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Safety of Current Therapies for Cardiogenic Cerebral Embolism: A Systematic Review

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Background: Cardiogenic cerebral embolism (CCE) accounts for approximately 20% of ischemic strokes and presents with severe neurological deficits and high mortality rates. The safety and effectiveness of current therapeutic strategies remain under evaluation. This systematic review aims to assess the safety profiles of current therapies, including thrombolysis, endovascular thrombectomy, anticoagulants, and antiplatelets, in patients with CCE.
Methods: A systematic search was conducted in Web of Science, Scopus, and PubMed for studies published up to May 2024. Articles were screened using the Rayyan intelligence tool, and their quality was assessed using the JBI critical appraisal tool. The review included randomized controlled trials (RCTs) and observational studies evaluating the safety and outcomes of different CCE treatment modalities.
Results: Ten studies met the inclusion criteria. Endovascular thrombectomy demonstrated improved functional outcomes with a reduced risk of mortality, although symptomatic intracranial hemorrhage (sICH) rates were comparable to other therapies. Intravenous thrombolysis with alteplase was associated with increased sICH risk but reduced 90-day mortality. Direct oral anticoagulants (DOACs), including apixaban and edoxaban, showed a favorable safety profile with no significant increase in intracranial bleeding. Antiplatelet therapy, particularly low-dose tirofiban, demonstrated reduced in-hospital mortality without increasing hemorrhagic risk.
Conclusion: While current therapies for CCE improve outcomes, their safety profiles vary. Endovascular thrombectomy appears effective for severe cases, whereas DOACs provide a safe alternative for long-term anticoagulation. Further large-scale trials are needed to refine treatment guidelines and minimize hemorrhagic risks.

Keywords: *Cardiogenic Cerebral Embolism; Stroke; Anticoagulants; Thrombolysis; Endovascular Thrombectomy; Antiplatelets*

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INTRODUCTION

Cerebral embolism, defined as the displacement of diverse emboli (including mural thrombi, atherosclerotic plaques, fat, tumor cells, fibrocartilage, or air) into cerebral arteries, may result in ischemic necrosis of brain tissue and localized neurological impairments. Cerebral embolism primarily occurs inside the internal carotid

artery system. Cerebral embolism constitutes roughly 15–20% of all ischemic strokes.

Cerebral embolism can be classified as cardiogenic or non-cardiogenic, depending on the origin of the emboli. Cardiogenic cerebral embolism (CCE) transpires when a thrombus or other substance from the heart migrates to the brain, resulting in an obstruction of the cerebral blood arteries. Emboli may present as white (non-hemorrhagic) or red (hemorrhagic) and frequently result in abrupt localized neurological impairments [1]. Cardiogenic cerebral embolism accounts for approximately 15% of all strokes and is considered one of the more preventable types of strokes [2].

Risk factors linked to cardiogenic cerebral embolism encompass several cardiac disorders, including atrial fibrillation (AF), ischemic heart disease, rheumatic mitral stenosis, and prosthetic heart valves. Atrial fibrillation, specifically, is pivotal, accounting for almost 75% of cardiogenic cerebral embolism cases. The pathogenesis entails emboli originating from the left atrium or left atrial appendage, traveling through the vascular system to obstruct brain arteries. The resultant neurological impairments can be catastrophic, impacting patients' quality of life and placing significant strains on families and healthcare systems [3,4].

Cardiogenic cerebral embolism presents with abrupt and frequently severe symptoms. These encompass hemiplegia (weakness or paralysis on one side of the body), sensory impairment, facial weakness, cognitive deficiencies, speech disturbances, nausea, vomiting, abrupt headache, and diminished eyesight [5,6]. Management of cardiogenic cerebral embolism entails multiple treatment strategies. Thrombolysis utilizing tissue plasminogen activator (tPA) can effectively dissolve blood clots when delivered within hours of stroke start, enhancing short-term and three-month outcomes by reinstating cerebral blood flow.

For individuals unable to undergo thrombolysis within 4.5 hours, anticoagulant treatment represents a safe and efficacious alternative. The combination of anticoagulant and antiplatelet treatment is advised. Approximately 41.2% of patients attain a favorable functional outcome (modified Rankin Scale score <2) at three months, and mortality rates exhibited variability but were not significantly different among therapy groups [2,4,7,8].

Cardiogenic cerebral embolism presents significant problems, requiring thorough assessment of existing treatments to improve safety and optimize patient care. The major aim of this systematic review is to evaluate the effectiveness of current treatments for cardiogenic cerebral embolism and to offer recommendations for innovative therapeutic strategies. Our objective is to enhance patient outcomes for this intricate disorder through a rigorous evaluation of the existing data.

METHODS

This systematic review adheres to the standards of the Preferred PRISMA2020 statement for Reporting Items in Systematic Reviews and Meta-Analyses. The research protocol has been documented in the Open Science Framework (OSF; registration doi: 10.17605/OSF.IO/KGPMQ).

Search Strategy

We collected original articles in this field by searching PubMed, Google Scholar, Web of Science, and Scopus databases for English-language literature published up to May 2024. The search was conducted based on ("cardiogenic cerebral embolism") or ("CCE"), AND ("therapy") or ("treatment") and a combination of a list of drugs and treatment modalities related to cardiogenic cerebral embolism as keywords. The full search strategy is reported in (Supplementary Table 1; Supplementary Digital Content is available online at https://doi.org/10.26676/ jevtm.40591).

Furthermore, duplicate records were omitted using EndNote version 21 and the Rayyan intelligence tool for systematic reviews. To identify other suitable studies, we also reviewed the references of relevant papers and reviews on the topic of safety of current therapies for cardiogenic cerebral embolism (Supplementary Table 1).

Eligibility criteria

Following the exclusion of animal research, the remaining studies were incorporated into the review if they adhered to the PICOS criteria:

P (Population): Patients with cardiogenic cerebral embolism.

I (Intervention): Current therapies.

C (Control group): Patients with cardiogenic cerebral embolism who have undergone sham trials or placebo trials.

O (Outcome): Patient's progression-free survival and responsiveness to treatment.

S (Study design): English-language randomized controlled trials (RCTs).

Study Selection and Quality Assessment

Two reviewers (MA, AM) employed the Rayyan intelligence tool for systematic reviews to evaluate and filter titles and abstracts in a blinded manner, identifying analogous works. The texts were acquired to evaluate the qualifications of the "Yes" and "Maybe" groups. In the event of conflicts, a third reviewer was engaged to facilitate consensus and resolve discrepancies. Conflicts were addressed by dialogue between the parties. Quality assessment and risk of bias for each included study were conducted utilizing JBI's critical appraisal methods.

RESULTS

Study Characteristics

A total of 14,236 studies were found in the screening database search, 5,740 of which were duplicate records. Two reviewers (MA, SH) examined article titles and/or abstracts. After screening 8,496 records (Figure 1), we excluded 8,443. In total, 53 studies were selected for full-text review. Forty-three reports were not retrieved due to the unavailability of full text. Ten studies met the inclusion criteria and were included in this review.

Results of Systematic Analysis of Current Therapies

Endovascular therapy

In this Chinese study from 2016, a total of 17 patients had thrombectomy with Solitaire stent [9]. Ten of these patients had intravenous recombinant tissue plasminogen activator (IV rtPA) thrombolysis with bridging arterial embolectomy, while seven of them had just undergone thrombectomy. The 16 patients in the control group only underwent IV rtPA thrombolysis. National Institutes of Health (NIH) Stroke Scale scores, Glasgow Coma Scale

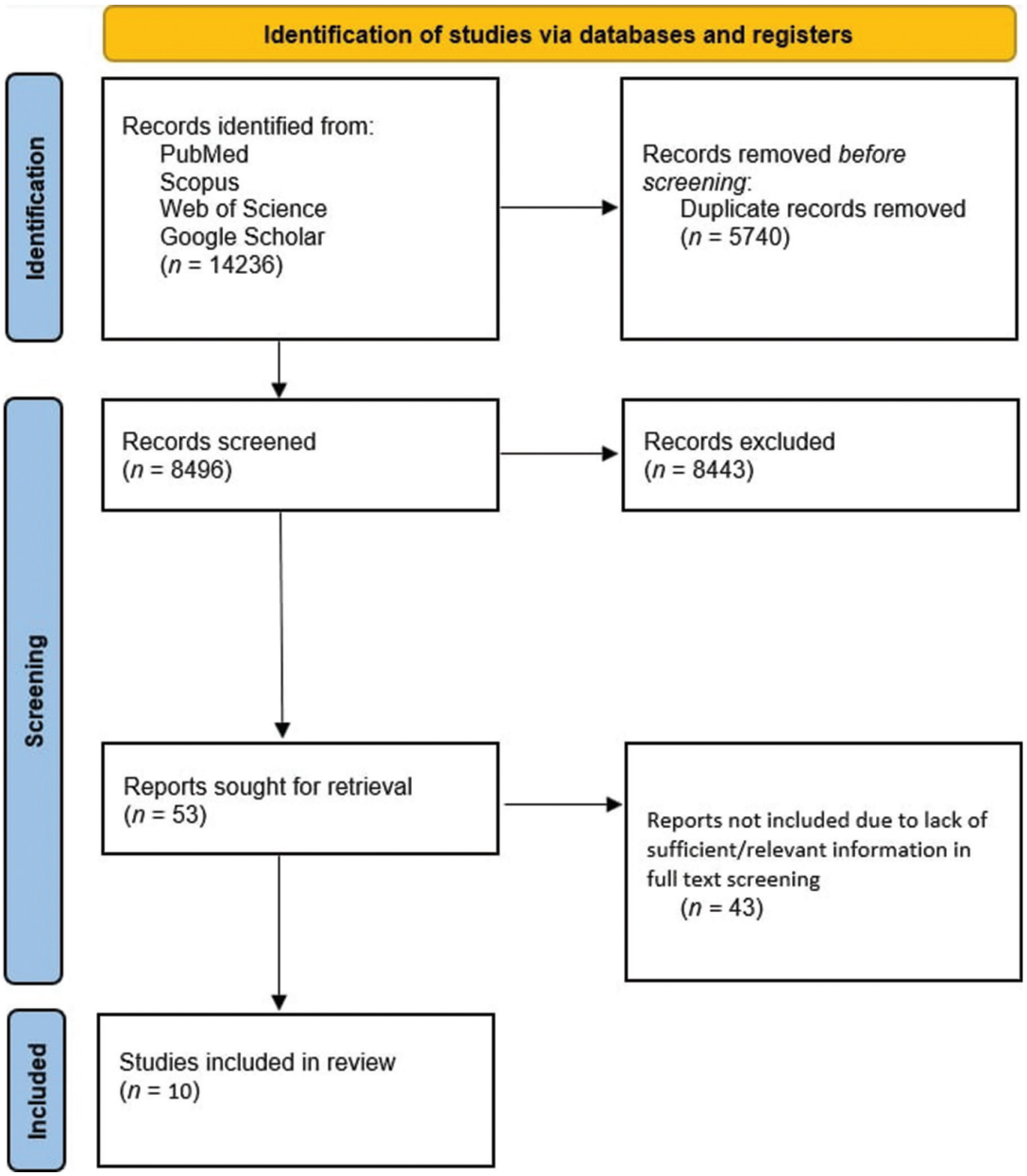

Figure 1 PRISMA flow diagram of the study selection procedure.

(GCS), symptomatic intracerebral hemorrhage, incidence of hernia, high perfusion encephalopathy, or mortality between the two groups were assessed [9].

In this Japanese study from 2019, a total of 555 patients were examined [10]. Among them, 374 patients underwent endovascular treatment (EVT), while 181 did not receive this treatment. The median age was 73 years (66–77 years). The main result was delayed hemorrhage. Any intracranial hemorrhage, symptomatic intracranial hemorrhage indicating neurological deterioration of >4 points on the NIH Stroke Scale (NIHSS) within 72 hours of stroke onset, and transient ischemic attack (TIA) or stroke recurrence within 90 days were the secondary outcomes [10].

Intravenous thrombolysis

The study by Cao et al. took place in China in 2022 [11]. In this study, 290 patients with cardioembolic (CE) stroke from the DIRECT-MT trial were included. Of these, 146 patients received direct mechanical thrombectomy (MT), and 144 received a combination therapy (endovascular thrombectomy with intravenous alteplase; bridging therapy group).

The primary outcome was the 90-day modified Rankin Scale (mRS) score [11].

In this study from 2021, they pooled data from stroke registries at eight comprehensive stroke centers across the US [12]. They retrospectively analyzed 1,367 patients (72.4%) who did not receive MT and 522 patients (27.6%) who received MT. They sought to determine whether alteplase treatment was related to 90-day mortality and the rate of hemorrhagic transformation [12].

In this study (2018), they analyzed data on patients treated with rtPA from the Safe Implementation of Treatments in Stroke–Eastern Europe (SITS-EAST) register of Central and Eastern Europe [13]. Thirty percent of all strokes were cardioembolic strokes (n = 4,131). Three-month mortality, symptomatic intracerebral hemorrhage (SICH) rate, excellent clinical outcome (mRS score 0–1) at three months following a stroke, and NIHSS score were reported as outcomes [13].

Direct oral anticoagulants (DOAC)

In this Italian study from 2020, 75 patients (median age: 78.3 years; 48 females, 27 males) were enrolled in the Prospective Observational Study of Safety of Early Treatment with Edoxaban at therapeutic dosage (60 mg/day) within five days of cardioembolic stroke onset [14]. NIHSS scores were evaluated upon admission and following revascularization, and were assessed at discharge. GCS, mRS score, intracranial bleeding, major and minor bleeding, and mortality were also reported [14].

In this US study from 2021, a total of 47 patients were randomized to the warfarin arm, and 41 patients received apixaban [15]. Early use of apixaban was started at days 0–3 for TIA, days 3–5 for small-sized acute ischemic stroke (AIS) (<1.5 cm), and days 7–9 for medium-sized AIS (≥1.5 cm, excluding entire cortical territory), while warfarin was started one week after TIA, or two weeks after AIS. The study participants' mean age (SD) was 73.5 (±12.7) years, with 56% of them being female. The incidence of the mRS score, NIHSS, and the primary composite safety outcome (fatal stroke, recurrent ischemic stroke, or TIA) were reported [15].

In this Italian study from 2016, 147 patients started DOAC within seven days of stroke onset [16]. Out of these, 97 (66%) started DOAC after 1–3 days, and 50 (34%) started DOAC after 4–7 days. The outcome variables on the follow-up were post-DOAC intracranial hemorrhage and post-DOAC recurrent ischemic stroke (any new ischemic infarct) [16].

Antiplatelets

In this study from 2000, they analyzed data from 449 patients at 45 Norwegian centers [17]. The patients were divided into two groups and given either dalteparin 100 IU/kg (low-molecular-weight-heparin; LMWH) subcutaneously twice a day along with placebo tablets daily or aspirin tablets 160 mg daily and placebo ampoules subcutaneously twice daily. The frequency of recurrent ischemic stroke and symptomatic cerebral hemorrhage during the first 14 days, mRS score, The International Stroke Trial scale, and deaths were reported as outcomes [17].

In this study from 2021, conducted at a stroke center in China, they included 288 cardioembolic stroke patients treated with endovascular therapy [18]. Out of these, 117 patients received tirofiban, whereas 171 patients did not. The primary outcome was sICH prior to discharge. The secondary outcomes included re-occlusion, in-hospital mortality, and three-month functional outcomes [18].

Effects of Interventions

Fu et al. demonstrated that patients undergoing embolectomy, either alone or in conjunction with thrombolytic therapy, had superior short- and long-term functional outcomes compared to patients receiving IV rtPA therapy alone [9]. Compared to the group that received thrombolytic treatment alone, the NIHSS score improvement for the Solitaire stent embolectomy group was noticeably more significant. The group with embolectomy showed a significantly higher GCS improvement than the group that received IV rtPA therapy alone. The long-term outcome that was assessed by measuring the mRS score was determined to be significantly better in stent patients [9]. The GCS is typically

performed upon arrival at the emergency department to assess the patient's initial level of consciousness. This is a crucial early evaluation to determine the severity of neurological impairment and guide immediate treatment decisions.

Matsukawa et al. demonstrated noticeably lower NIHSS scores in the EVT group [10]. Patients in the EVT group had a better clinical course (mRS score 0–2) than those in the no-EVT group. The EVT group had a significantly lower mortality rate within 90 days than the no-EVT group. The proportions of any intracranial bleeding and symptomatic intracranial bleeding within 72 hours and recurrence of stroke or transient ischemic attack within 90 days were similar between the two groups [10].

According to Cao et al., direct mechanical thrombectomy may be more beneficial for individuals with mild to moderate cardioembolic stroke than bridging therapy [11]. There were no significant differences in the outcome and mortality rate of CE stroke patients with an NIHSS >15 between the two treatment groups, but patients with an NIHSS ≤15 in the direct MT group were linked to better outcomes and lower mortality than those in the bridging therapy group.

The results from Zhao et al. showed that patients who received tirofiban experienced fewer decompressive craniotomies and cerebral hernia than those who did not [18]. There was a significant difference in the three-month mortality rates between patients who received tirofiban (20.5%) and those who did not (31.6%).

Yaghi et al. discovered that individuals with AIS in the context of AF who were not treated with MT had a lower mortality rate when they received IV alteplase [12]. Among patients undergoing MT, there was a non-significant reduction in the number of passes and deaths in subjects treated with intravenous alteplase compared to those who did not receive intravenous alteplase. Alteplase-treated patients were more likely to have an initial NIHSS score with a higher median (interquartile range) (8 [4–15] versus 6 [2–14], $P = 0.002$).

According to Vaclavik et al., there is no association between cardioembolic strokes (CS) and higher mortality rates [13]. After intravenous thrombolysis (IVT), patients with CS had better outcomes and were less likely to have sICH [13].

Frisullo et al. found that 53 (70.7%) of the 75 patients had excellent functional outcomes at three months (defined as mRS score 0–1), two (2.7%) patients had gastrointestinal bleeding, and 11 (14.7%) patients had minor bleeding (five epistaxis, three gingival bleedings, and three cutaneous hematomas) [14]. None of the 75 patients had significant intracranial hemorrhage at three months.

Cappellari found no correlation between the early introduction of DOAC and intracranial bleeding [16]. No patients experienced recurrent ischemic stroke.

The study conducted by Berge provides no evidence that high-dose LMWH is superior to aspirin for the prevention of recurrent ischemic stroke during the first 14 days [17]. The study showed no significant increase in sICH or improved outcome on LWMH compared with aspirin.

According to Labovitz et al., the early use of the DOAC apixaban did not increase the number of intracranial hemorrhages, including hemorrhagic transformation (HT) and intracranial hemorrhages (ICH) [15].

The summary of the outcomes is shown in Table 1.

DISCUSSION

This systematic review summarizes the safety and effectiveness of available therapies in treating cardiogenic cerebral embolism using actual patient data.

Cardiogenic cerebral embolism is a highly hazardous condition with a high rate of occurrence, disability, death, and recurrence [28,29]. It can cause immediate and critical neurological symptoms, and the high risk of bleeding and poor rate of recanalization might reduce the effectiveness of even very timely therapy [9].

Mechanical Thrombectomy

Endovascular mechanical recanalization technology is rapidly being used as a first-line treatment for acute cerebral infarction since the development of catheter and neural intervention techniques, especially in patients with occluded major cerebral arteries. Large intracranial vessels, such as the basilar artery, the middle cerebral artery, the anterior cerebral artery, and the end of the internal carotid artery, frequently become blocked due to cardioembolisms. The recanalization rate of such occluded arteries is relatively low, about 10%, when rtPA thrombolytic therapy is the only treatment used. Furthermore, the bleeding conversion rate is estimated to be 10.23%. Using IV rtPA thrombolysis alone to treat cerebral embolism often does not achieve satisfactory results [28,30].

The MR-CLEAN trial [31] revealed the first indication that mechanical thrombectomy performed within six hours of symptom onset improved 90-day clinical outcomes (mRS score) compared to a group receiving standard medical care, with 90.6% receiving IV rtPA within 4.5 hours. According to the Fu et al. study, the stent group had significantly higher NIHSS and GCS scores during admission and discharge than the group that received drug therapy alone. In addition, the group that underwent mechanical thrombectomy had considerably better long-term clinical outcomes [9].

For the first time, a sub-analysis of an extensive prospective registry indicated that EVT could reduce the incidence of delayed hemorrhage and had no influence on neither any intracranial hemorrhage nor on symptomatic intracranial hemorrhage within 72 hours

Table 1 Summary of study characteristics and findings.

Author	*Year*	*Country*	*Participants*	*Age*	*Treatment*	*Efficacy*	*Outcome*	*Conclusion*
Maolin Fu [19]	2016	China	Embolectomy group = 17, Control = 16	Case = 55.24 ± 12.55 years, Control = 63.31 ± 13.40 years	7 thrombectomy and 10 IV rtPA thrombolysis with bridging arterial embolectomy (Solitaire stent embolectomy), Control = IV rtPA thrombolysis	–	• Reduction of NIHSS score • Better GCS at discharge • Low score of modified rankin scale	Embolectomy has better short-term and long-term outcomes compare to rtPA
Giovanni Frisullo [20]	2020	Italy	75 patients	78.3 years median	Edoxaban at therapeutic dose (60 mg/day) within five days from cardioembolic stroke onset in 90 days	–	• Reduction of NIHSS SCORE • Significant reduction of intracranial bleeding	Looks eligible in acute phase, but required large group study
Shadi Yaghi [21]	2021	The United States	1,889 patients, Study group = 1,367 patients (72.4%) alteplase, Control = 522 patients (27.6%) received MT	77.2 ± 11.8 years	Alteplase	Reduced risk of 90-day mortality = 14.3% (43/300)	Alteplase increases risk of hemorrhagic transformation, but reduced 90 days mortality risk	Alteplase without MT reduced risk of mortality
Daniel Vaclavik [22]	2018	Czech Republic and Central and Eastern Europe	13,772 patients, 4,131 CCE (30%)	70.8 ± 11.49 years	Intravenous thrombolysis (IVT)	No significant difference in mortality rate	• The risk of sICH is reduced • Higher chance of getting better within 24 h	Improves patient outcome
Wenbo Zhao [23]	2021	China	288 patients, Study group = 117, Control = 171	Case = 70.1 ± 11.0 years Control = 69.6 ± 11.0 years	Tirofiban therapy = 5 mg diluted with 100 ml NL saline at standard rate 1 mL/min (doses ranging from 0.25 mg to 0.5 mg). Tirofiban IV administered at a rate of 4–8 mL/h (i.e., 0.2 to 0.4 mg/h) for 12–24 h	Mortality rate significantly reduced	• Re-canalizations time onset gets faster • No difference in ICH risk • Reduced risk of hernia and decompressive craniectomy • Small difference in mRS scores	Tirofiban reduced mortality death, but no difference in ICH risk
Eivind Berge [24]	2000	Norway	449 patients, 224 dalteparin, 225 aspirin	80 years median	LMWH, dalteparin (100 IU/kg subcutaneously twice a day), aspirin (160 mg every day)	Dalteparin increases risk of mortality rate	• No difference in the rate of recurrent ischemic stroke within 14 days • No significant difference in symptomatic and asymptomatic ICH • ICH more severe in dalteparin • Dalteparin increases risk of mortality rate in 14 days but no difference after three months	No difference in functional outcomes between dalteparin and aspirin

Arthur J Labovitz [25]	2021	The United States	88 randomized, warfarin = 47, apixaban = 41	73.5 ± 12.7 years	Apixaban	Rate of death is reduced	Rates of fatal stroke, recurrent ischemic stroke, symptomatic ICH, and death reduced but rate of symptomatic HT increased	Apixaban seems secure and eligible for early anticoagulant therapy
Manuel Cappellari [26]	2016	Italy	147 patients, DOAC between 1 and 3 days (n = 97), Control = 4–7 days (n = 50)	Case = 78.8 ± 9.1 years, Control = 79.3 ± 6.5 years	DOAC within the first three days of stroke onset		• Reduced mean stroke onset • Lower NIHSS score • Rate of intracranial bleeding reduced in small infarct but increases in large infarct • No correlation between early DOAC and risk of intracranial bleeding after DOAC administration	• Safe and eligible early applying DOAC for nVAF patients with small and medium sized infarct • The only factor for prediction of intracranial bleeding is large infarct
Hidetoshi Matsukawa [10]	2019	Japan	562 patients, Study group (EVT) = 374, Control = 188	Case = 73 (66–77) years, Control = 72 (66–7) years	Endovascular treatment	Significant reduction of mortality rate	• Lower NIHSS score • Lower mRS score • More likely to require IV rtPA • Less chance of decompressive hemicraniectom • Same ICH risk	Reduce the risk of DH with no change in ICH risk
Jie Cao [27]	2022	China	290 patients, 146 received direct MT, 144 combination therapy with intravenous alteplase and endovascular thrombectomy (bridging therapy group)	18–60 years 73 years median	Direct mechanical thrombectomy, Control = alteplase and MT	No significant difference in mortality rate	No significant difference between the two groups in primary outcome (modified Rankin scale)	No difference of mRS scores in MT with and without alteplase within 90 days
			100/290 NIHSS ≤ 15 (47 MT/53 BT)			Reduced mortality risk	Primary and secondary outcomes (Functional independence, mRS (mRS 0–3) at 90 days, NIHSS after 24 h, NIHSS at 5–7 days or discharge) are better with MT only	Direct MT has better outcome for low risk CCE
			190/290 NIHSS > 15 (99 MT/91 BT)			No significant difference in mortality rate	No significant difference between the two groups in primary and secondary outcomes	Only slight difference in outcomes for high risk CCE

BT, bridging therapy (combination of intravenous alteplase and endovascular thrombectomy); CCE, cardioembolic stroke; DH, delayed hemorrhage; DOAC, direct oral anticoagulant; EVT, endovascular treatment; GCS, Glasgow Coma Scale; HT, hemorrhagic transformation; ICH, intracranial hemorrhage; IV rtPA, intravenous recombinant tissue plasminogen activator; IVT, intravenous thrombolysis; LMWH, low molecular weight heparin; mRS, modified Rankin Scale (a measure of functional outcome after stroke); MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale (a measure of stroke severity); NVAF, non-valvular atrial fibrillation; rtPA, recombinant tissue plasminogen activator; sICH, symptomatic intracranial hemorrhage.

in patients with cardioembolic proximal intracranial occlusion in the anterior circulation [10].

Intravenous Thrombolysis

The question of whether individuals with acute ischemic stroke and atrial fibrillation should be treated with heparin as an anticoagulant has long been debated [32–34].

The results of the study by Berge et al. provide no evidence that high-dose LMWH is better than aspirin for improving outcomes at 14 days or three months, or in preventing recurrent ischemic stroke or any other event during the first 14 days [17].

Yaghi et al. discovered that patients with acute ischemic stroke in the setting of AF who were not treated with MT had a lower 90-day mortality rate when they received intravenous alteplase medication [21]. These results support the findings of the previous extensive cohort studies [21].

When MT patients received IV alteplase treatment as opposed to those who did not, there was a non-significant reduction in the number of passes and deaths among the former group [12]. This aligns with the pivotal thrombectomy trials, which showed no impact on mortality or outcome [35,36]. This is also consistent with recent trials demonstrating no substantial additional benefit of alteplase usage in patients with proximal blockage undergoing MT [34,37,38]. These findings may be attributable to alteplase's poor ability to achieve reperfusion in patients with proximal large-artery occlusion successfully. However, our results emphasize the need for more research on this matter.

In addition, based on the RCT by Cao et al., patients with mild and moderate cardioembolic stroke may benefit more from direct mechanical thrombectomy than from bridging therapy [11].

DOCA

For individuals with nonvalvular AF, DOACs such as apixaban, dabigatran, edoxaban, and rivaroxaban are now the main treatment option for preventing stroke [39]. One in six stroke patients who are eligible for IVT are expected to have been administered DOACs after the switch from vitamin K antagonists (VKAs) to DOACs. In situations of ischemic stroke, the recommendation suggests against administering IVT to patients who have recently administered DOACs (within the last 48 hours). This advice is based on the assumption that there is a higher risk of sICH. Nevertheless, there is not much data on when oral anticoagulation should be started following an acute stroke [40].

A prospective, non-randomized study found that early initiation of edoxaban, within five days, does not seem to lead to any symptomatic intracranial bleeding or recurrent stroke after three months. However, two gastrointestinal major bleedings and 11 minor bleedings were reported [14]. A prospective analysis showed no association between early initiation of DOAC (1–3 days after stroke onset) and intracranial bleeding in stroke patients with non-valvular atrial fibrillation [16]. However, the major weakness in these studies was the absence of a control group with delayed anticoagulant treatment.

Based on our review, a randomized controlled trial was done comparing the safety of early use of apixaban versus warfarin in a 1:1 ratio. It revealed that apixaban had numerically smaller but statistically comparable rates of death, fatal stroke, recurrent strokes/TIA, and symptomatic hemorrhages. Early anticoagulant initiation following TIA or small- or medium-sized AIS from AF does not seem to impair patient safety [15]. However, more extensive pivotal trials are necessary to ascertain the possible effectiveness of the early initiation of DOCA.

Antiplatelets

The standard treatment for patients with AIS due to large-vessel obstruction is EVT [41–43]. Conversely, endothelial damage might be an unavoidable consequence that results in early re-occlusion and infarction extension [44]. Significant interest has been shown in the adjunctive administration of antiplatelet medications to reduce the rate of ischemia complications and increase the rate of favorable reperfusion.

Earlier research demonstrated that tirofiban was linked to a greater possibility of functional independence in AIS patients receiving EVT. It was also associated with a decreased risk of re-occlusion and an improved rate of favorable reperfusion [45,46].

However, a prospective study of 288 cardioembolic stroke patients found no correlation between the administration of low-dose tirofiban and three-month mortality. Additionally, there was no association with hernia, decompressive craniectomy following EVT, or different types of intracranial hemorrhage, including ICH, sICH, or fatal ICH.

Furthermore, there was no association between the use of tirofiban and a low incidence of re-occlusion after EVT. On the other hand, tirofiban was linked to a lower risk of in-hospital mortality [18]. The study design and the number of patients in this study may have caused bias. Further studies are needed to confirm these results and improve the best treatment course that can benefit this patient population.

The main strength of this study is that it explicitly addresses cardioembolic stroke patients, which is the first review of different available treatment modalities for these patients. The primary limitation of our investigation is the small sample size of the included studies. More large-scale multicenter randomized controlled trials are necessary to validate these findings.

LIMITATIONS

This systematic review has several limitations that should be acknowledged. First, the included studies exhibited variability in study designs, sample sizes, and patient characteristics, which may have introduced heterogeneity in the results. The diversity in treatment protocols and outcome measures among different studies limits direct comparability and the generalizability of findings to broader populations.

Second, while RCTs were included in this review, some of the studies were observational, which may be subject to selection bias and confounding factors. The absence of uniform inclusion criteria across studies further complicates the interpretation of treatment efficacy and safety profiles.

Third, the small sample size in certain studies, particularly those evaluating specific anticoagulants and antiplatelet therapies, restricts the ability to draw definitive conclusions regarding their long-term safety and effectiveness. Larger multicenter trials with longer follow-up durations are needed to validate these findings.

Additionally, publication bias may have influenced the results, as studies reporting positive outcomes are more likely to be published, whereas negative or inconclusive findings may be underrepresented in the literature. The reliance on published data also limits access to unpublished clinical trial results, which may provide a more comprehensive understanding of treatment risks and benefits.

Lastly, the review primarily focuses on available studies up to May 2024, and emerging therapeutic advancements or novel interventions beyond this timeframe may not be captured. Continuous research and real-world data collection are necessary to further refine treatment strategies for cardiogenic cerebral embolism.

CONCLUSION

This systematic review highlights the safety profiles of current therapeutic strategies for CCE, a major cause of ischemic stroke with significant morbidity and mortality. Endovascular thrombectomy emerged as a highly effective intervention, particularly in severe cases, improving functional outcomes without increasing intracranial hemorrhage risk. Intravenous thrombolysis with alteplase demonstrated benefits in reducing 90-day mortality but carried an increased risk of sICH. DOACs such as apixaban and edoxaban exhibited a favorable safety profile, offering a viable alternative for long-term anticoagulation with minimal risk of hemorrhagic complications. Additionally, low-dose tirofiban showed potential in reducing in-hospital mortality without elevating bleeding risks.

Despite these promising findings, variability in study methodologies and sample sizes underscores the need for further large-scale RCTs to refine treatment guidelines. Future research should focus on optimizing therapeutic strategies to balance efficacy and safety, particularly in high-risk patient populations. Tailored approaches integrating patient-specific factors will be crucial in improving long-term outcomes for individuals with CCE.

Ethics Statement

(1) All the authors mentioned in the manuscript have agreed to authorship, read and approved the manuscript, and given consent for submission and subsequent publication of the manuscript.
(2) The authors declare that they have read and abided by the JEVTM statement of ethical standards including rules of informed consent and ethical committee approval as stated in the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Author Contributions

Study concept and design: MAA, SKSR. Acquisition of data: KKH, NH, AM. Analysis and interpretation of data: SM, MAA. Drafting of manuscript: OR. Critical revision of the manuscript for important intellectual content: MA, AA, MR, MAB, SHK. Administrative, technical, and material support: AHA, AIP. Study supervision: MAA, SKSR.

SUPPLEMENTARY DIGITAL CONTENT

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Supplementary Table 1. Database search strategy.

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