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Percutaneous transluminal angioplasty and stenting (PTAS) in patients with symptomatic intracranial vertebrobasilar artery stenosis (IVBS)

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ABSTRACT

Background Approximately 20% of all transient ischaemic attacks (TIAs) and ischaemic strokes occur within the posterior circulation, with vertebrobasilar stenosis identified as the cause in roughly 25% of the cases. Studies have shown that about a quarter of these patients have atherosclerotic stenosis of at least 50% of the vertebrobasilar artery. Stenosis has been shown to be associated with an increased risk of 90-day recurrent vertebrobasilar stroke, particularly in the first few weeks, which is significantly higher when compared with patients with stenosis of the anterior circulation. Therefore, aggressive treatment is important for the patient's prognosis. Stenting is emerging as a promising therapeutic strategy for persistent ischaemia events that do not respond to the best medical treatment, but it is not without complications. We systematically reviewed the literature on percutaneous transluminal angioplasty and stenting (PTAS) for intracranial vertebrobasilar artery stenosis (IVBS).

Methods PubMed, Web-of-Science and Scopus were searched upon the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to include prospective/retrospective cohort, randomised/non-randomised clinical trials and case series studies describing PTAS for IVBS. Pooled rates of intervention-related complications and outcomes were analysed with random-effect model meta-analysis using StataMP V.18.0 software.

Results 31 studies were found eligible which included 1928 cases. 1103 basilar artery stenosis cases were reported in 27 studies 0.65 (95% CI 0.53, 0.76), I^2: 99.72%. 648 vertebral cases were reported in 18 studies 0.60 (95% CI 0.49, 0.70), I^2: 97.49%. In four studies, the rate of vertebrobasilar stenosis cases calculated as a proportion of the total sample size was 0.10 (95% CI 0.05, 0. 15). Mean stenosis in 21 included studies was found to be 0.83 (95% CI 0.79, 0.88), I^2: 0.00%, which shows variation of baseline stenosis between studies was minimal. 51 deaths were recorded in 24 studies. Meta-analysis of mortality showed the overall rate of mortality was 0.03 (95% CI 0.02, 0.05), I^2: 44.90%. In 14 studies, symptomatic intracranial haemorrhage events were recorded at an overall rate of 0.01 (95% CI 0.00, 0.02), I^2: 0.00%. Generally, a follow-up period of at least 3 months was reported in the included studies. Furthermore, procedural stroke/TIA was evaluated in seven studies, four of which reported no events (0.03 (95% CI 0.00, 0.08), I^2: 20.38%). Mean time from initial symptoms to recanalisation was 23.98 (95% CI 18.56, 29.40), I^2=98.8%, p=0.00 days.

Conclusion In certain individuals with medically unresolved, severe, symptomatic and non-acute IVBS,

WHAT IS ALREADY KNOW ON THIS TOPIC

⇒ Stroke is a significant cause of morbidity and mortality in adults, with atherosclerotic vertebrobasilardisease being the primary cause. Diagnosing posterior circulation stroke is challenging due to itsprogressive nature. Patients with brainstem infarctions often suffer from significant debilitation.Treatment options include thrombolysis and surgical bypass. However, symptomatic individuals withsevere basilar artery stenosis face a high risk of ischemic stroke recurrence and death. The use ofstents as a therapeutic intervention for recurrent ischemic episodes is growing, with primary stent-angioplasty, also known as percutaneous transluminal angioplasty (PTAS), being extended tomanage atherosclerotic intracranial stenosis.

WHAT THIS STUDY ADDS

⇒ In this systematic review and meta-analysis study we summerized the rates of mortality, restenosis,periprocedural complications as sICH and TIA after percutaneous transluminal angioplasty andstenting of patients with intracranial vertebrobasilar artery stenosis. As concluded based on ourmeta-analysis, in certain individuals with medically unresolved, severe, symptomatic, and non-acuteIVBS, elective vertebrobasilar PTAS appears to be both safe and effective.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Analysis provides insights into PTAS in patients with intracranial vertebrobasilar stenosis, but cautionis advised due to study quality and limitations. The findings emphasize the need for ongoingresearch and collaboration to optimize patient care, enhance intervention safety, and improve long-term outcomes, with future studies focusing on addressing identified gaps.

elective vertebrobasilar PTAS appears to be both safe and effective. Various stent designs and angioplasty-assisted techniques should be taken into consideration based on the specific clinical and radiological traits of the lesions. Future randomised controlled trials are required to verify these results.

INTRODUCTION

Stroke stands as a prominent contributor to both morbidity and mortality in the adult population.[1] Impairment of blood circulation within the posterior circulation (PC) accounts for over 20% of ischaemic stroke instances, with atherosclerotic vertebrobasilar disease identified as the primary cause.[2 3] Patients with brainstem infarctions commonly suffer from significant debilitation due to residual morbidity. In accordance with the progressive and non-lateralising nature of the signs and symptoms, there is difficulty in diagnosing PC stroke.[4] The most common symptoms reported are dizziness, dysarthria, headache, nausea, unilateral limb weakness, impairment of consciousness and coma. Patients can exhibit characteristic clinical symptoms like hemiballismus, visual loss, pupil abnormalities and gaze palsies as 'top of basilar syndrome' owing to strokes related to top of basilar vascular region.[5] Prior to the advancement of stents and angioplasty balloons capable of manoeuvring through intricate posterior cerebral arteries, thrombolysis and surgical bypass were among the treatment options.[6] However, it has been documented that symptomatic individuals with severe stenosis of the basilar artery (BA), despite being on antithrombotic medications, face a significantly high risk of ischaemic stroke recurrence and death.[7 8] Furthermore, surgical interventions for intracranial vertebrobasilar stenosis are associated with a significant incidence of complications, including periprocedural haemorrhage, graft failure, postprocedural infection and haematoma formation.[7]

The rising interest in using stenting as a therapeutic intervention for recurrent ischaemic episodes that are unresponsive to optimal medical treatment has become a noteworthy subject. The utilisation of primary stent-angioplasty, also known as percutaneous transluminal angioplasty and stenting (PTAS), has been extended to the management of atherosclerotic intracranial stenosis. The purpose of primary PTAS is to mitigate the occurrence of problems and enhance the overall efficacy of endovascular therapy for atherosclerotic intracranial stenosis, thereby leading to improved long-term outcomes. This development has stemmed from the application of highly flexible coronary stents, initially employed for the acute treatment of complications such as aortic dissection or vessel occlusion following angioplasty.[9] However, the application of stent-assisted angioplasty has historically been limited due to its technical feasibility, potential procedural complications, and the outcomes in both short and long terms.[8] Despite the persistent presence of challenges, recent advancements in the tools employed for angioplasty and stent deployment have improved manoeuvrability and flexibility. Additionally, insights gleaned from prior studies on cerebral angioplasty and stent implantation have played a crucial role in refining the treatment, resulting in a generally safer procedure with a reduced periprocedural and postprocedural complication rates.[10–13]

In the present study, we analysed data from 31 reports encompassing 1928 cases to evaluate the effectiveness and safety of PTAS in patients with medically refractory vertebrobasilar artery stenosis. This reproducible, methodologically rigorous meta-analysis offers valuable insights into the clinical outcomes and potential complications associated with the use of PTAS for the management of vertebrobasilar stenosis. In this study, we aimed to provide a comprehensive and methodological evaluation of scholarly articles pertaining to the utilisation of PTAS in the treatment of intracranial vertebrobasilar artery stenosis (IVBS).

MATERIALS AND METHODS

The current systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14] The protocol of current study has been submitted on The International Prospective of Systematic Reviews (PROSPERO) website (CRD42023353063).

Search strategy and study selection

Our study includes prospective/retrospective cohort, randomised/non-randomised clinical trial and case series studies. Systematic search in Google Scholar, PubMed, Web of Science and Scopus databases was carried out in September 2022 by six reviewers (RP, KS, SZ, RH, AJ and SG). The following search strategies were [("Basilar" OR "vertebrobasilar" OR (("Intracranial" OR "cerebral") AND "vertebral")) AND ("stenting" OR "stent" OR "endovascular" OR "angioplasty") AND ("occlusion" OR "stenosis" OR "atherosclerosis" OR "insufficiency" OR "stroke" OR "ischemia" OR "infarction")]. All final records are imported into EndNote X20 software (Thomson Reuters, San Francisco, CA). Results were collected after duplicate removal by authors (RP, KS, SZ, RH, AJ and SG). To identify findings that were eligible, a three-step screening process that involved assessing each title, abstract and full-text was implemented. Five reviewers (RP, SZ, RH, AJ and SG) performed screening separately, and disagreements were solved by referring to a third author (RP). All included studies were updated until March 2023.

For this study, the inclusion criteria were: (1) >50% or moderate to severe stenosis, or equivalent in at least one patient with any age or sex with symptomatic stenosis; (2) patients have symptoms related to intracranial vertebral or BA stenosis; (3) studies that included other intracranial stenosis were included if stenosis in intracranial vertebrobasilar artery could be extracted separately; (4) an average follow-up of at least 3 month; (5) studies allowing any acceptable endovascular technique for treatment of IVBS (eg, balloon catheter or primary stenting);

(6) articles providing details on the primary outcome measures (procedure related stroke/TIA; periprocedural stroke rate and death from any cause within 30 days of treatment; vertebrobasilar stroke or TIA during clinical follow-up period; rate of restenosis (>50%) during follow-up) are enrolled and considered for further analysis; (7) clinical studies of any kind including randomised and non-randomised trials, cohorts, cross sectional studies, case–control studies and case series; (8) studies included without language restrictions if it is translatable with online translators; and (9) there are no limitation for publication date of included studies. The exclusion criteria were: (1) patients with asymptomatic IVBS; (2) studies that did not report complications of the interventional therapy; (3) loss of follow-up of >40% of the study population; and (4) case reports, letter to editors, conference papers, book chapters, opinion articles, systematic reviews, meta-analysis and review articles are excluded.

Data extraction

Three reviewers (RP, SZ and PA) separately extracted data in piloted formats from 31 eligible studies. Through consulting with two additional reviewers (RH and AJ), consensus agreement in extracted form was achieved. The following data was retrieved for each study: first author's name, PubMed link, year of publication, country where the study piloted, single/multi-centre, number of patients, prevalence of male gender, basilar stenosis cases prevalence, intracranial vertebral stenosis cases prevalence, vertebrobasilar stenosis cases prevalence, age, initial National Institutes of Health Stroke Scale score at admission, risk factors (eg, hypertension (HTN), dyslipidaemia, diabetes mellitus (DM), coronary heart disease and smoking), time from onset symptom to procedure, drug information, stenosis percentage at admission and device type used for procedure. The extracted outcomes of interest included follow-up period, mortality, mTICI 2b/3, symptomatic intracranial haemorrhage (sICH), procedure stroke/TIA rates, periprocedure stroke rate and death from any cause (within 30 days of treatment), rate of stroke/TIA during clinical follow-up period and rate of restenosis.

Data synthesis and quality assessment

Statistical analyses were performed using Stata V.18.0 MP (StataCorp, Texas, USA).[15] For dichotomous variables, number of outcomes (binary) was recorded. For continuous outcomes, mean±SEM was extracted (or estimated using meta-analysis level formula from other statistical measures) to calculate raw propositions and perform single-rate meta-analysis. The quantitative analyses used a fixed effects model in homogenous case studies, while a random-effects model was employed in heterogeneous cases (based on the study design and/or I^2 heterogeneity >30%). Subgroup analysis was performed to draw conclusions on data from different regions of the world. Post-hoc analyses were conducted, and meta-regression was carried out using age as a predictor of effects. Leave-one-out analysis was also performed. Finally, cumulative meta-analysis sorted by year was performed to investigate if there were potentially any trends in outcomes observed following our procedures of interest throughout the years. Results were considered significant at the threshold 0.05 for p value.

Reviewers assessed the risk of bias and quality of evidence for each article based on National Institute of Health tool, and studies categorised into good, fair and poor.[16] By considering the combined risk of bias of all included studies, the total risk of bias in this review was evaluated (online supplemental file 1).

RESULTS

Study selection and basic characteristics

Figure 1 illustrates the literature screening. 31 studies comprising 16 cohort studies, 13 case series studies and 2 non-randomised clinical trials were included in the present systematic review. A total of 1928 cases were included (table 1). The mean age was 63.16 (95% CI 61.34, 64.98). The average follow-up for 18 studies was 26.08 (95% CI 21.00, 31.15), I^2: 98.89% months.[17–34] Based on inclusion criteria, studies reported a follow-up of at least 3 months to be included (online supplemental figure 1A). Interestingly, cumulative analysis of follow-up length suggested there may possibly be an increasing trend in follow-up duration in more recent years[17–34] (online supplemental figure 1B). Moreover, the time from symptoms onset to the procedure was 20.67 (95% CI 16.99, 24.36) days[20 2233 35–39] (online supplemental figure 1C).

Patients presented with various comorbidities, including HTN, hyperlipidaemia and DM, smoking. The prevalence of HTN in 22 studies comprising 1332 positive cases was 0.84 (95% CI 0.80, 0.88), I^2: 79.61%.[17–20 23 29–43] The prevalence of DM in 22 studies comprising 579 positive cases was 0.34 (95% CI 0.30, 0.37), I^2: 46.99%.[17–20 23 29–43] Additionally, in 19 studies including 742 dyslipidaemia cases, the overall rate of comorbidity was 0.51 (95% CI 0.40, 0.63), I^2: 95.94%.[17–20 22 23 25 29 30 32–39 41 42] In 20 studies, about half of the cases had a history of smoking (0.43 (95% CI 0.35[18 20 22 23 29–44], 0.52), I^2: 91.53%)[17–20 22 23 29 30 32–43] (figure 2).

Proportion of vertebral and basilar cases

Random-effects meta-analysis of 18 studies including 648 intracranial vertebral stenosis cases showed the rate of intracranial vertebral cases was 0.60 (95% CI 0.49, 0.70), I^2: 97.49%. The proportion of intracranial vertebral cases varied remarkably among studies. Subgroup meta-analysis was performed based on the country in which the study was performed. For Australia, one study showed a rate of 0.62 (95% CI 0.35, 0.88).[44] For China, nine studies showed an overall rate of 0.59 (95% CI 0.42, 0.75), I^2: 99.00%.[20 22 26 32 36 37 39 40] For France, one study showed a rate of 0.33 (95% CI 0.07, 0.60).[33] For Germany, one study showed a rate of 0.62 (95% CI 0.41, 0.83).[24] For Japan,

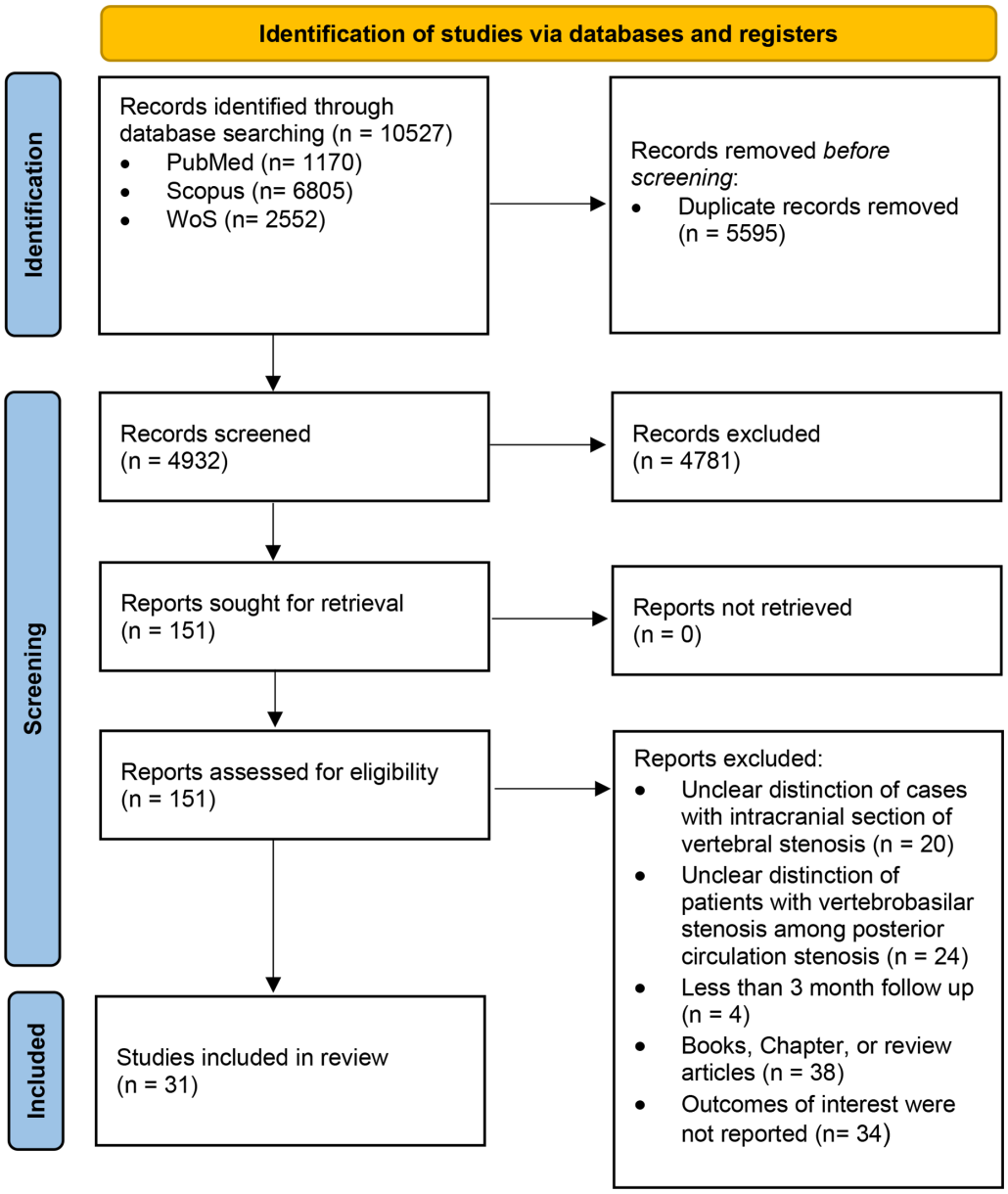

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram for new systematic reviews which included searches of databases and registers only. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

two studies showed a rate of 0.78 (95% CI 0.62, 0.94), I^2: 49.32%.[27 45] For Korea, one study showed a rate of 0.76 (95% CI 0.56, 0.97).[18] For the UK, one study showed a rate of 0.80 (95% CI 0.66, 0.94).[21] For the USA, two studies showed a rate of 0.40 (95% CI 0.22, 0.57), I^2: 31.55%.[31 46] Leave-on-out and cumulative quantitative analyses were also performed (online supplemental figures 3–5). Moreover, a random-effects meta-analysis of 27 studies including 1103 basilar stenosis cases showed a rate of 0.65 (95% CI 0.53, 0.76), I^2: 99.72%. For Australia, one study showed a rate of 0.38 (95% CI 0.12, 0.65).[44] For China, 11 studies showed an overall rate of 0.65 (95% CI 0.57, 0.82), I^2: 99.86%.[17 22 26 28 32 35 37–40 43] For France, one study showed a prevalence of 0.50 (95% CI 0.22, 0.78).[33] For Germany, two studies had an overall rate of 0.72 (95% CI 0.17, 1.00), I^2: 96.32%.[19 24] For Japan, two studies showed a rate of 0.22 (95% CI 0.06, 0.38), I^2: 49.32%.[27 45] For Korea, one study showed a rate of 0.35 (95% CI 0.13, 0.58).[18] For Portugal, one study showed a rate of 0.96 (95% CI 0.87, 1.00).[42] Further, one study from Spain showed a rate of 0.94 (95% CI 0.79, 1.00).[41] A single study from the UK showed a rate of 0.20 (95% CI 0.06, 0.34).[21] Finally, six USA studies showed a summary rate of 0.83 (95% CI 0.64, 1.00), I^2: 92.71%.[29–31 34 46 47] Mostly, rates were homogenous in neither of the subgroup analyses. In four studies, the rate of vertebrobasilar stenosis cases calculated as a proportion of the total sample size was 0.10 (95% CI 0.05, 0.15)[32 33 37 43] (online supplemental figures 6–10).

Table 1 Summary of basic characteristics and outcomes

Characteristics	Value
Cohort size (n)	1928
Demographics	
Age (years), mean (SD) (n=1889)	63.4±NA
Gender (male) (n=1889)	1490 (78.87%)
Risk factors	
Hypertension (n=1657)	1332 (80.39%)
Diabetes mellitus (n=1657)	579 (34.94%)
Coronary artery disease (n=706)	162 (22.95%)
Dyslipidaemia (n=1375)	742 (53.96%)
Tobacco smoking (n=1630)	811 (49.75%)
Outcome	
Mean time from onset symptom to recanalisation day (n=1139)	21.188±NA
Procedure stroke/TIA rates (n=64)	9 (14.06%)
Periprocedural stroke rate and death from any cause (within 30 days of treatment) (n=891)	63 (7.07%)
Mean follow-up (months) (n=1928)	18.96±NA
Rate of stroke/TIA during clinical follow-up period (n=1398)	108 (7.73%)
Rate of restenosis (>50%) during follow-up (n=1059)	102 (9.63%)
Mortality (n=1090)	51 (4.68%)
Studies quality (n=31)	
Good	16 (51.61%)
Fair	13 (41.93%)
Poor	2 (6.45%)

NA, not applicable; TIA, transient ischaemic attack.

Cumulative evaluation of the rate of vertebral and basilar cases suggested that, in recent years, basilar cases are on a downward trend while intracranial vertebral cases are on an upward trend (online supplemental table 1).

Procedural stroke, sICH and TIA rates

Procedural stroke/TIA was evaluated in seven studies, four of which reported no events (0.03 (95% CI 0.00, 0.08), I^2: 20.38%)[25 28–30 41 42] (online supplemental figure 11A, online supplemental table 2). The rate of sICH was 0.01 (95% CI 0.00, 0.02), I^2: 0.00% in 14 studies[17–19 22 23 25 28 30 31 38 39 41 44 45 47] (online supplemental figure 12A). Importantly, the rate of sICH followed a downward trend when studies were cumulatively analysed by publication year (online supplemental figure 13A). It may be essential to investigate the reason for such observations in sICH trends.

Risk of restenosis and mean stenosis

The average rate of restenosis across 21 included studies was 0.08 (95% CI 0.05, 0.11), I^2: 79.59%[17 18 22 24 27–30 32–39 43–47] (online supplemental table 2). Mean stenosis in 21 included studies was found to be 0.83 (95% CI 0.79, 0.88), I^2: 0.00%, which shows a variation of baseline stenosis between studies was minimal (online supplemental figures 13A and 14A). Subgroup analysis revealed the highest rates of mean stenosis among the Chinese studies (0.84 (95% CI 0.80, 0.89), I^2: 0.00) and the lowest in the study by Steinfort *et al* from Australia 0.68 (95% CI 0.31, 1.05) (online supplemental figure 13B). Leave-one-out analysis was conducted, indicating that the exclusion of the study by Jia *et al* resulted in the most significant deviation from the overall calculated rates (online supplemental figure 13C). A total of 102 postprocedural restenotic events were documented in 22 studies, yielding a rate of 0.08 (95% CI 0.05, 0.11), I^2: 79.59%. Additionally, subgroup analysis by country highlighted the highest rate of restenosis in the study by Djurdjevic *et al* performed in the UK 0.17 (0.03, 0.30), and the lowest rate of restenosis in the study by Kim *et al* from Korea (0.03 (95% CI 0.00, 0.10)).[18 21] The wide CI in the former study may suggest that the point value for restenosis may be better interpreted as speculative.

Following our a priori protocol, meta-regression analysis was performed. This investigation showed mean age (coeff. 0.005 (95% CI −0.0013, 0.0111), p=0.12) and sample size (coeff. −0.0002 (95% CI −0.00050, −0.00004), p=0.02) were directly and inversely related to risk of restenosis, respectively. These findings have the potential to address the high heterogeneity in the risk of restenosis, with statistical significance observed for sample size but not for age (online supplemental figure 15A,B). Overall, this indicates that the age of participants in a particular experiment may possibly be valuable to consider when interpreting the risk of restenosis.

Mortality

A total of 51 deaths were recorded in 24 studies, yielding an overall mortality rate of 0.03 (95% CI 0.02, 0.05), I^2: 44.90%[18–23 26 28–31 34 36–39 41–47] (online supplemental figure 16A). Subgroup analysis was also performed by country (online supplemental figure 16B). An apparent downward trend in mortality rates was speculated in recent years, particularly with a noticeable decline from 2000 to 2010 (online supplemental figure 16C). Meta-regression with sample size as a predictor of mortality showed a significant negative relationship (coeff. −0.0002 (95% CI −0.0004, −0.00005), p=0.01) (online supplemental figure 17).

Critical appraisal

This analysis encompassed a total of 31 studies, including 16 cohort studies. Among the cohort studies, 12 exhibited a good risk of bias, while 2 were assessed as having a fair risk of bias. Conversely, two cohort studies were categorised as having a poor risk of bias. Furthermore, the dataset included 13 case series studies, with 10 of them demonstrating a good risk of bias, 2 presenting a poor risk of bias and 1 being assessed as having a fair risk of bias. Additionally, the dataset featured two non-randomised

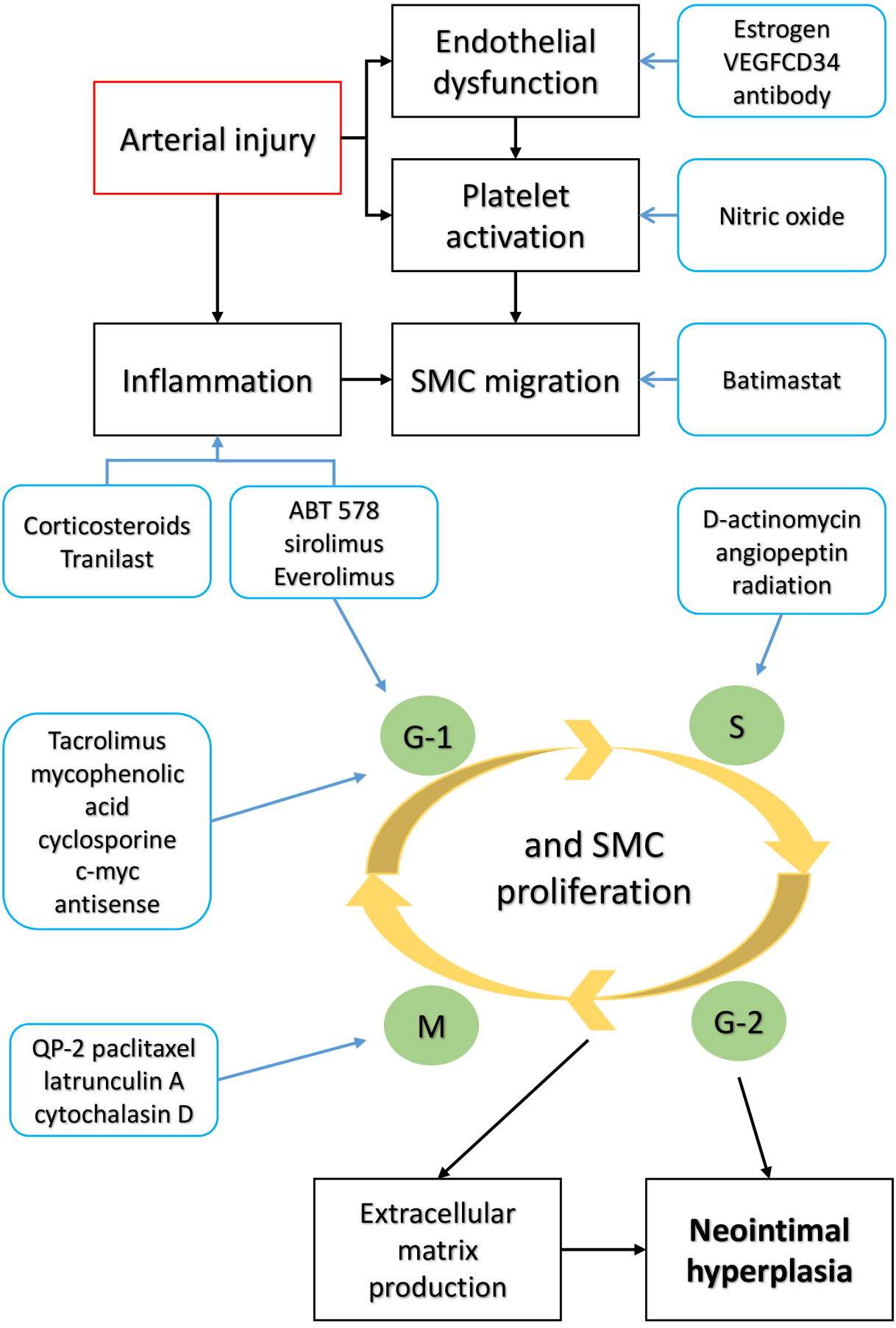

Figure 2 Mechanism of different medications inhibiting the neointimal hyperplasia.

clinical trials, with one study classified as having a good risk of bias and the other as fair, as indicated in online supplemental table 2.

DISCUSSION

The management of IVBS has posed a significant clinical challenge due to its devastating complications and high mortality rates. Prior studies, including those by Levy *et al* and Tsivgoulis *et al*, have shed light on the complexities associated with endovascular interventions for IVBS.[31 48] Levy and colleagues reported on the treatment of 11 IVBS patients, revealing periprocedural deaths in three cases and one delayed death due to a pontine stroke. Similarly, Tsivgoulis *et al* conducted a systematic review and meta-analysis, revealing a higher risk of stroke or death within 2 years in the PC subgroup of symptomatic intracranial artery stenosis when treated with PTAS in comparison to medical therapy.[48]

Moreover, SAMMPRIS and VISSIT trials showed higher perioperative stroke and death rates when comparing PTAS to the medical therapy.[11 12] Collectively, these studies do not endorse stenting as a first-line treatment for IVBS, underscoring the challenges and complications associated with this approach. However, it is important to note that the landscape of neuro-interventional surgery has evolved, with device advancement and growing expertise among neuro-interventionists, potentially improving the safety profile of PTAS for IVBS. An encouraging perspective was offered by Miao *et al*, who treated 159 intracranial atherosclerotic disease patients with a combination of balloon-mounted and self-expanding stents, reporting a 30-day rate of stroke, TIA and death at 4.3%.[49] Recent trials, namely the WEAVE and CASSISS studies, have provided noteworthy insights. WEAVE demonstrated notably low periprocedural complication rates, endorsing the favourable safety profile of the Wingspan stent in the context of PTAS for intracranial artery stenosis. Furthermore, the CASSISS trial revealed that there were no significant differences in the 30-day risk of stroke or death between the use of medical therapy alone and the combination of medical therapy with stenting for the treatment of severe symptomatic intracranial artery stenosis.[50 51]

In the context of IVBS, it is crucial to recognise that PC intracranial artery stenosis represents a unique entity compared with anterior circulation intracranial artery stenosis.[6 52] The high density of perforators in this region, supplying eloquent brain areas, translates to a notable risk of debilitating neurological and functional impairments, whether due to the natural course of the disease or as an outcome of therapeutic interventions. For example, the middle segment of the BA, which is the origin of a significant number of perforators, can cause clinically significant neurological deficits and heightened risks of post-treatment adverse events.[17 18]

The technical challenges of addressing PC vessel stenosis, owing to their greater tortuosity and smaller calibre, necessitate careful consideration of the endovascular procedures.[22] While aggressive antiplatelet therapy and risk factor control are generally regarded as first-line options for these patients, the unfavourable prognosis of symptomatic, refractory cases has prompted the exploration of second-line treatments, including balloon angioplasty and stenting.[53 54] These interventions are being pursued as alternatives to the highly challenging and high-risk bypass surgery.

Various studies have explored the use of angioplasty and stenting procedures for of IVBS management, each with its unique attributes and considerations.[55 56] While the initial series employed angioplasty alone, subsequent investigations have favoured angioplasty-assisted stenting due to its ability to achieve lower rates of residual postintervention stenosis.[57] This transition can be traced to the initial experiences with coronary balloon-expandable stents exhibiting superior stenosis resolution when compared with angioplasty alone.[29 31 47] Nevertheless, the limited flexibility and the requirement for high-pressure inflation during deployment posed challenges in navigating the tortuous PC, elevating the risk of iatrogenic vessel injuries.

The introduction of balloon-mounted Apollo stent (MicroPort Neurotech Limited (‘MicroPort NeuroTech’)) and the self-expanding Wingspan stent has contributed to some improvements in periprocedural outcomes, particularly through the careful selection of stent types and angioplasty-assisted procedures on an individualised basis.[35 38 58] Literature suggests that the Apollo stent is preferable for straight Mori type-A lesions, characterised by its rigidity and better radial support, making it suitable for heavily calcified lesions without any predilation angioplasty (ie, direct stenting).[49 58] Conversely, the Wingspan stent appears better suited for tortuous and longer Mori type-B and type-C lesions, especially when carried out after submaximal angioplasty inflation (ie, conventional stenting).[38 39 52] Several more studies have highlighted the distinctions between balloon-mounted and self-expanding stents, noting the rigidity and suitability of balloon-mounted stents for calcified lesions, while flexibility of self-expanding is advantageous for treating tortuous vessels.[49 58] Self-expanding stents, however, exhibit lower radial force and are more suitable for less calcified lesions.[59]

While the ligature points to the effectiveness and safety of PTAS in IVBS, it is essential to recognise that these insights were derived from heterogeneous series reported subjectively, primarily in institutions with a substantial caseload. Considering potential under-reporting of early suboptimal experiences, the highly positive results should be interpreted with caution, as they may not fully represent clinical outcomes in other settings. Objective assessments of operators’ learning curves and cross-operator comparisons of postinterventional outcomes should be conducted to validate the reproducibility of the aggregated findings.

Demographics and comorbidities

The mean age of the study population was 63.16 years, reflecting the typically expected age range for patients with vertebrobasilar artery stenosis. The patients in the reviewed studies had a range of comorbidities, with a significant prevalence of HTN, DM and dyslipidaemia.[11–13 60] Notably, the rates of HTN and DM were significantly high, emphasising the importance of prevention and management of these comorbid conditions in the context of vertebrobasilar stenosis. Furthermore, a history of smoking has been observed in approximately half of the patient population, signifying the role of smoking as a contributing factor in vascular disorders.[13 17 29 30 38 47 58] In addition to HTN and DM, it is noteworthy that dyslipidaemia was prevalent among the study population, with an overall comorbidity rate of 0.51 (95% CI 0.40, 0.63). These findings underscore the need for comprehensive medical management and lifestyle modifications in patients undergoing PTAS for vertebrobasilar and BA stenosis.[13]

Proportion of vertebral and basilar cases

Our meta-analysis revealed that the proportion of vertebral involvement was present in 60% of cases, while the proportion cases with basilar involvement was roughly 65%.[6] Subgroup analysis based on the country of the study suggested some variability in the prevalence of these cases.[6 50–52] In recent years, there has been an observable decline in incidences of basilar cases, juxtaposed with a discernible increase in occurrences of vertebral cases.[13] These trends could reflect evolving clinical practices, patient demographics or regional variations in disease prevalence. Further investigation into the underlying causes of these trends may provide valuable insights into the changing landscape of vertebrobasilar artery stenosis and guide future treatment strategies.

Follow-up duration and trends

Our analysis revealed an average follow-up duration of 26.08 months for the included studies, with substantial heterogeneity (I^2: 98.89%). Intriguingly, an upward trend in follow-up duration was observed in the more recent studies.[13] This trend underscores the importance of assessing long-term outcomes following PTAS, as it allows for a comprehensive evaluation of the intervention's effectiveness and potential complications.

Procedural outcomes

Procedural stroke/TIA and sICH are commonly recognised complications of PTAS. However, our analysis indicated low rates for procedural TIA (0.03 (95% CI 0.00, 0.08)) and sICH (0.01 (95% CI 0.00, 0.02)), suggesting that PTAS was associated with minimal peri-interventional risks in this patient population.[11 12 50 51 61] While some studies reported minimal or no complications, others, such as those by Zhang *et al* and Wang *et al*, demonstrated rates exceeding 10% and 20%, respectively.[36 37] Importantly, our analysis revealed a declining trend in the rate of sICH when cumulatively examining studies by publication year. This suggests potential improvements in procedural safety over time. Nevertheless, further investigation is warranted to elucidate the reasons and factors contributing to this observed trend. In-stent restenosis (ISR) is the major drawback of percutaneous coronary interventions (PCIs), and is found in approximately 10%–40% of the cases. Lately, new stents have surfaced that are loaded with anti-inflammation, anti-migration, anti-proliferative or pro-healing medication. These compounds are supposed to suppress inflammation and neointimal growth and consequently ISR. A key factor of uncertainty regarding the efficiency of drug-eluting stents is the utilisation of polymers. It is not determined if the used polymers remain stable over an extended interval of time and if they are fully inert. In a new work, polymethacrylate triggered smooth muscular cell death in vitro.[62] Poly-methylacrylate is the key element of the polymer used in the sirolimus-eluting stent. The polymer may also be disrupted because of calcifications and overlapping stenting, that could lead to insufficient drug release and restenosis. This may be considered in the assessment of long-term influence.[63]

Risk of restenosis

The average rate of restenosis across the studies was approximately 80%, with some variability among different countries.[38] While not statistically significant, our analysis revealed a positive association between age and the risk of restenosis. This suggests that the age of participants in a specific study might hold some relevance when interpreting the risk of restenosis, warranting consideration in the overall analysis. In contrast, the sample size exhibited a significant inverse relationship with the risk of restenosis, implying that larger sample sizes may contribute to mitigating the notable heterogeneity observed in restenosis risk across various studies.[13 38] A familial history of CHD, history of type 2 DM, HTN, smoking, and drinking, discontinuation of aspirin, consumption of traditional dosage statins, calcified lesions, ≥3 stent implantations, stent size ≥30 mm, stent diameter <3 mm and tandem stenting are predisposing factors for ISR within 2 years following PCI. Many of these factors could have contributed to the high average risk of ISR in our study. The drug is a biologically active agent that has to inhibit the formation of neointimal hyperplasia by suppression of platelet induction, inhibition of inflammatory feedback, suppression of smooth muscle cell migration or proliferation, as well as promotion of healing. The possible mechanisms are provided in online supplemental figure 18. The risk of myocardial infarction, adverse events and restenosis may be due to off-label use of stents. However, evidence is not consistent in this regard. For instance, recent retrospective research compared the in-hospital and long-term outcomes of the on-label and off-label uses of drug-eluting stents. They showed that off-label use of drug-eluting stents was not associated with increased adverse events after a 1-year follow-up and that such use

was not linked with enhanced in-hospital myocardial infarction or mortality.[64] Another study indicates off-label use of drug-eluting stents is associated with higher event rates compared with on-label use of drug-eluting stents, which is consistent with a higher risk clinical and lesion profile. However, event rates with off-label use of drug-eluting stents are lower compared with off-label use of bare-metal stents.[65] In a single-centre study of 5383 cases subject to PCI between 2004 and 2006, 380 had mortality and myocardial infarction after a 1-year follow-up. In this case–control evaluation, off-label utilisation of DES was independently linked with ST within a 1-year follow-up, even though the enhanced risk was moderate.[66]

Mortality

Our analysis showed an overall mortality rate of 0.03, indicating that mortality was relatively low in this patient population.[11 12 50 51 61] Subgroup analysis by country suggested some variability in mortality rates, with a speculated downward trend observed in studies published in more recent years. Furthermore, meta-regression analysis indicated a significant negative relationship between sample size and mortality.[11 12 50 51 61]

Study-specific considerations

A study by Jia *et al* raised specific considerations regarding the risk of perforator strokes. Patients with diabetes, preprocedure stenosis <88.4%, and less than 18 days from the last symptom to the procedure had higher risks of perforator strokes.[38] Due to the limited available data on this specific topic, an analysis could not be performed. However, understanding these risk factors and their potential impact on procedural outcomes is essential in refining patient selection criteria and optimising the safety of PTAS procedures.

Furthermore, the availability of data from studies across various countries highlighted differences between different countries in the prevalence and management of vertebrobasilar and BA stenoses. Variations in patient demographics, clinical practices and healthcare systems may contribute to the observed disparities, emphasising the importance of tailoring interventions to local contexts and implementing international collaboration to improve patient care.[13 17 29 31 38 47 58]

Implications and future directions

The results of this systematic review suggest that elective PTAS may be an effective and safe intervention for selected patients with medically refractory severe vertebrobasilar artery stenosis. Careful patient selection and treatment planning remain crucial for achieving favourable outcomes.[11–13]

Limitations

Several limitations should be considered within the context of our review. First, we emphasise that our findings are subject to the limitations and potential biases present in the included studies. Notably, our inability to conduct comparative analyses between PTAS and standard medical management for BAS is due to the scarcity of published trials directly comparing these two treatment strategies. The majority of articles included in our review were retrospective series, making them susceptible to inherent selection bias. It is crucial to acknowledge the likelihood of reporting bias on an institutional level, which may lead to the preferential publication of series with positive and favourable outcomes, potentially overshadowing those with higher complication rates.

Additionally, heterogeneity in indications, the definition of successful intervention, outcome assessments, and follow-up durations may have introduced confounding variables. Our inability to access individual patient-level data hindered the performance of multivariate analyses to assess the impact of distinct clinical, radiological and procedure-related characteristics on outcomes and complications. The variability in follow-up times between studies, along with the limited availability of outcome data, prevented us from conducting meta-analyses on the outcomes collected at varying time points. Although the mean follow-up duration was acceptable, longer follow-up periods would be more ideal for a comprehensive evaluation of long-term outcomes and the accurate detection of restenosis rates, as well as the need for re-operation.

CONCLUSION

In conclusion, our analysis provides insights into the clinical characteristics, outcomes and complications associated with PTAS in patients with intracranial vertebrobasilar stenosis. While our results are encouraging, they should be interpreted with caution due to the quality and inherent limitations of the included studies. The findings underline the need for ongoing research and collaboration to optimise patient care, enhance intervention safety, and improve long-term outcomes for those affected by this condition. Future studies and multicentre efforts should focus on addressing the identified gaps and refining the management of vertebrobasilar artery stenosis.

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