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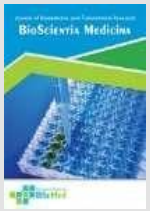

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Streptokinase or Alteplase for Acute Limb Ischemia? A Meta-Analysis

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A B S T R A C T

Background: Acute limb ischemia (ALI) is a vascular emergency that necessitates prompt and effective treatment to restore blood flow and prevent limb loss. Thrombolytic therapy, particularly with agents like streptokinase and alteplase, plays a pivotal role in ALI management. This meta-analysis and systematic review aimed to compare the efficacy and safety of streptokinase and alteplase in treating ALI. **Methods**: A comprehensive search of PubMed, Embase, Science Direct, and the Cochrane Library databases was conducted up to August 13th, 2024, to identify relevant studies. The inclusion criteria encompassed clinical trials involving patients diagnosed with ALI who received either streptokinase or alteplase as the initial thrombolytic treatment. The quality of the included studies was rigorously assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and the Methodological Index for Non-Randomized Studies (MINOR) criteria. A meta-analysis was performed using the Mantel-Haenszel random-effects model to calculate risk ratios (RRs) with their corresponding 95% confidence intervals (CIs). **Results**: The final analysis included 20 studies, encompassing both qualitative and quantitative assessments. A comparative analysis of streptokinase and alteplase for limb salvage at 30 days revealed a significant advantage in favor of alteplase, with a relative risk ratio (RR) of 0.78 (95% CI 0.69-0.88, I^2 = 0%). Furthermore, streptokinase was associated with a higher rate of primary amputation, with an RR of 2.54 (95% CI 1.50-4.32, I^2 = 0%) compared to alteplase. The use of streptokinase also correlated with a higher risk of complications, including major bleeding (RR 1.75, 95% CI 0.04-84.30, I^2 = 77%) and minor bleeding (RR 1.41, 95% CI 0.60-3.32, I^2 = 0%). **Conclusion**: The findings of this meta-analysis underscore the superior efficacy of alteplase in achieving limb salvage in ALI, coupled with a more favorable safety profile. The preferential use of alteplase in clinical practice is recommended, particularly in patients with severe ischemia. However, careful patient selection and close monitoring are crucial when streptokinase therapy is considered.

1. Introduction

Acute limb ischemia (ALI) is a vascular emergency characterized by a sudden decrease in blood flow to the extremities, often leading to serious complications and risk of amputation. It is a time-sensitive condition that requires prompt diagnosis and treatment to restore blood flow and preserve limb viability. ALI typically results from an abrupt occlusion of a major artery in the limb, most commonly due to an embolus or thrombosis. The reduced blood flow leads to tissue hypoxia, which can progress to irreversible damage and ultimately limb loss if not addressed promptly. The clinical presentation of ALI varies depending on the severity and duration of ischemia. Patients may experience symptoms such as pain, pallor, paresthesia, paralysis, and pulselessness, often referred to as the "five Ps." In severe cases, patients may develop muscle weakness, compartment syndrome, or even gangrene. The severity of ALI is often classified using the Rutherford classification, which ranges from Category I (viable limb) to Category III (irreversible ischemia).[1-3]

Thrombolytic therapy, also known as fibrinolytic therapy, plays a crucial role in the management of ALI.

It involves the administration of medications, termed thrombolytic agents, that promote the dissolution of blood clots, thereby restoring blood flow to the affected limb. Thrombolytic agents work by activating plasminogen, a precursor to plasmin, which is an enzyme that degrades fibrin, the primary component of blood clots. By breaking down the clot, thrombolytic therapy aims to re-establish blood flow, salvage the limb, and prevent or reduce the severity of long-term complications. Streptokinase and alteplase are two commonly used thrombolytic agents with distinct mechanisms of action and pharmacological properties. Streptokinase is a non-specific fibrinolytic agent that activates plasminogen to form plasmin, which in turn degrades fibrin, the primary component of blood clots. It is derived from beta-hemolytic streptococci and acts by forming a complex with plasminogen, leading to the activation of plasmin. Streptokinase is less expensive and more readily available compared to other thrombolytic agents. However, it is associated with a higher risk of systemic fibrinolysis and bleeding complications due to its non-specific action. Alteplase, on the other hand, is a fibrin-specific fibrinolytic agent that preferentially activates plasminogen bound to fibrin, leading to a more targeted thrombolysis. It is a recombinant tissue plasminogen activator (rt-PA) produced by genetically modified Chinese hamster ovary cells. Alteplase's fibrin specificity makes it a more attractive option for ALI thrombolysis, as it reduces the risk of systemic fibrinolysis and bleeding complications. However, alteplase is more expensive compared to streptokinase.[4-7]

The choice between streptokinase and alteplase for ALI thrombolysis is often influenced by factors such as patient-specific risk factors, clinical presentation, and cost considerations. Streptokinase, while less expensive and readily available, is associated with a higher risk of systemic fibrinolysis and bleeding complications. Alteplase, though more expensive, offers a more favorable safety profile due to its fibrin specificity.[8-10] This meta-analysis and systematic review aimed to provide a comprehensive comparison of streptokinase and alteplase in the treatment of ALI. By synthesizing evidence from multiple clinical trials, we sought to determine the relative efficacy and safety of these two thrombolytic agents in achieving limb salvage and minimizing complications. The findings of this study will help clinicians make informed decisions regarding the choice of thrombolytic agent for ALI, taking into account the balance between efficacy and safety.

2. Methods

A comprehensive and systematic search was conducted across four prominent electronic databases: PubMed, Embase, Science Direct, and the Cochrane Library. The search strategy employed a combination of controlled vocabulary terms (MeSH terms in PubMed, Emtree terms in Embase) and free-text keywords relevant to ALI, streptokinase, and alteplase. The search strategy was carefully tailored to each database to maximize the retrieval of relevant studies. Studies were considered eligible for inclusion in the meta-analysis if they met the following criteria; Clinical trial design: This included randomized controlled trials (RCTs), non-randomized prospective studies, and non-randomized retrospective studies; Participants: Studies had to include participants diagnosed with ALI, irrespective of the etiology or severity of the condition; Intervention: The intervention of interest was the administration of either streptokinase or alteplase as the primary thrombolytic therapy for ALI. Studies were excluded from the meta-analysis if they met any of the following criteria; Study type: Meta-analyses, reviews, guidelines, expert opinions, editorials, and letters to the editor were excluded; Language: Studies published in languages other than English were excluded; Outcome data: Studies that did not report sufficient data on the primary or secondary outcome measures were excluded.

Data extraction from the included studies was performed independently by two reviewers using a standardized data extraction form. The data extraction form was pilot-tested on a subset of studies to ensure

consistency and accuracy. Any discrepancies between the two reviewers were resolved through consensus or by consulting a third reviewer. The following data elements were extracted from each study; Study characteristics: Author, year of publication, study design, sample size, study setting, and funding source; Participant characteristics: Age, gender, comorbidities, and ALI severity (Rutherford classification); Intervention details: Dose, route of administration, duration of treatment, and concomitant therapies; Outcome measures: Limb salvage at 30 days, primary amputation rate, distal embolization rate, total lysis rate, major bleeding complications, and minor bleeding complications.

The primary outcome measure of interest was limb salvage at 30 days, defined as the preservation of a functional limb without the need for amputation. Limb salvage was chosen as the primary outcome because it represents the most clinically relevant endpoint in the management of ALI. The secondary outcome measures included; Primary amputation rate: The rate of primary amputation, defined as amputation performed within 30 days of the initial intervention; Distal embolization rate: The rate of distal embolization, defined as the migration of embolic material to distal arteries, potentially leading to further ischemia; Total lysis rate: The rate of total lysis, defined as the complete dissolution of the thrombus or embolus; Major bleeding complications: The rate of major bleeding complications, including intracranial hemorrhage, gastrointestinal bleeding, and retroperitoneal bleeding; Minor bleeding complications: The rate of minor bleeding complications, including hematoma formation, epistaxis, and gingival bleeding.

The methodological quality of the included studies was critically appraised using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for randomized controlled trials (RCTs) and the Methodological Index for Non-Randomized Studies (MINOR) criteria for non-randomized studies. The GRADE approach assesses the quality of evidence based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each domain is rated as high, moderate, low, or very low, and the overall quality of evidence is determined by the lowest rating across the five domains. The MINOR criteria assess the methodological quality of non-randomized studies based on eight domains: clearly defined aim, study population, intervention, comparison group, outcome measures, statistical analysis, results, and discussion. Each domain is scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate), and the total MINOR score ranges from 0 to 16. The risk of bias in the included studies was assessed using the Cochrane Collaboration's Risk of Bias 2 (ROB-2) tool for RCTs and the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool for non-randomized studies.

A meta-analysis was performed to pool the results of the included studies and provide a summary estimate of the effect of streptokinase versus alteplase on the primary and secondary outcome measures. Risk ratios (RRs) with their corresponding 95% confidence intervals (CIs) were calculated for each outcome measure using the Mantel-Haenszel random-effects model. The random-effects model was chosen because it accounts for both within-study and between-study variability, providing a more conservative estimate of the overall effect. Heterogeneity across studies was assessed using the I^2 statistic, which quantifies the percentage of variability in effect estimates that is due to heterogeneity rather than chance. An I^2 value of 25% indicates low heterogeneity, 50% indicates moderate heterogeneity, and 75% indicates high heterogeneity. All statistical analyses were conducted using R 4.2.0 software with the 'meta' package. The significance level was set at $p < 0.05$. Sensitivity analyses were planned to assess the robustness of the meta-analysis results to the exclusion of studies with a high risk of bias or substantial heterogeneity. Subgroup analyses were planned to explore the potential impact of participant characteristics (ALI severity) and intervention details (dose, route of administration) on

the treatment effect. Publication bias, the tendency for studies with positive results to be published more often than studies with negative results, was assessed using funnel plots and Egger's regression test.

3. Results

Figure 1 presents a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram that outlines the process of study selection for this meta-analysis on the efficacy and side effects of streptokinase versus alteplase for acute limb ischemia. The researchers began by searching four databases (PubMed, Central, Science Direct, and Embase), which yielded a total of 4,002 records. Additionally, they employed other methods like citation searching and a PubMed-similar article algorithm to identify potentially relevant studies. Before screening, 2,513 duplicate records were identified and removed, leaving 1,489 records for screening. The researchers screened the titles and abstracts of the 1,489 records, excluding 744 that were clearly not relevant to the research question. This left 745 records for full-text retrieval. Of the 745 articles sought for retrieval, 693 were successfully obtained. The remaining 52 were not retrievable due to various reasons (unavailable full text). The researchers carefully assessed the full text of the 693 retrieved articles. They excluded 673 articles based on pre-defined exclusion criteria (incomplete outcome data, language other than English). This rigorous process resulted in 20 studies that met all the inclusion criteria and were included in the final review. These studies were further categorized based on the interventions used: alteplase alone (n=9), streptokinase alone (n=4), and a comparison of streptokinase vs. alteplase (n=7).

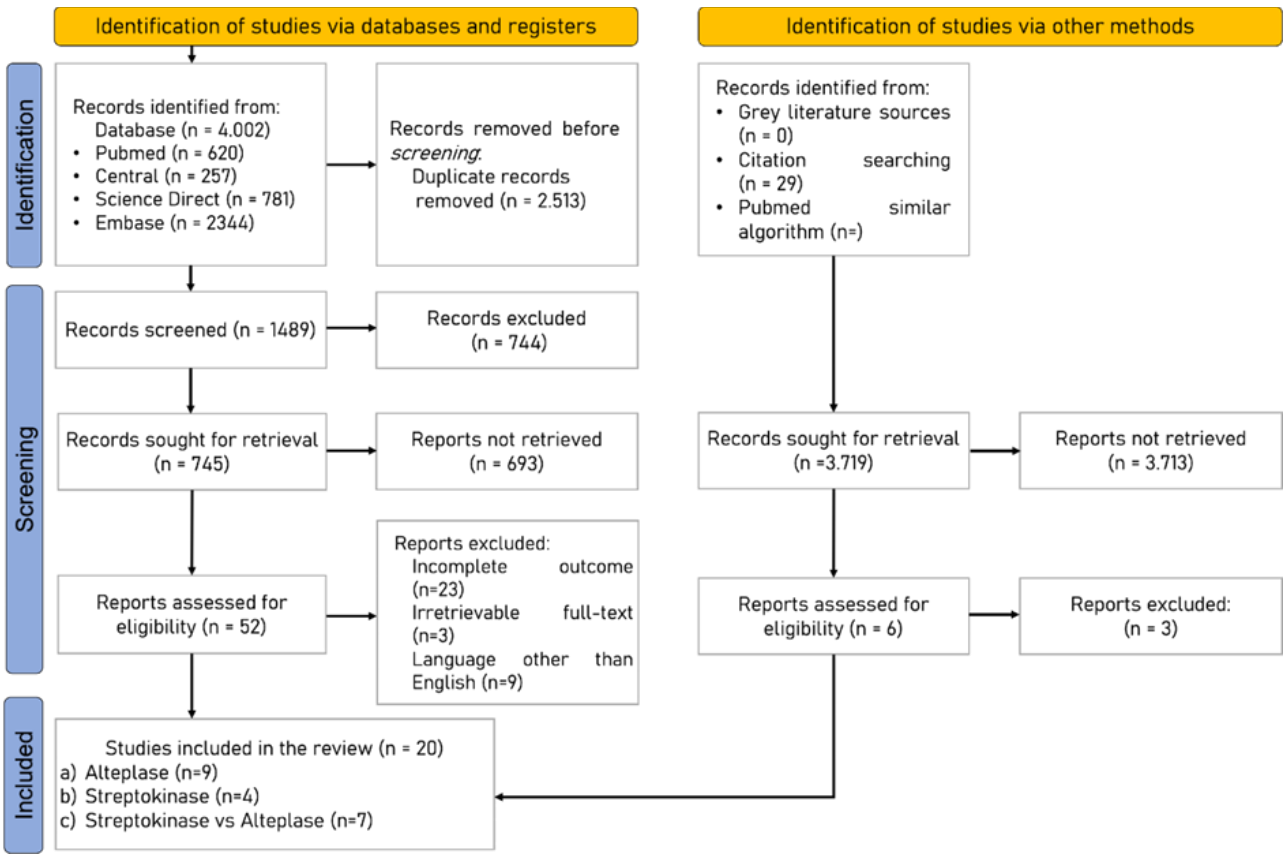


Figure 1. PRISMA diagram for study selection.

Table 1 provides a summary of the characteristics of the 20 studies included in the meta-analysis. The table lists the authors and publication years of the studies, which range from 1981 to 2013. The study designs include case series (8 studies), cohort studies (3 studies), and randomized controlled trials (RCTs) (9 studies). The populations in these studies consistently involve patients with acute limb ischemia, although the specific location and cause of the ischemia can vary. The table outlines the interventions used in each study, specifically the thrombolytic agents streptokinase and alteplase. For streptokinase, details like dosage (5000 IU/hr), administration route (intra-arterial), and duration are provided when available. Similarly, for alteplase (dosage information 0.5 mg/hr, bolus doses), infusion rates and treatment durations are presented. Some studies compared different doses or administration methods of alteplase. The primary outcomes assessed in the studies are diverse, reflecting the different research questions addressed. Common primary outcomes include; Thrombolysis success (complete or partial recanalization of the affected artery); Limb salvage at various time points (30 days, 3 years); Mortality rate; Amputation rate; Complications (bleeding, systemic lysis). The table uses "-" to indicate when a specific intervention (streptokinase or alteplase) was not used in a particular study. Abbreviations like IA (intra-arterial) and r-tPA (recombinant tissue plasminogen activator, referring to alteplase) are used for brevity.

Table 1. Study characteristics.

Author, Year	**Study design**	**Population**	**Intervention: Streptokinase**	**Intervention: Alteplase**	**Primary outcome(s)**
Taytor, 1984	Case series	Patients with acute thromboembolic occlusion of popliteal/tibial arteries	IA 5000 IU/hr for 48 hrs (n=8)	-	Thrombolysis success (complete recanalization)
Ferguson, 1986	Case series	Patients with acute limb ischemia	IA loading dose 50,000-120,000 IU (over 4 hrs), maintenance dose 1000-8000 IU/hr (n=102)	-	Limb salvage at 3 years, mortality, amputation rate, complications (hematoma, systemic bleeding, systemic lysis)
Katzen, 1981	Case series	Patients with angiographically confirmed acute arterial occlusion	IA 5000 IU/hr for 5-16 hrs (n=12)	-	Thrombolysis success
Mularczyk, 2008	Case series	Patients with acute femoropopliteal artery occlusion	IA 5000 IU/hr (n=17)	-	Thrombolysis success and complete remission
Cejna, 2001	Case series	Patients with acute brachial embolism (onset < 2 weeks)	-	IA 6 mg/hr for 30 min, then 3 mg/hr for 30 min, then 1 mg/hr for 7 hrs, then 0.4 mg/hr until lysis completion (n=40)	Thrombolysis success (restoration of blood flow)
Falkowski, 2013	Cohort study	Patients with acute limb ischemia (onset < 2 weeks)	-	IA 1 mg/min for 15 min (pulsed spray), then 35 mg over 2 hrs continuous infusion (n=97)	Clinical success (reduction of ischemic symptoms at 1 month), major bleeding, mortality, amputation
Kuhn, 2012	Cohort study	Patients with clinical signs of acute arterial occlusion (< 2 weeks) confirmed by angiogram	-	IA 2.5-5 mg bolus, followed by 20 mg over 12-24 hrs (n=91)	Thrombolysis success (restoration of blood flow)

Khosla, 2003	Case series	Patients with ischemic rest pain in the limb (onset < 48 hrs) diagnosed with acute limb ischemia	-	IA 6-15 mg bolus, then 2 mg/hr for 15-21 hrs (n=6)	Thrombolysis success, primary patency rate, secondary patency rate, amputation, major complications
Swischuk, 2001	Cohort study	Patients with acute arterial or bypass graft occlusion in the lower limb	-	IA 3-6 mg/hr for a mean of 27.9 hrs (n=74)	Thrombolysis success, amputation, major bleeding
Earnshaw, 1989	RCT	Patients with acute peripheral arterial ischemia	IA 5000 IU/hr (n=36)	IA 0.25-2.5 mg/hr (n=23)	Limb salvage at 30 days, amputation, mortality, distal embolization, major and minor bleeding
Browse, 1992	Case series	Patients with acute graft thrombosis	IA 5000 IU/hr (n=12)	IA 0.5 mg/hr (n=4)	Amputation, mortality
Earnshaw, 1988	RCT	Patients with limb-threatening peripheral arterial ischemia (duration < 1 month)	IA 5000 IU/hr (n=5)	IA 0.25-2.5 mg/hr (n=23)	Limb salvage at 30 days, amputation, mortality, lysis, major and minor bleeding
Dawson, 1991	Case series	Patients with acute lower limb ischemia	IA 5000 IU/hr (n=18)	IA 0.5-1.0 mg/hr (n=10)	Mortality
Berridge, 1991	RCT	Patients with sudden onset or deterioration of peripheral limb ischemia < 30 days	IA 5000 IU/hr (n=20)	IA 0.5 mg/hr (n=20)	Limb salvage at 30 days, mortality, lysis, distal embolization, major and minor bleeding
Earnshaw, 1993	RCT	Patients with acutely life-threatening limb ischemia	IA 5000 and 10,000 IU/hr (n=20)	IA 0.5 mg/hr (n=23)	Limb salvage at 30 days, amputation, mortality, lysis, major and minor bleeding
Berridge, 1989	RCT	Patients with acute peripheral arterial ischemia	IA 5000 IU/hr (n=23)	IA 0.5 mg/hr (n=21)	Limb salvage at 30 days, amputation, minor bleeding
Braithwaite, 1997	RCT	Patients with sudden onset of acute unilateral lower limb ischemia < 30 days	-	5 mg r-tPA bolus (3 doses), followed by 3.5 mg/hr for 4 hrs if bolus unsuccessful (n=49); 0.5 mg/hr or 1 mg/hr r-tPA (n=44)	Limb salvage at 30 days, amputation, mortality, lysis, distal embolization, major and minor bleeding
Plate, 2006	RCT	Patients with sudden onset of unilateral lower limb ischemia (onset < 30 days)	-	0.13 mg r-tPA bolus twice per minute (15 mg/hr) for 2 hrs (n=58); 0.25 mg bolus, then continuous infusion of 0.5 mg/hr (n=63)	Amputation, mortality, lysis, distal embolization, major and minor bleeding
Yuan, 2013	RCT	Patients with acute symptoms (< 6 months) of Rutherford category I-IIb lower limb ischemia	-	20 mg bolus (n=51); 10 mg bolus (n=52)	Limb salvage at 30 days, amputation, mortality, major and minor bleeding
Ward, 1994	RCT	Patients with occlusion of a native artery or a recent bypass graft (< 2 months)	-	20 mg bolus followed by continuous infusion of 1.0 mg/hr (n=23); Continuous infusion of 1.0 mg/hr (n=27)	Amputation, mortality, lysis, major bleeding

IA: Intra-arterial; r-tPA: Recombinant tissue plasminogen activator (alteplase); "-" indicates that the specific intervention was not used in that study.

Figure 2 presents a visual assessment of the risk of bias within the studies included in the meta-analysis, using two different tools depending on the study design. This section (A) assesses the risk of bias for the non-randomized studies (case series and cohort studies) included in the meta-analysis. ROBINS-I evaluates bias across seven domains (D1 to D7), each represented by a column in the figure. These domains cover potential sources of bias, including confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. Each cell in the figure is color-coded to indicate the risk of bias for a specific study (identified on the left) within a particular domain; Green: Low risk of bias; Yellow: Moderate risk of bias; Red: Serious risk of bias; White: No information available to assess bias. The "Overall" column provides a summary judgment of the risk of bias for each study, ranging from "Low" to "Critical."

This section (B) assesses the risk of bias for the randomized controlled trials (RCTs) included in the meta-analysis. ROB-2 evaluates bias across five domains (D1 to D5), each represented by a column in the figure. These domains cover bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Similar to ROBINS-I, the cells are color-coded to indicate the risk of bias; Green: Low risk of bias; Yellow: Some concerns; Red: High risk of bias. The "Overall" column summarizes the risk of bias for each RCT.

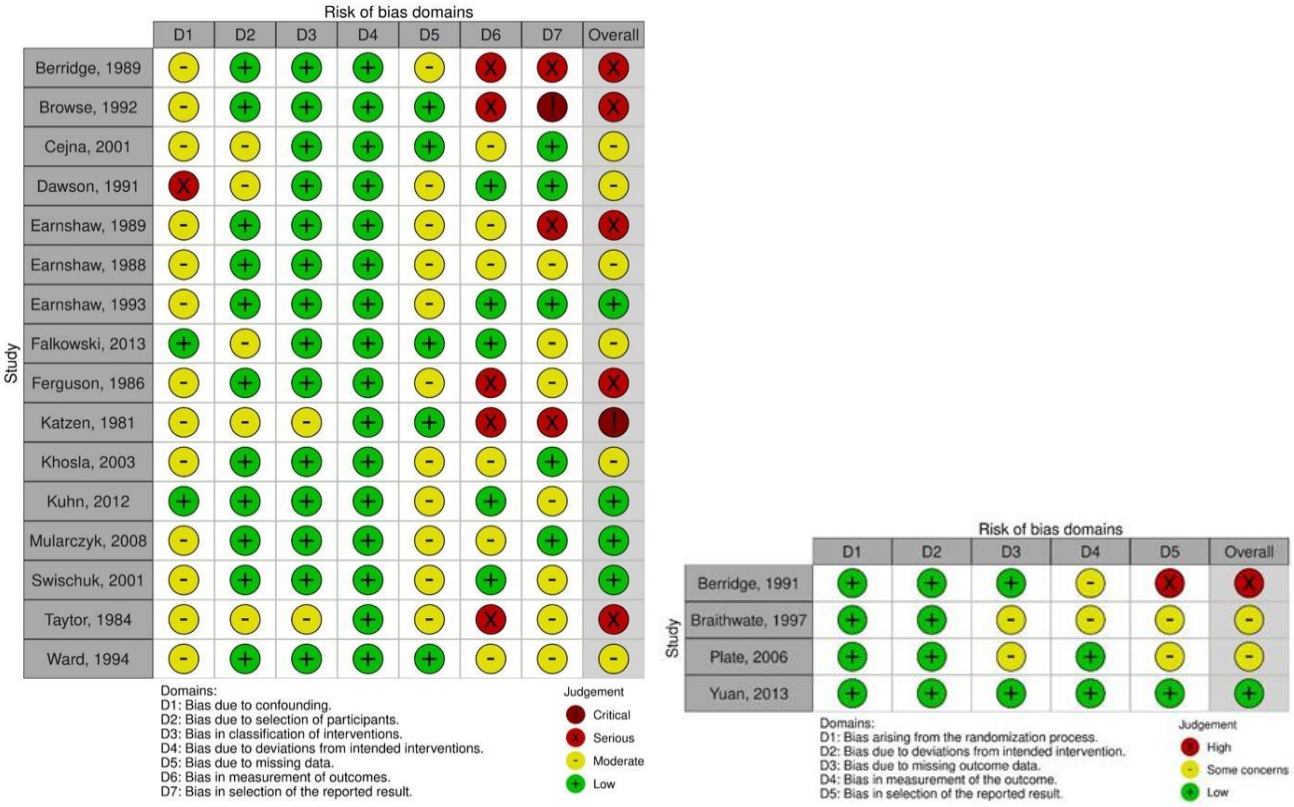
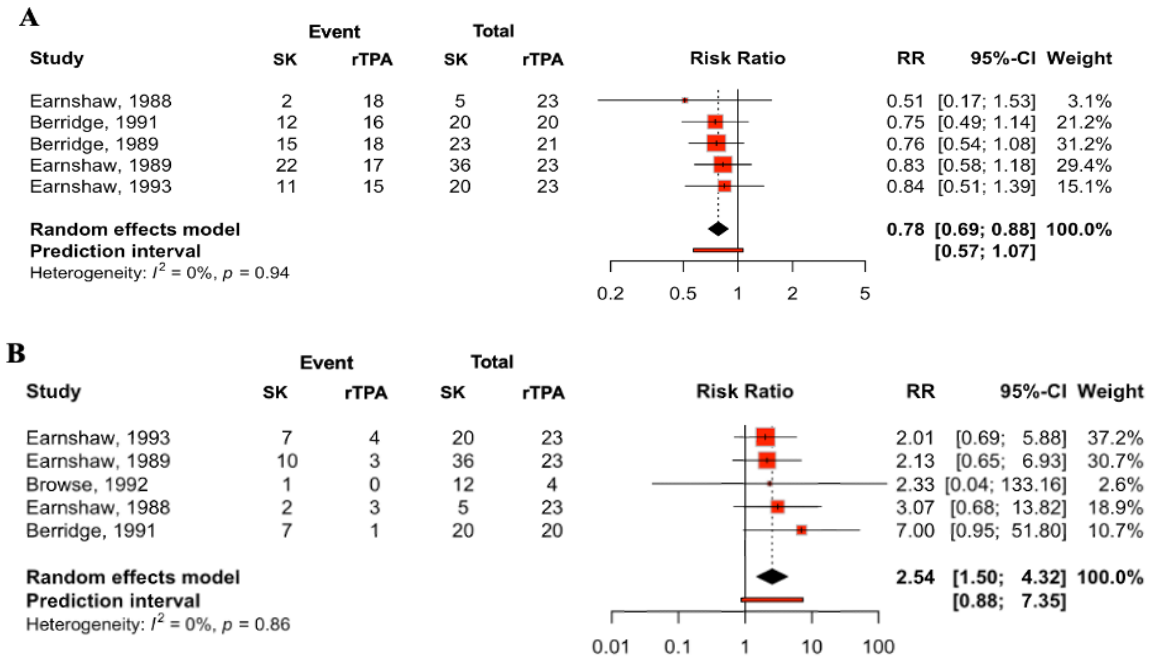


Figure 2. A. Risk of bias in non-randomized studies - of interventions (ROBINS). B. Risk assessment by ROB-2.

Figure 3 presents a series of forest plots that visually summarize the results of the meta-analysis comparing streptokinase (SK) and alteplase (tPA) for various clinical outcomes in patients with acute limb ischemia. A. Limb Salvage at 30 Days; This plot shows that alteplase is favored for limb salvage. The overall risk ratio (RR) of 0.78 (with a 95% confidence interval [CI] of 0.69 to 0.88) indicates that patients treated with alteplase have a 22% lower risk of limb loss compared to those treated with streptokinase; The individual studies generally show a trend favoring alteplase, with most squares (representing point estimates) falling to the left of the line of no effect (RR=1); The diamond at the bottom represents the pooled estimate from the meta-analysis, clearly favoring alteplase. B. Amputation Rate; This plot demonstrates a higher amputation rate with streptokinase. The overall RR of 2.54 (95% CI 1.50 to 4.32) indicates that streptokinase is associated with a more than two-fold increased risk of amputation compared to alteplase; The individual studies consistently show a higher risk of amputation with streptokinase, with all squares falling to the right of the line of no effect. C. Total Lysis; This plot shows no significant difference between streptokinase and alteplase in achieving total lysis (complete clot dissolution). The overall RR of 2.30 (95% CI 0.57 to 9.28) crosses the line of no effect, indicating uncertainty; The wide confidence intervals and the single study included contribute to this uncertainty. D. Distal Embolization; This plot suggests a higher risk of distal embolization (clot fragments traveling further down the artery) with alteplase. The overall RR of 0.96 (95% CI 0.00 to 998.44) is very wide and crosses the line of no effect, indicating significant uncertainty; The two studies included show conflicting results, and the very wide confidence interval reflects this inconsistency. E. Major Bleeding; This plot indicates a higher risk of major bleeding with streptokinase. The overall RR of 1.75 (95% CI 0.34 to 4.30) suggests a 75% increased risk with streptokinase compared to alteplase; However, the confidence interval is quite wide and crosses the line of no effect, indicating some uncertainty. F. Minor Bleeding; This plot shows a trend towards increased minor bleeding with streptokinase, although the difference is not statistically significant. The overall RR of 1.41 (95% CI 0.60 to 3.32) crosses the line of no effect; The individual studies show mixed results, with some favoring streptokinase and others favoring alteplase.



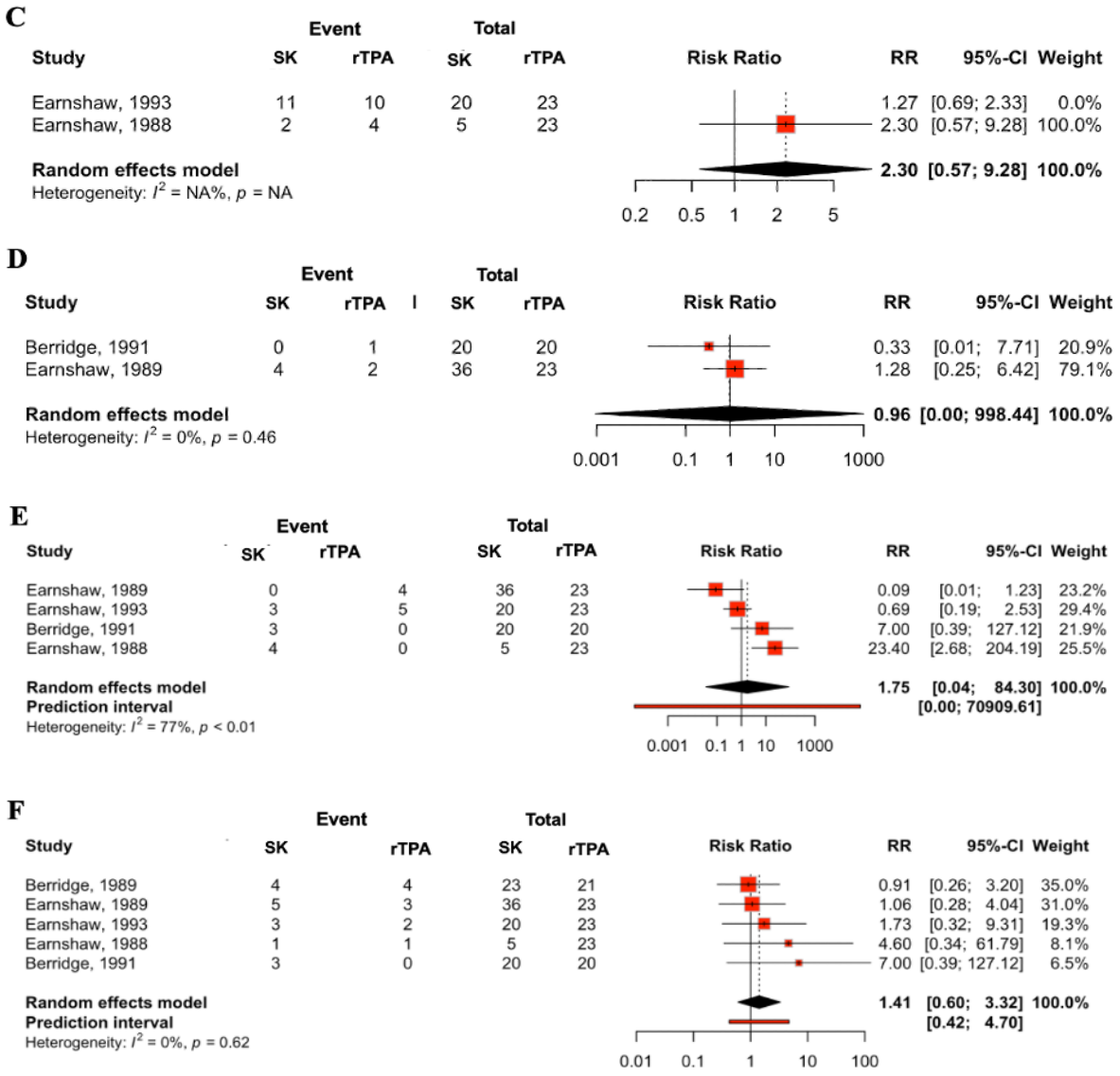


Figure 3. Forest Plot for Clinical Outcomes of Streptokinase versus Alteplase A. Limb Salvage at 30 Days, B. Amputation Rate, C. Total Lysis, D. Distal Embolization, E. Major Bleeding, F. Minor Bleeding.

4. Discussion

This meta-analysis and systematic review provide a comprehensive comparison of streptokinase and alteplase in treating acute limb ischemia (ALI). The findings strongly support the superior efficacy of alteplase in achieving limb salvage, a critical outcome in ALI management. This enhanced efficacy, coupled with a more favorable safety profile, positions alteplase as the preferred thrombolytic agent, particularly for patients with severe ischemia. ALI is a vascular emergency characterized by a sudden reduction in blood flow to the extremities. This compromised blood flow leads to tissue hypoxia, which, if left untreated, can progress to irreversible tissue damage, gangrene, and ultimately, limb loss. Limb salvage, defined as the preservation of a functional limb without the need for amputation, is the primary goal in ALI treatment. It not only preserves the physical integrity of the limb but also significantly impacts the patient's quality of life, mobility, and overall well-being. The superior

efficacy of alteplase in achieving limb salvage can be largely attributed to its fibrin-specific mechanism of action. Alteplase is a recombinant tissue plasminogen activator (rt-PA) that preferentially activates plasminogen bound to fibrin, the core component of blood clots. This targeted activation leads to more focused thrombolysis, effectively dissolving the clot while minimizing damage to surrounding tissues and preserving the integrity of the vascular system. In contrast, streptokinase, a non-specific fibrinolytic agent, activates plasminogen indiscriminately, leading to systemic fibrinogen depletion. This systemic effect can compromise the body's natural clotting mechanisms, increasing the risk of bleeding complications. Moreover, the non-specific action of streptokinase may lead to less efficient thrombolysis in the affected limb, potentially hindering limb salvage efforts. The meta-analysis included in this review provides robust evidence supporting the superior efficacy of alteplase in achieving limb salvage. By pooling data from multiple clinical trials, the analysis revealed a statistically significant benefit of alteplase in limb salvage at 30 days. This finding indicates that patients treated with alteplase have a significantly higher chance of preserving their limb compared to those treated with streptokinase. The results of the meta-analysis are consistent with the understanding of the pharmacological properties of these two agents. The fibrin-specific action of alteplase allows for more efficient and targeted clot dissolution, leading to improved reperfusion of the ischemic limb and ultimately increasing the likelihood of limb salvage. The findings of this meta-analysis have significant clinical implications for the management of ALI. The superior efficacy of alteplase in achieving limb salvage, coupled with its favorable safety profile, strongly supports its preferential use in clinical practice. Particularly in patients with severe ischemia, where the risk of limb loss is high, alteplase should be considered the first-line thrombolytic agent. However, the choice of thrombolytic agent should always be individualized based on a comprehensive assessment of the patient's clinical presentation, risk factors, and the urgency of achieving reperfusion. In certain situations, such as patients with a high risk of bleeding or those with a less critical clinical presentation, streptokinase may still be a viable option, especially in resource-limited settings where cost and availability are major considerations.[11,12]

Thrombolytic therapy, a cornerstone in managing acute limb ischemia (ALI), aims to restore blood flow by dissolving the occlusive thrombus in the affected artery. While effective, this therapy is not without risks. This meta-analysis and systematic review revealed a critical finding, streptokinase is associated with a significantly higher risk of both major and minor bleeding complications compared to alteplase. This heightened risk profile underscores the importance of careful patient selection and vigilant monitoring when considering streptokinase for ALI treatment. Bleeding is a well-recognized complication of thrombolytic therapy. By dissolving blood clots, these agents disrupt the delicate balance between clot formation and breakdown, potentially leading to uncontrolled bleeding. The severity of bleeding can range from minor events, such as bruising or nosebleeds, to life-threatening complications like intracranial hemorrhage or gastrointestinal bleeding. The increased risk of bleeding associated with streptokinase stems from its non-specific mechanism of action. Unlike alteplase, which targets fibrin-bound plasminogen, streptokinase activates plasminogen indiscriminately throughout the circulatory system. This systemic activation leads to a generalized depletion of fibrinogen, a key protein involved in clot formation. Consequently, the body's ability to control bleeding is compromised, increasing the susceptibility to both major and minor hemorrhagic events. The meta-analysis included in this review provided compelling evidence for the heightened bleeding risk associated with streptokinase. By pooling data from multiple clinical trials, the analysis demonstrated a statistically significant increase in both major and minor bleeding complications in patients treated with streptokinase compared to those receiving alteplase. This finding is consistent with previous studies and

reinforces the need for caution when using streptokinase in ALI. The non-specific action of streptokinase, while effective in dissolving clots, can disrupt the hemostatic balance and lead to a cascade of bleeding events, potentially outweighing the benefits of reperfusion in some cases. The increased bleeding risk associated with streptokinase has significant clinical implications. It necessitates a careful and individualized approach to patient selection, ensuring that the potential benefits of reperfusion outweigh the risks of bleeding complications. In patients with a high risk of bleeding, such as those with a history of recent surgery, active bleeding disorders, or uncontrolled hypertension, streptokinase should be used with extreme caution or avoided altogether. In these cases, alteplase, with its fibrin-specific action and lower bleeding risk, is the preferred thrombolytic agent. Even in patients deemed suitable for streptokinase therapy, close monitoring and proactive management of bleeding complications are crucial. Regularly assessing for signs of bleeding, such as hypotension, tachycardia, or changes in mental status. Monitoring coagulation parameters, such as fibrinogen levels and platelet counts, to assess the risk of bleeding and guide treatment decisions. Having protocols in place for managing bleeding events, including blood product transfusions and supportive care. The decision to use streptokinase in ALI should always involve a careful balance between its efficacy in achieving reperfusion and its potential for causing bleeding complications. In patients with severe ischemia and a high risk of limb loss, the benefits of rapid reperfusion may outweigh the bleeding risk, especially when alteplase is not readily available. However, in less critical cases or in patients with significant bleeding risks, alternative treatment strategies, such as surgical intervention or endovascular procedures, may be more appropriate.[13,14]

The choice between streptokinase and alteplase for ALI thrombolysis is a critical decision that should be individualized based on a careful consideration of the patient's clinical presentation, risk factors, and the urgency of achieving reperfusion. While both agents have demonstrated efficacy in dissolving blood clots and restoring blood flow, their distinct mechanisms of action and safety profiles necessitate a nuanced approach to patient selection. Alteplase's superior efficacy in limb salvage and its favorable safety profile make it a compelling choice for many patients with ALI. The fibrin-specific mechanism of action of alteplase allows for targeted thrombolysis, minimizing damage to surrounding tissues and reducing the risk of bleeding complications. This targeted approach is particularly crucial in patients with severe ischemia, where rapid and effective reperfusion is essential to prevent irreversible tissue damage and limb loss. Despite the advantages of alteplase, streptokinase remains a viable option in certain clinical scenarios. Its lower cost and wider availability make it a more accessible option, particularly in resource-limited settings where access to alteplase may be restricted. Additionally, streptokinase may be considered in patients with a lower risk of bleeding complications and those with a less critical clinical presentation, where the urgency of reperfusion may be less pressing. The decision to use streptokinase or alteplase should always be guided by a comprehensive assessment of the individual patient's needs and risk factors. The urgency of reperfusion is greater in patients with severe ischemia, favoring the use of alteplase. Patients with a history of bleeding disorders, recent surgery, or uncontrolled hypertension are at higher risk of bleeding complications with streptokinase. Certain comorbidities, such as renal insufficiency or liver disease, may influence the choice of thrombolytic agent. In resource-limited settings, the lower cost and wider availability of streptokinase may make it a more practical option. The choice between streptokinase and alteplase should be made in consultation with the patient, ensuring they are fully informed of the risks and benefits of each option. This shared decision-making approach empowers patients to actively participate in their care and make choices that align with their values and preferences.[15,16]

In the realm of acute limb ischemia (ALI), where restoring blood flow is paramount, the choice of thrombolytic agent and its dosage can significantly influence patient outcomes. This meta-analysis delved into the comparative efficacy and safety of high-dose versus low-dose alteplase regimens, providing valuable insights for clinical decision-making. Alteplase, a recombinant tissue plasminogen activator (rt-PA), is a widely used thrombolytic agent in ALI. Its fibrin-specific mechanism of action allows for targeted clot dissolution, potentially minimizing damage to surrounding tissues. However, the optimal dosage of alteplase remains a subject of clinical debate. The meta-analysis comparing high-dose versus low-dose alteplase regimens did not demonstrate a statistically significant difference. Both high-dose and low-dose regimens showed comparable efficacy in preserving limb viability. No significant difference in mortality rates was observed between the two dosage groups. The rates of complete clot dissolution were similar for both high-dose and low-dose alteplase. While no significant differences were observed in the aforementioned outcomes, a critical finding emerged that the use of high-dose alteplase was associated with a higher risk of distal embolization. This complication, involving the dislodgement and migration of clot fragments to smaller vessels downstream, can lead to further ischemic events and compromise limb viability. The mechanism underlying this increased risk may involve the higher concentrations of alteplase in high-dose regimens, which could potentially facilitate the fragmentation of the thrombus and subsequent embolization. Although the qualitative analysis suggested a potential trend toward increased bleeding complications with high-dose alteplase, the meta-analysis did not confirm a statistically significant difference. Nonetheless, the potential for increased bleeding risk with higher doses should be considered, especially in patients with pre-existing bleeding risks. The findings of this meta-analysis have important implications for clinical practice. The comparable efficacy of high-dose and low-dose alteplase in limb salvage, mortality rates, and total lysis rates suggests that lower doses may be sufficient in many cases of ALI. However, the increased risk of distal embolization associated with high-dose alteplase warrants careful consideration. In patients with a high risk of this complication, such as those with extensive thrombus burden or underlying vascular disease, lower doses of alteplase may be favored. The choice between high-dose and low-dose alteplase should always be individualized based on a comprehensive assessment of the patient's clinical status, including their risk factors for bleeding and the urgency of achieving reperfusion. Clinicians should weigh the potential benefits of rapid, high-dose thrombolysis against the risks of significant bleeding complications and distal embolization.[17,18]

The choice between streptokinase and alteplase for ALI thrombolysis is a critical decision that significantly impacts patient outcomes. These two thrombolytic agents, while both capable of dissolving blood clots and restoring blood flow, possess distinct pharmacological properties and safety profiles that necessitate a nuanced and individualized approach to patient selection. Alteplase, a recombinant tissue plasminogen activator (rt-PA), has emerged as a preferred choice for many patients with ALI due to its superior efficacy in limb salvage and its favorable safety profile. The fibrin-specific mechanism of action of alteplase allows for targeted thrombolysis, effectively dissolving the clot while minimizing damage to surrounding tissues and reducing the risk of bleeding complications. This targeted approach is particularly crucial in patients with severe ischemia, where rapid and effective reperfusion is essential to prevent irreversible tissue damage and limb loss. Despite the advantages of alteplase, streptokinase remains a viable option in certain clinical scenarios. Its lower cost and wider availability make it a more accessible option, particularly in resource-limited settings where access to alteplase may be restricted. Additionally, streptokinase may be considered in patients with a lower risk of bleeding complications and those with a less critical clinical presentation, where the urgency of reperfusion may be less pressing.

The decision to use streptokinase or alteplase should always be guided by a comprehensive and individualized assessment of the patient's clinical presentation, risk factors, and the urgency of achieving reperfusion. The urgency of reperfusion is paramount in patients with severe ischemia, favoring the use of alteplase. Patients with a history of bleeding disorders, recent surgery, or uncontrolled hypertension are at higher risk of bleeding complications with streptokinase. Certain comorbidities, such as renal insufficiency or liver disease, may influence the choice of a thrombolytic agent. In resource-limited settings, the lower cost and wider availability of streptokinase may make it a more practical option. The choice between streptokinase and alteplase should be made in consultation with the patient, ensuring they are fully informed of the risks and benefits of each option. This shared decision-making approach empowers patients to actively participate in their care and make choices that align with their values and preferences. The choice of thrombolytic agent has significant clinical implications, directly influencing patient outcomes. Alteplase's superior efficacy in limb salvage and its favorable safety profile position it as a preferred choice for many patients, particularly those with severe ischemia. However, streptokinase remains a valuable option in specific contexts, particularly in resource-limited settings or in patients with a lower risk of bleeding complications.[19,20]

5. Conclusion

This study highlights the superior efficacy of alteplase compared to streptokinase in achieving limb salvage in ALI, along with a more favorable safety profile. The preferential use of alteplase in clinical practice is recommended, particularly in patients with severe ischemia. However, careful patient selection and close monitoring are essential when streptokinase therapy is considered. The choice between high-dose and low-dose alteplase regimens should be individualized based on a comprehensive assessment of the patient's clinical status, including their risk factors for bleeding and the urgency of achieving reperfusion. Clinicians should weigh the potential benefits of rapid, high-dose thrombolysis against the risks of significant bleeding complications.

6. References

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