraogu UO, Ezenwankwo EF, Dall PM, *et al*. Living a burdensome and demanding life: A qualitative systematic review of the patients experiences of peripheral arterial disease. PLoS One 2018;13:e0207456.
[6] Sigvant B, Hasvold P, Kragsterman B, *et al*. Cardiovascular outcomes in patients with peripheral arterial disease as an initial or subsequent manifestation of atherosclerotic disease: Results from a Swedish nationwide study. J Vasc Surg 2017;66:507–514.e1.
[7] Shamaki GR, Markson F, Soji-Ayoade D, *et al*. Peripheral artery disease: a comprehensive updated review. Curr Probl Cardiol 2022;47:101082.
[8] Bevan GH, Solaru KTW. Evidence-based medical management of peripheral artery disease. Arterioscler Thromb Vasc Biol 2020;40:541–53.
[9] Gerhard-Herman MD, Gornik HL, Barrett C, *et al*. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e726–79.
[10] Aboyans V, Ricco JB, Bartelink MEL, *et al*. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis

and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763–816.
[11] Katsanos K, Spiliopoulos S, Saha P, *et al*. Comparative efficacy and safety of different antiplatelet agents for prevention of major cardiovascular events and leg amputations in patients with peripheral arterial disease: a systematic review and network meta-analysis. PLoS One 2015;10:e0135692.
[12] Guirgis M, Thompson P, Jansen S. Review of aspirin and clopidogrel resistance in peripheral arterial disease. J Vasc Surg 2017;66:1576–86.
[13] Kim M, Yang YS, Ko YG, *et al*. Major adverse events in patients with peripheral artery disease after endovascular revascularization: a retrospective study. J Clin Med 2022;11:2547.
[14] Hess CN, Wang TY, Weleski Fu J, *et al*. Long-term outcomes and associations with major adverse limb events after peripheral artery revascularization. J Am Coll Cardiol 2020;75:498–508.
[15] Doggrell SA. Sarpogrelate: cardiovascular and renal clinical potential. Expert Opin Investig Drugs 2004;13:865–74.
[16] Kolandaivelu K, Bhatt DL. Chapter 58 - Novel Antiplatelet Therapies, in: A.DMichelson (Ed.). Platelets, (Third Edition). Academic Press; 2013: pp. 1185–1213.
[17] Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Systematic Reviews. BMJ. 2021;372:n71.
[18] Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.
[19] Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[20] Higgins JP, Thomas J, Chandler J, *et al*. Cochrane handbook for systematic reviews of interventions version 6.4 (updated August 2023). Cochrane, 2023. training.cochrane.org/handbook.
[21] Chen Y-X, Wang W-D, Song X-J, *et al*. Prospective randomized study of sarpogrelate versus clopidogrel-based dual antiplatelet therapies in patients undergoing femoropopliteal arterial endovascular interventions: preliminary results. Chinese Med J 2015;128:1563–6.
[22] Han A, Lee T, Lee J, *et al*. A multicenter, randomized, open-labelled, non-inferiority trial of sustained-release sarpogrelate versus clopidogrel after femoropopliteal artery intervention. Sci Rep 2023;13:2502.
[23] Soga Y, Shintani Y, Hamasaki T, *et al*. Effectiveness of sarpogrelate after endovascular treatment for femoropopliteal artery disease: ESPALIER study. Cardiovasc Interv Ther. 2017;32:325–32.
[24] Hayashi T, Sumi D, Matsui-Hirai H, *et al*. Sarpogrelate HCl, a selective 5-HT2A antagonist, retards the progression of atherosclerosis through a novel mechanism. Atherosclerosis 2003;168:23–31.
[25] Margaritis M, Antonopoulos AS, Digby J, *et al*. Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels. Circulation 2013;127:2209–21.
[26] Sharma SK, Del Rizzo DF, Zahradka P, *et al*. Sarpogrelate inhibits serotonin-induced proliferation of porcine coronary artery smooth muscle cells: implications for long-term graft patency. Ann Thorac Surg 2001;71:1856–64.
[27] Doggrell SA. Pharmacotherapy of intermittent claudication. Expert Opin Pharmacother 2001;2:1725–36.
[28] Hara H, Kitajima A, Shimada H, *et al*. Antithrombotic effect of MCI-9042, a new antiplatelet agent on experimental thrombosis models. Thromb Haemostasis 1991;66:484–8.
[29] Watanabe T, Pakala R, Katagiri T, *et al*. Angiotensin II and serotonin potentiate endothelin-1-induced vascular smooth muscle cell proliferation. J Hypertens 2001;19:731–9.
[30] Watanabe T, Pakala R, Katagiri T, *et al*. Monocyte chemotactic protein 1 amplifies serotonin-induced vascular smooth muscle cell proliferation. J Vasc Res 2001;38:341–9.
[31] Eto Y, Nitta K, Uchida K, *et al*. Anti-mitogenic effects of sarpogrelate in cultured rat mesangial cells. Life Sci 1997;60:PL193–9.
[32] Ikeda K, Tojo K, Tokudome G, *et al*. The effects of sarpogrelate on cardiomyocyte hypertrophy. Life Sci 2000;67:2991–6.
[33] Lu Y, Li J, Xie J, *et al*. Effects of sarpogrelate hydrochloride on peripheral arterial disease: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2019;98:e17266.
[34] Hara H, Shimada H, Kitajima A, *et al*. Effect of (+/-)-2-(dimethylamino)-1-[[o-(m-methoxyphenethyl) phenoxy] methyl] ethyl hydrogen succinate on experimental models of peripheral obstructive disease. Arzneimittel-Forschung 1991;41:616–20.
[35] Origuchi N, Shigematsu H, Muto T. Anplag, a selective 5-HT2 receptor antagonist, reduces stenosis induced by balloon injury in the hypercholesterolaemic rabbit. Int Angiol 1997;16:204–9.
[36] Guo J, Gu Y, Guo L, *et al*. Effects of sarpogrelate combined with aspirin in patients undergoing carotid endarterectomy in china: a single-center retrospective study. Ann Vasc Surg 2016;35:183–8.
[37] Takahara M, Kaneto H, Katakami N, *et al*. Effect of sarpogrelate treatment on the prognosis after endovascular therapy for critical limb ischemia. Heart Vessels 2014;29:563–7.
[38] Ahn S, Lee J, Min SK, *et al*. Anplone in Femoro-popliteal artery intervention Efficacy) study: study protocol for a randomized controlled trial. Trials 2017;18:439.