Role of Tissue Plasminogen Activators, Streptokinase and Other Thrombolytics in the Treatment of Myocardial Infarction

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Review Article

ABSTRACT

In the United States, coronary artery disease is the most frequently occurring cause of mortality. A century ago, the obstruction of CA was recognized as the root cause of myocardial infarction. Through research, streptokinase was discovered as a beneficial treatment for acute myocardial infarction, lowering mortality. More recent agents, such as tissue plasminogen activators like Tenecteplase, reteplase, and alteplase have also been developed. Today, primary percutaneous coronary intervention and thrombolytic therapy have transformed the way acute myocardial infarction is treated, leading to a significant decrease in cardiovascular-related deaths. This paper offers an outline of the different antifibrinolytic agents used to manage acute myocardial infarction.

1. INTRODUCTION

Acute myocardial infarction is a serious condition that affects 1.1 million Americans annually, with 460,000 of these cases resulting in death [1]. Many of these deaths occur within an hour of symptom onset and before the patient can reach a hospital [2]. In 1912, a doctor named Herrick identified the obstruction of the proximal segment left anterior descending artery as the cause of AMI during an autopsy examination [3]. In 1958, thrombolytic therapy, using drugs to break up blood clots, was first used to treat AMI [4]. Since then, various thrombolytic drugs such as TPA and streptokinase have been developed, including tenecteplase, reteplase, and alteplase [5]. Today, thrombolytic therapy and primary percutaneous coronary intervention are widely used to treat AMI and have led to a major decline in heart disease-related mortality [6]. The goal of these treatments is to quickly and fully restore the flow of blood in the "infarct-related coronary artery". A systematic search was conducted using search string (Plasminogen Activator or Tissue or Tissue Activator D-44 or Tissue Activator D 44 or Tisokinase or Tissue-Type Plasminogen Activator) and (Streptase or Streptodecase) and (Infarction or Myocardial Infarctions or Myocardial or Stroke or Cardiovascular Stroke or heart attack) and retrieved articles from 2010-2022 Those articles which were according to our topic were selected. They were evaluated, and data was taken from them.

Thus, the aim of this review article is to explore the most popular and commonly used thrombolytics and see what role they play in preventing the risk and events of myocardial infarction at all levels. This article also focuses on reviewing these thrombolytic drugs in such a manner that all their side effects, drug interactions, and everything else is kept into perspective for physicians to be aware of when prescribing either of these drugs.

2. THE EVOLUTION OF THROMBOLYTIC THERAPY: A HISTORICAL PERSPECTIVE

Thrombolytic therapy, a treatment for dissolving blood clots, has a rich history that began in "1933" when "Dr. William Tillett" discovered streptokinase (SK) [7]. Through his observation that "streptococci agglutinated plasma but not serum", he deduced that fibrinogen, a component of plasma, was responsible for the agglutination [8]. This led to the understanding that any plasma containing streptococci would not clot and laid the foundation for thrombolysis in various medical settings [9]. In 1945, the term "streptokinase" was coined by MacLeod and Christensen. Initially, SK was used to treat patients with tuberculous meningitis and hemorrhagic pleural effusions [10].

In the case of acute myocardial infarction, SK produced by different types of streptococci can bind to and activate human plasminogen, resulting in fibrinolysis. While several small studies had previously demonstrated the benefits of SK in decreasing thirty-day or annual deaths, the GISSI ("Grupo de Analisis de la Cardiopat ıa´Isquemica Aguda-1") and ISIS ("International Study of Infarct Survival-2") research analyzed the effectiveness of "intravenous" SK in managing AMI patients [11]. The GISSI trial found an 18% reduction in overall hospital mortality in patients treated with SK compared to the control group. The study found that the extent of the benefit of the treatment with Streptokinase (SK) was related to the time between the onset of chest pain and the infusion of SK. The study found that the relative risk was 0.74, 0.80, 0.87, and 1.19 in the 0-3 hours, 3-6 hours, 6-9 hours, and 9-12 hours subgroups respectively [11]. Similar results were found in the ISIS-2 trial, where patients with acute myocardial infarction who received aspirin and SK had a significant reduction in reinfarction, death, and stroke compared to those who received no treatment [12]. The study found that the early survival benefits of the combination treatment of aspirin and Streptokinase (SK) for acute myocardial infarction persisted for up to ten years during the duration of follow-up [12].

3. THE COMPARISON BETWEEN STREPTOKINASE AND TISSUE PLASMINOGEN ACTIVATOR

To allow for bolus administering, increased longevity, specificity for fibrin, and immunity to inhibitors like plasminogen activator inhibitor-1, new thrombolytic agents have been developed. Table 1 includes the newer agents and their attributes. After the groundbreaking utilization of SK in treating AMI patients and the arrival of novel drugs, the focus turned to determining which anti-thrombosis drug was the best. Three clinical researches ISIS-3, GISSI-2, and GUSTO evaluated the application of IV SK and TPA in managing AMI [13]. The 12,490 patient GISSI-2 trial found that TPA and SK were equally found to

be effective and safe in the management of AMI and the researchers were not able to find major variations between these two drugs in decreasing severe left ventricular damage and mortality (SK 22.5% vs TPA 23.1%; RR 1.04). Although patients who received SK and heparin treatment had a notably higher major bleed rate with TPA 0.5% vs. SK 1.0% and a confidence interval of 95%, the general risk of stroke was the same across all groups who received treatment [13]. The ISIS-3 trial was a study that looked at the effects of three different treatments SK, TP, and APSAC on 41,299 suspected AMI patients. The study found that there was no significant difference in two important outcomes, mortality, and reinfarction, at 35 days after treatment. Specifically, the study found that 10.6% of patients who received SK died, while 10.5% of patients who received APSAC died. For reinfarction, 3.47% of patients who received SK had a recurrence, while 3.55% of patients who received APSAC had a recurrence [13].

Right after the drug was administered, APSAC was found to have a slightly higher rate of strokes with cerebral hemorrhage accounting for the majority of these strokes with 0.55% APSAC and 0.24% SK [14]. The GUSTO study compared the usual treatment regimen of TPA (administered over 3 hours) with an accelerated regimen of TPA (administered within 90 minutes, with two-thirds of the dose given within the first 30 minutes) [14]. The results showed that the accelerated regimen of TPA resulted in a significant decrease in death and debilitating strokes among AMI patients. At 30 days after treatment, the group that received the accelerated TPA regimen had a 14% lower mortality rate compared to the group that received SK. However, there was found to be a little bit increase in the number of hemorrhagic strokes (bleeding in the brain) in the group that received the accelerated TPA regimen compared to the SK group. Despite this increase, the overall outcome of death or debilitating stroke was still reduced in the accelerated TPA group [15].

4. OTHER THROMBOLYTIC AGENTS

4.1 The Use of Alteplase (rTPA)

Alteplase, also known as recombinant TPA (rTPA), is a "serine protease" found on "endothelial cells" that are produced using biotechnology. It converts plasminogen to plasmin [16]. Studies have shown that a 90-minute accelerated infusion of alteplase is more effective than a double dose treatment, as it has a slightly lower rate of intracranial bleeding (1.12% vs. 0.81%) [16]. The TIMI trial also demonstrated that the use of rTPA in AMI patients resulted in twice as many reperfused infarct-related arteries in the first 90 minutes of treatment compared to SK [17].

4.2 Reteplase

With a longer half-life of 13–16 minutes, reteplase is a "recombinant nonglycosylated" form of "human TPA" made in "Escherichia coli". Reteplase has the ability to enter thrombi and bind fibrin. It has been shown that reteplase does not significantly reduce 30-day mortality among patients with AMI when compared to an accelerated alteplase infusion regimen [18].

According to studies [19,20], using reteplase in conjunction with abciximab did not result in a statistically significant improvement in patients' 30-day survival rates. However, in the RAPID experiment, a double dosage of reteplase ("10 + 10 MU") was utilized, and it resulted in a full, fast, and persistent thrombolysis of IRA at ninety minutes and 5-14 days when compared to alteplase's results. Additionally, as a consequence of this, both localized and global left ventricular function improved before the patient was discharged. At the time of hospital discharge, the global ejection fraction and regional wall motion in the reteplase group were superior to those in the TPA group ("53 1.3% vs. 49 1.3%, P = 0.034") [21]. In addition, the RAPID II RCT verified that reteplase is superior to accelerated alteplase because it results in increased rates of prompt reperfusion in IRA patients and requires fewer '"acute coronary interventions" [22]. However, in the INJECT study ("International Joint Efficacy Comparison of Thrombolytics"), the enhanced IRA patency rates that were seen in the RAPID trials did not transfer into superior clinical results. The study found no statistically significant difference between the effectiveness of reteplase and that of SK in lowering mortality after 35 days [23,1].

4.3 Tenecteplase

It is a glycoprotein that contains 527 amino acids and is produced by making modifications to the "complementary DNA" for natural human TPA. It accomplishes this by first attaching to fibrin, then "converting thrombus-bound plasminogen" into plasmin in a selective manner, which ultimately

breaks down the fibrin matrix of the thrombus. Compared to native TPA, TNK has a greater fibrin specificity and increase resistance to inactivation by its endogenous inhibitor (PAI-1) [24]. In the TIMI 10A trial, A solo bolus of TNK was shown to be fibrin definite and was connected to greater IRA "patency rates" in the TIMI 10A experiment ("64% TIMI 3 flow with a 50 mg bolus dose") produced comparable rates of TIMI grade 3 flow at 90 minutes in the TIMI 10B trial [25]. Consequently, the "ASSENT 1 trial" ("Assessment of the Safety and Efficacy of a New Treatment") revealed that TNK's "safety profile" was similar to that of alteplase [25]. The ASSENT-2 trial compared the safety and effectiveness of two treatments for heart attacks: "single-bolus TNK" and alteplase. The results showed that both treatments had similar mortality rates, with 6.18% of patients who received TNK dying, and 6.15% of patients who received alteplase dying. Rates of intracranial hemorrhage (ICH) were exactly equivalent between alteplase and TNK (0.93 and 0.94%, respectively), TNK was associated with a lower incidence of non-brain bleeding complications and a lower likelihood of blood transfusion compared to the other treatment. The results were statistically significant, with a p-value of 0.0003 and 0.0002 respectively. At 30 days, the death rate or nonfatal stroke was directly analogous between TNK and alteplase (7.11 percent vs. 7.04 percent, relative risk = 1.01 [95% confidence interval = 0.91 to 1.14]) [26]. In addition, the ASSENT 3 trial showed that the inclusion of enoxaparin or abciximab in TNK decreased ischemic difficulties. The groups treated with enoxaparin and abciximab had a lower rate of "in-hospital reinfarction", combined 30-day mortality, and recurrent reinfarction compared to the group treated with unfractionated heparin [27]. Despite the disparities noted between thrombolysis-causing drugs in different studies, a later meta-analysis found no statistically significant distinctions between the different thrombolytic agents in terms of mortality reduction [28].

4.4 Saruplase

Saruplase, also known as prourokinase or scuPA, is a naturally found "glycoprotein" that is transformed by "plasmin" into "urokinase" and has the ability to activate "plasminogen" [29]. It is produced through "recombinant technology" in E. coli. Studies, such as the PRIMI and COMPASS trials, have been conducted to compare the effectiveness of saruplase with other treatment options like SK. Results from the PRIMI research showed that while the death ratio was similar between streptokinase and saruplase, SK had a slight advantage in reducing reinfarction rates. Similarly, the COMPASS trial found that the "30-day mortality rates" were found to be similar between streptokinase and saruplase, but saruplase had a higher occurrence of hemorrhagic strokes [29]. Another study compared saruplase to alteplase and found that both had similar effectiveness in terms of complication rates, reocclusion rates, and early "coronary artery patency rates" [30]. However, saruplase has been limited in its use due to increased rates of reinfarction and hemorrhagic strokes.

4.5 Staphylokinase

Staphylokinase is a protein composed of 136 amino acids that are produced by specific "Staphylococcus aureus strains" and has a novel method of "fibrin selectivity" [31]. It has been shown that recombinant staphylokinase (STAR) has favorable impacts on AMI patients. The purpose of the randomized trial was to compare the effectiveness of the thrombolytic medications, safeness, and fibrin selectivity of STAR to that of "accelerated alteplase" [32]. Sixty-two percent of STAR subjects and fifty-eight percent of rTPA patients achieved TIMI flow grade 3 at 90 minutes (RR 1.1, 95 percent confidence interval 0.76 to 1.5).

Complications such as electric, hemorrhagic, mechanical, or allergic reactions were not found to be related to STAR therapy. However, some patients who received STAR therapy developed an immune response that neutralized the therapy's effects, beginning two weeks after treatment [32]. A different treatment, "regulated staphylokinase", was studied in the "CAPTORS II trial" [33]. The results showed that "PEG-Sak" at doses ranging from "0.01875-0.0375 mg/kg" lead to TIMI 3 flow rates of thirty-three percent, while the highest dose of PEG-Sak studied resulted in a TIMI 3 flow rate of 41%. The results of PEG-Sak were found to be comparable to those of another treatment, rTPA, which also had a TIMI 3 flow rate of 41% [1].

4.6 Lanoteplase

Lanoteplase, also known as nPA, is a variation of TPA that has a stronger ability to break down blood clots and is eliminated from the bloodstream more slowly [34]. A study called

"Intravenous NPA for the Treatment of Infarcting Myocardium Early" showed that administering nPA lead to similar effectiveness as "alteplase" in order reducing sixth-month mortality rates (8.8% for alteplase vs. 8.7% for nPA) [34]. However, nPA was found to have a higher risk of causing hemorrhagic strokes (0.64% for alteplase vs. 1.12% for nPA, P=0.004).

5. CHALLENGES AND RESTRICTIONS OF THROMBOLYTIC THERAPY

5.1 Thrombolysis Contraindications

Fibrinolytic therapy, also known as thrombolysis, is a treatment used to dissolve blood clots. It has been shown to reduce mortality in certain cases, but it also has limitations. According to the findings of one study, 10.3% of patients do not meet the criteria for thrombolysis due to possible contraindications, which include conditions such as prior stroke, recent bleeding, and hypertension [35]. Other contraindications include brain surgery in the duration of 6 months, head trauma, Stroke history, CNS damage within one year, dementia, intracranial malignancy internal bleeding in the duration of 6 weeks, suspected aortic dissection, known bleeding disorder and active bleeding, trauma, major surgery. There are also relative contraindications to thrombolysis, such as acute pancreatitis, pregnancy, oral intake of anticoagulants, infective endocarditis, dementia, active cavitating pulmonary tuberculosis intracranial thrombosis, uncontrolled hypertension, and advanced liver disease.

5.2 Duration of Treatment with Thrombolytics

As the interval between the beginning of symptoms and delivery of fibrinolytic therapy rises, its advantages diminish. Studies have shown that prehospital administration of thrombolysis within 70 minutes of the onset of symptoms can result in a reduction in death, stroke, serious bleeding, and infarct size [36]. Additionally, prehospital administration has been shown to decrease the duration of thrombolysis and decrease "all-cause" mortality.

Studies have shown that fibrinolytic therapy is most effective when administered within the first 2 hours of symptom onset. Using data from randomized clinical studies that compared fibrinolytic therapy to placebo or control, Boersma conducted research to investigate the connection between delaying treatment and an increased risk of death in the short term [36]. The study found that the greatest benefit was observed in patients who received fibrinolytic therapy within the first hour of symptom onset, with (65 [SD 14]) saved per 1000 treated patients. Furthermore, the study found that a proportional reduction in mortality was highly observed among individuals who were treated within 2 hours compared to those treated later (44% vs. 20%, P = 0.001). These findings emphasize the importance of early administration of fibrinolytic therapy for optimal outcomes [2].

The GUSTO-1 trial discovered that females, elderly individuals, and diabetics were more likely to have prolonged delays in receiving thrombolysis [37]. A study examined the correlation between patients' baseline characteristics and three-time variables – "symptom onset to treatment", "symptom onset to hospital arrival", and "hospital arrival to treatment" [38]. They found that a previous heart infarction or bypass surgery also increased the risk of treatment delay. The study found that patients who received thrombolysis within 2 hours of symptom onset had a lower overall mortality rate compared to those who received it later. Longer delays in presentation and treatment were linked to higher mortality rates. Additionally, reinfarction and recurrent ischemia were less frequent as treatment time increased, but there were also more cases of stroke, heart failure, and shock [38]. These findings suggest that administering thrombolysis as early as possible is crucial for optimal outcomes.

5.3 Cerebrovascular Events in Stroke

Fibrinolytic therapy, which is used to treat certain conditions, can lead to serious complications such as stroke. Studies have shown that thrombolysis increases the risk of stroke when compared to control patients [39]. For example, the "Fibrinolysis Therapy Trialists" found that the risk of stroke was 1.2% in patients who received thrombolysis and 0.8% in control patients, a statistically significant difference (P < 0.00001). Additionally, a study that was part of the GUSTO-1 trial, revealed that the overall risk of stroke that occurred as a result of fibrinolytic medication treatment was 1.4%, and 95% of those strokes occurred within the duration of 5 days. When compared to therapy with SK alone, treatment with SK in conjunction with TPA was related to a higher stroke rate, with 1.64% of patients experiencing a stroke when receiving

combination therapy and 1.19% when receiving SK alone (P < 0.007) [40]. Furthermore, 41% of these strokes were fatal. The research also discovered that ICH emerged in 0.46% of patients who were treated with SK and in 0.88% of patients who were treated with combination therapy (P 0.001); additionally, another analysis demonstrated a modest increase in ICH among patients who were given TPA (0.95%) [40]. These results suggest that while fibrinolytic therapy can be effective in certain cases, it also increases the risk of stroke and other serious complications.

5.4 Infarct Artery Patency

Fibrinolytic therapy, a treatment for infarct-related artery blockages, may not always result in the successful reopening of the blocked artery. This is supported by data from angiography studies, which have shown that normal blood flow (TIMI flow grade 3) is only achieved in 40-60% of patients [41]. The GUSTO trial compared the use of accelerated TPA to the use of SK and found that the TPA group had a higher rate of successful patency (81%) at 90 minutes compared to the SK group (54%, P<0.001). Furthermore, the TPA group also had a higher rate of normal blood flow (54%) compared to other treatment options, such as "SK + subcutaneous heparin", "SK + intravenous heparin", and combination heparin, streptokinase and TPA (40%) [41]. Patients with the reduced flow (TIMI flow grade 2 or less) had a higher mortality rate at 30 days compared to those with the normal flow (TIMI flow grade 3). The death rate was 8.9% for patients with reduced flow and 4.4% for patients with normal flow, with a statistically significant difference between the two groups (P=0.009) [41].

5.5 Reinfarction and Recurrent Ischemia

Thrombolysis is a commonly used treatment for blocked infarct-related arteries, but it also has limitations. One of these limitations is the frequent incidence of reocclusion of the infarct artery, "recurrent ischemia", and reinfarction [42]. According to data from the GUSTO trial, after undergoing thrombolysis, there is a 4.9-6.4% chance of reocclusion within 5-7 days and a 4.3% chance of reinfarction (a repeat heart attack) at a median of 3.8 days [42]. The risk of death within 30 days of treatment was higher for patients who experienced reinfarction, compared to those who did not.

5.6 Age Considerations

The mortality rate increases with age, both in the short-term and long-term, as demonstrated by several studies [43]. For example, in a trial, 30-day mortality rates were 3.0% for patients under 65, 9.5% for patients between 65 and 74, 19.6% for patients between 75 and 85, and 30.3% for patients over 85 [37]. Additionally, the incidence of stroke, cardiogenic shock, bleeding, and reinfarction also increases with age. A study found that accelerated TPA had fewer deaths or disabling strokes in all age groups except the oldest, in which a weak drift towards decreased rate was seen with "SK plus subcutaneous heparin" [37]. Additionally, a study by Weaver et al. found that twenty-eight percent of patients admitted to hospitals for AMI were 75 or older, but only five percent of these individuals were given a "systemic thrombolytic agent" [44]. The mortality rates were higher in these older patients, with rates of 2% or less in patients 55 or younger, 4.6% in patients between 55 and 64, 12.3% in patients between 65 and 74, and 17.8% in patients 75 or older. However, even with these higher risks, the absolute and relative risk decline linked with fibrinolytic treatment in older individuals remained beneficial [44].

5.7 Infarct Size and Site

The in-hospital outcome and effectiveness of thrombolytic therapy are more greatly affected by the size and location of the infarct (area of heart muscle damage) rather than the location of the injury [45]. The study found that the size of the heart infarction, rather than the location, had a greater impact on hospital-related mortality and the effectiveness of thrombolytic treatment [45]. Patients were divided into groups based on the location of the infarct as seen on a standard ECG and the involvement of ST-segment elevation. The study found that SK was effective in reducing mortality only in patients with front and multiple-site infarcts. In addition, the study discovered that the fatality rate rose as the size of the infarct continued to increase, with a percentage of 6.5percent in tiny infarcts, 9.6percent in modest infarcts, 14.3percent in big infarcts, and 21.7percent in vast infarcts. The rate was lowest in tiny infarcts, with a rate of 6.5%, and the highest rate was found in extensive infarcts, with a rate of 21.7% [45].

Table 1. Comparison of different thrombolytic agents

Agent	Plasma half-life(min)	Molecular weight(D)	Plasminogen activation	Fibrin specificity	Dose	Antigenicity
Tenecteplase	20	70000	Direct	+++	0.5mg/kg bolus	–
Lanoteplase	23	53500	Direct	+	120IU/kgbolus	–
Streptokinase	23–29	47000	Indirect	–	1.5MIU/60min	+
Alteplase	4–8	70000	Direct	++	100mg/90min	–
Saruplase	9	46500	Direct	±	80mg/60min	–
Staphylokinase	6	16500	Indirect	++++	20–30mg/30min	+
Reteplase	15	39000	Direct	+	2×10IUboluses30minapart	–

6. THROMBOLYTIC THERAPY IN THE MODERN ERA: UTILITY AND ADVANCEMENTS

6.1 Improving Thrombolytic Outcomes with Early PCI Transfer

Primary PCI is currently the preferred therapy for acute myocardial infarction (AMI) due to its benefits and low complication rate [46]. However, in some areas where PPCI facilities are not readily available, thrombolytic therapy is still used as an alternative. Recent studies have shown that transferring patients to a PPCI center after administering fibrinolytic agents can lead to better outcomes [46].

The CARESS-in-AMI study found that timely transfer to a PPCI center after administering fibrinolytic agents improved outcomes for patients with STEMI in comparison with a conservative watchful waiting approach [47]. The study included 600 patients who were treated previously with abciximab, aspirin, half-dose reteplase, and heparin. Patients were then assigned to either an easy transition for PCI or a transfer that would only occur in the event that the initial reperfusion attempt failed or the patient's condition worsened. According to the findings, the immediate transfer technique resulted in a lower mortality rate after 30 days (4.4% vs. 10.7%, P = 0.004) without increasing bleeding events [47].

The TRANSFER AMI research provides additional evidence that demonstrates the advantages of prompt transfer to a PPCI facility after the intake of fibrinolytic medications [48]. The study found that transferring patients to a PPCI center within 6 hours of thrombolysis led to decreased number of ischemic complications in comparison with standard therapy, which includes delayed angiography or rescue PCI. The primary outcome of the research, a combination of "recurrent ischemia", mortality,

new occurrence or previous severe congestive cardiac failure, reinfarction, or "cardiogenic shock" within a period of thirty days, was considerably lower in the regular "early PCI group" than in the usual therapy group [48]. Additionally, there was no major variation in the incidence of major bleeding between the two groups.

A study that combined the results of multiple previous studies found that moving patients to a facility for PCI (a procedure to open blocked heart vessels) soon after receiving thrombolysis (a treatment for heart attack) led to a significant decrease in both the number of deaths and reinfarctions (recurrent heart attacks) within 30 days to 1 year, compared to a strategy of monitoring for symptoms of recurrent chest pain before deciding to perform PCI [49]. The NORDISTEMI trial also found that the overall rate of death, reinfarction, stroke, or new ischemia 12 months after treatment was significantly lower in the group that received early invasive treatment (6%) compared to the group that received a more cautious approach (16%) [49].

6.2 Intracoronary (IC) Thrombo-Lytic Therapy

The use of intracoronary fibrinolytic therapy (ICFT) was first reported by Rentrop in AMI management. Studies have shown that ICFT using staphylokinase (SK) can improve microvasculature perfusion in severely "ischemic myocardium" after restoring coronary flow. This is due to SK's ability to inhibit "red-cell aggregation" and reduce platelet aggregation in vitro [50]. This approach has been shown to be effective in patients undergoing primary PCI. A study found that IC administration of SK (250 kU over 3 minutes) improved "microvascular resistance", "collateral flow index", "mean coronary wedge pressure", "diastolic deceleration time" and

coronary blood flow reserve two days after the process compared to a control group [51]. However, these improvements did not lead to better "left ventricular size" or function at six months. It is important to note that the research was not large enough to determine variations in clinical procedures or left ventricular function at six months [51]. Additionally, "IC TNK" is recognized to be an effective and safe treatment for managing thrombotic problems in "high-risk complex PCI" [52]. Research showed that "TNK-supported PCI" improves the "no-reflow" occurrence in PCI patients with high risk [53]. A study conducted by Abbas and colleagues examined the use of IC TPA for recanalizing "chronically occluded arteries with tapering morphology" in patients who had previously experienced failed PCI attempts and were experiencing progressive symptoms [54]. This study showed that chronically occluded arteries with tapering morphology could be successfully recanalized when fibrin-specific fibrinolytic were administered [54].

6.3 Risks and Adverse Effects Associated with TPA

Bleeding is the most common serious adverse event associated with the administration of TPA, as supported by several studies [55-57]. There are two categories of bleeding: internal and superficial or surface bleeding. Intracranial bleeding is the most serious internal bleeding associated with alteplase therapy, with an incidence rate ranging from 0.4% to 15.4%, followed by respiratory bleeding, genitourinary bleeding (4%), retroperitoneal bleeding and gastrointestinal bleeding (5%). Superficial or surface bleeding usually occurs at sites such as arterial punctures, venous cutdowns and recent surgical intervention sites, while spontaneous bleeding may include epistaxis (less than 1%), gingival bleeding (less than 1%) and ecchymosis (1%) [58]. Additionally, a study of 24,556 patients with ST-segment elevation myocardial infarction (STEMI) who received fibrinolytic therapy reported that tPA was associated with an increased risk of bleeding (OR 1.65; 95% CI, 1.29 to 2.11; p < 0.0001) compared with streptokinase [59].

6.4 Relative Risk of Increasing Comorbidities with TPA Use

Clinical studies of adult patients with acute ischemic stroke have reported a higher incidence of intracranial bleeding, particularly symptomatic intracranial bleeding, in patients receiving tPA compared to placebo. However, there was no increase in the incidence of 90-day mortality or severe disability in patients receiving tPA [58]. According to these studies, the incidence of intracranial bleeding is dose-related, with a higher percentage occurring at a dosage of 150 mg (1.3%) compared to 100 mg (0.4%), and rates of adverse events, including bleeding, correlate to the total exposure of tPA [58].

In addition to bleeding, tPA administration may also lead to cardiac dysrhythmias and allergic reactions, including anaphylactic-type reactions [58]. Cardiac dysrhythmias are related to the re-establishment of tissue perfusion rather than drug exposure. The rapid conversion of plasminogen to plasmin signals a complement cascade leading to mast cell degranulation and subsequent anaphylactic reaction [58]. Numerous studies have reported on the risks associated with administering tissue plasminogen activator (tPA), with two in particular highlighting increased risks of bleeding. The Third International Study of Infarct Survival (ISIS-3) trial, a large-scale study evaluating tPA use for acute myocardial infarction, found tPA to be associated with significantly increased risks of both intracranial hemorrhage (odds ratio [OR] 1.92; 95% confidence interval [CI], 1.56 to 2.35; p < 0.0001) and extracranial bleeding (OR 1.46; 95% CI, 1.27 to 1.68; p < 0.0001) [60-62].

7. CONCLUSION

In the 20th century, Thrombolytic therapy has greatly improved the way in which patients with acute myocardial infarction (AMI) are treated. In the 21st century, primary percutaneous coronary intervention (PPCI) is considered the best treatment plan for managing AMI, but it is not always accessible to all individuals. In such cases, thrombolytic treatment combined with an immediate referral for "coronary angiography" and percutaneous coronary intervention is recommended as an alternative treatment option. Additionally, it is worth mentioning that intracoronary thrombolytic therapy may also be an effective option during the treatment with PPCI.

8. CLINICAL RECOMMENDATIONS

The "2009 ACC/AHA guidelines" recommend primary PCI for patients presenting to PPCI centers. This suggestion is classified as a "class I recommendation". While patients going to non-

PPCI centers, it is recommended that patients at higher risk who receive fibrinolytic therapy be transferred promptly to a PCI-capable facility for further treatment, either through PCI or a pharmacoinvasive strategy. This suggestion is classified as a class IIa recommendation.

KEY INSIGHTS

The main management approach for patients with acute myocardial infarction is still thrombolytic therapy. However, primary percutaneous coronary intervention (PPCI) has become the recommended treatment strategy for managing AMI. Patients who arrive at a facility that can perform PPCI should be treated with this approach without major delays. For patients who present at a facility that does not offer PPCI, thrombolysis with immediate transfer to a facility that can perform PPCI should be considered as an alternative.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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