Utilization of PCI After Fibrinolysis

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Peter McKavanagh, George Zawadowski,
and Warren J. Cantor

5.1 Introduction

It is estimated that there are 1.5 million hospitalizations with acute coronary syndromes (ACS) per year in the United States, with 30–45% being a ST-segment elevation myocardial infarction (STEMI) presentation [1, 2]. STEMI occurs due to an acute occlusion of an infarct-related artery (IRA) that can cause irreversible ischemia-induced myocardial necrosis within 20–60 min of onset. Untreated STEMI patients have higher mortality and poor clinical outcomes compared to those who receive a reperfusion strategy [3–10]. The mainstay of STEMI management is rapid intervention aimed at relieving the IRA thrombotic obstruction and thus reducing infarct size, preserving left ventricular function, and decreasing morbidity and mortality. In the 1980s, fibrinolysis became the standard means to achieve reperfusion. Subsequently, a number of randomized trials and meta-analyses showed that primary PCI (PPCI), when performed rapidly, was associated with improved clinical outcomes compared to fibrinolytic therapy [11–18]. However, the mortality benefit of primary PCI is reduced with treatment delays, with no benefit observed when the difference between time of fibrinolysis and time of PCI exceeds 115 min [19, 20]. Current guidelines recommend the use of fibrinolytic therapy when the time from first medical contact to PCI is anticipated to be greater than 120 min [17, 18]. Despite these recommendations, data from the US National Cardiovascular Data Registry showed that only 51% of STEMI patients transferred for primary PCI

P. McKavanagh
Ulster Hospital, Belfast, UK

G. Zawadowski
Interventional Cardiology, St. Michael's Hospital, University of Toronto,
Toronto, ON, Canada

W. J. Cantor (✉)
Southlake Regional Health Centre, University of Toronto, Toronto, ON, Canada
e-mail: cantorw@rogers.com

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achieved the recommended first door-to-balloon time of <120 min [21]. Similar European data show that 65% of transferred patients had a delay of >120 min, which was associated with increased mortality [22].

Many strategies have been developed to increase the number of patients who can undergo timely primary PCI, including prehospital identification of STEMI and establishment of networks that allow ambulances to bypass the closest hospital and take patients directly to PCI facilities [23–34]. Nevertheless, there will always be a cohort of patients who are too far from PCI centers, and fibrinolytic therapy remains the treatment of choice for these patients [35, 36]. Transporting patients to a PCI center for routine early PCI after fibrinolysis, the so-called pharmacoinvasive strategy, has been shown to reduce the risks of reinfarction and recurrent ischemia with no increase in major bleeding. Within the literature, there exist examples of successful implementation of a combined primary PCI and pharmacoinvasive strategies depending on patient distance from facilities [37], with regional systems proposed [38]. This chapter addresses the evidence for PCI after fibrinolytic therapy, illustrating how and when it should be used.

5.2 Fibrinolytic Therapy

The use of fibrinolytic therapy in STEMI is long established, with pioneering work in 1976 by Chazov et al. showing benefit [39]. Prior to the development of fibrinolytic therapy, treatment of STEMI was limited to analgesia, antiplatelets, anticoagulants, and blood pressure management. The use of fibrinolytic therapy became the standard practice after the pivotal randomized clinical trials Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) and Second International Study of Infarct Survival (ISIS-2) [40, 41]. These two studies used intravenous streptokinase (SK) showing a mortality benefit when compared to placebo, especially in combination with aspirin. Based on these studies, SK became standard treatment for STEMI. However there remained concerns about bleeding and limited efficacy, leading to the development of fibrin-specific fibrinolytic agents. These included tissue plasminogen activator (alteplase) [42, 43], recombinant plasminogen activator (reteplase) [44, 45], and tenecteplase [46]. Overall there have been over 40 trials comparing different fibrinolytic regimens. A recent meta-analysis indicated that the lowest mortality and bleeding rates were seen with the use of reteplase, alteplase, and tenecteplase in combination with parenteral anticoagulant therapy [47].

The main advantage of fibrinolytic therapy is the ease of administration, which includes the ability to be given in small rural hospitals and in the prehospital setting. It is most effective when administered early (especially within the first 2 h of symptom onset). To help with appropriate administration, there are time recommendations for each step (Table 5.1). There are however substantial limitations of fibrinolytic therapy, and it is essential that its use is appropriate (Figs. 5.1 and 5.2). Firstly, there is risk of major bleed, including intracranial bleeding, with SK having the highest risk [47]. Secondly, only 40–50% of all patients treated with fibrinolytic

Table 5.1 Time targets for fibrinolytic therapy

Intervals	Time targets
Maximum time from FMC to 1st ECG and STEMI diagnosis	≤10 min
Maximum time from STEMI diagnosis to fibrinolytic therapy	≤10 min
Time from fibrinolytic therapy to assessment of reperfusion efficacy	60–90 min
Time from fibrinolytic therapy to angiography (if fibrinolysis is successful)	2–24 h

FMC first medical contact. Adapted from 2017 ESC STEMI Guidelines [17]

Indications:

- Chest pain or other ischemic symptoms < 12 hours duration
- Persistent ST elevation in ≥ 2 contiguous leads
  - ≥ 2 mm in anterior leads (≥ 1.5mm in women)
  - ≥ 1 mm in inferior leads
  - Absence of LBBB, LVH or other STEMI mimics

Absolute Contraindications:

- Any prior intracranial hemorrhage
- Intracranial vascular or malignant lesion (AVM, tumour)
- Ischemic stroke within 3 months
- Sustained Hypertension: SBP > 180 or DBP > 110 mm Hg
- Active bleeding or bleeding diathesis (not incl menses)
- Significant closed head or facial trauma within 3 months

Relative Contraindications:

- Cardiogenic Shock
- Traumatic or prolonged CPR
- Major surgery within past 3 weeks
- Internal bleeding within past 4 weeks
- Active peptic ulcer disease
- Non-compressible vascular puncture
- Pregnancy
- Current use of anticoagulants

Fig. 5.1 Indications and contraindications for fibrinolytic therapy

1. Use Fibrin-specific Agent (Accelerated tPA, Reteplase, Tenecteplase)
2. Administer ASA 160 mg chewed, Clopidogrel 300 mg (75 mg if patient > 75 years of age)
3. Administer parenteral anticoagulant
   a. UFH 60 U/kg bolus (max 4000 U) then 12 U/kg per hour (max 1000 U/hr)
   b. Enoxaparin 30 mg IV plus 1mg/kg sc (Avoid for elderly patients or renal insufficiency)
   c. Fondaparinux IV bolus followed by 2.5 mg sc dose 24 hours later
4. Transfer patient to PCI center immediately after fibrinolytic therapy for pharmacoinvasive protocol if possible
5. If pharmacoinvasive strategy not possible, transfer to PCI hospital for hemodynamic instability or evidence of failed reperfusion (persistent chest pain or ST elevation) at 60-90 minutes after fibrinolysis

Fig. 5.2 Fibrinolysis checklist

therapy achieve normal TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow, with this figure even lower in elderly patients or those with cardiogenic shock [48–51]. Even patients with TIMI grade 3 flow may have evidence of failed myocardial perfusion [52]. Noninvasive identification of successful reperfusion after fibrinolytic therapy is challenging, with limited positive and negative predictive values for resolution of chest pain and ST-segment elevation. Furthermore, approximately 5% of patients will reinfarct after initial successful reperfusion [53].

5.3 PCI-Based Approaches

Given these limitations of fibrinolytic therapy, and the time dependency of primary PCI, it has been questioned whether combining fibrinolytic therapy and PCI could be the ideal treatment strategy, particularly for patients who cannot undergo timely primary PCI. This combined strategy would minimize treatment delays using rapid administration of fibrinolytic therapy but also achieve complete and sustained reperfusion using PCI. The use of PCI after fibrinolytic therapy can be classified based on the timing and indications for PCI (Table 5.2).

5.3.1 Rescue PCI

Patients who have persistent chest pain and ST elevation after fibrinolytic therapy require urgent cardiac catheterization and rescue PCI to restore flow to the occluded infarct-related artery. Rescue PCI is indicated in the case of suspected failed fibrinolysis (i.e., ST-segment resolution <50% within 60–90 min of fibrinolytic administration) or hemodynamic instability [18]. The landmark rescue PCI trials were Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis (REACT) and the Middlesbrough Early Revascularization to Limit Infarction (MERLIN) [54, 55]. REACT compared rescue PCI, medical management, and

Table 5.2 Reperfusion strategies combining fibrinolytic therapy and PCI

Strategy	Definition
Rescue PCI	Emergent PCI performed for failed reperfusion after fibrinolytic therapy
Facilitated PCI	Administration of fibrinolytic therapy (and/or GP IIb/IIIa inhibitors) prior to emergent PCI to bridge PCI-related time delays (PCI within 2 h of fibrinolytic therapy)
Pharmacoinvasive strategy	Administration of fibrinolytic therapy followed by immediate transfer to a PCI center; emergent PCI for patients with evidence of failed reperfusion, hemodynamic instability, or reinfarction; and PCI within 24 h of fibrinolytic therapy for patients who are stable with successful reperfusion

repeat fibrinolytic therapy for patients with clinical evidence of failed reperfusion after fibrinolysis. Rescue PCI was associated with a reduction in reinfarction, with no mortality difference between treatments. The trial was terminated prematurely raising concerns about the true benefit. MERLIN compared rescue PCI and conservative therapy but did not show significant reduction of the primary endpoint, all-cause mortality. In addition, in both trials, patients who underwent rescue PCI had increased bleeding. Meta-analyses have been performed to help guide practice. Patel et al. included five trials and found a 36% decrease in the risk of death with rescue PCI (RR 0.64, 95% confidence interval 0.41–1.00, $p = 0.048$) and a marginally significant 28% decrease in the risk of heart failure (RR 0.72, 95% confidence interval 0.51–1.01, $p = 0.06$) [56]. Wijeysundera et al. analyzed eight trials and found that rescue PCI was not associated with a significant reduction in mortality but was associated with significant reductions in heart failure (RR 0.73, 95% CI 0.54–1.00) and reinfarction (RR 0.58, 95% CI 0.35–0.97) when compared with conservative treatment [57]. Rescue PCI was also associated with an increased risk of stroke (RR 4.98, 95% CI 1.10–22.5) and minor bleeding. Another meta-analysis by Testa et al. had similar findings. Rescue PCI was associated with a 70% reduction in the risk of reinfarction [OR 0.32 (0.14–0.74), $p = 0.008$], with a number needed to treat of 17. On balance rescue PCI is superior to conservative therapy for patients with failed reperfusion after fibrinolytic therapy and has a Class I indication in the guidelines [17, 18].

5.3.2 Facilitated PCI

Initial attempts to routinely combine pharmacological reperfusion therapy and PCI focused on administering fibrinolytic agents and/or glycoprotein IIb/IIIa inhibitors to patients being transferred for immediate PCI to help bridge the treatment delay. This strategy was termed “facilitated PCI” and was assessed in two large randomized trials.

The Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) randomized patients to either PPCI ($n = 838$) or facilitated PCI using full-dose tenecteplase ($n = 829$) [58]. The median time from tenecteplase to first balloon inflation was 104 min. The primary endpoint (death or congestive heart failure or shock within 90 days) was found in 19% of patients assigned to facilitated PCI vs. 13% of those randomized to PPCI (relative risk 1.39, 95% CI 1.11–1.74, $p = 0.0045$). During hospital stay, significantly more strokes (1.8% vs. 0, $p < 0.0001$) were reported in patients assigned to facilitated rather than standard PPCI. There were also more ischemic cardiac complications, such as reinfarction (6% vs. 4%, $p = 0.0279$) or repeat target vessel revascularization (7% vs. 3%, $p = 0.0041$) within 90 days.

The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) study randomized 2452 patients to undergo facilitated PCI using a combination of abciximab plus half-dose reteplase, facilitated PCI using abciximab alone, or primary PCI [59]. The primary endpoint was the composite of death from all causes, ventricular fibrillation occurring more than 48 h after randomization, cardiogenic shock, and congestive heart failure during the first 90 days after randomization. The primary endpoint occurred in 9.8, 10.5, and 10.7% of the patients in the combination-facilitated PCI group, abciximab-facilitated PCI group, and primary PCI group, respectively ($p = 0.55$); 90-day mortality rates were 5.2, 5.5, and 4.5%, respectively ($p = 0.49$).

A meta-analysis comparing facilitated and primary percutaneous coronary intervention was published by Keeley et al.[60]. In this they identified 17 trials of patients with STEMI assigned to facilitated ($n = 2237$) or primary ($n = 2267$) PCI. The facilitated PCI group had higher rates of death (5% vs. 3%; 1.38, 1.01–1.87), nonfatal reinfarction rates (3% vs. 2%; 1.71, 1.16–2.51), and urgent target vessel revascularization rates (4% vs. 1%; 2.39, 1.23–4.66). Facilitated PCI was associated with higher rates of major bleeding than PPCI (7% vs. 5%; 1.51, 1.10–2.08). Hemorrhagic stroke was also higher in fibrinolytic therapy facilitated regimens compared with primary PCI (hemorrhagic stroke 0.7% vs. 0.1%, $p = 0.0014$; total stroke 1.1% vs. 0.3%, $p = 0.0008$). The overall conclusion was that facilitated PCI offers no benefit over PPCI and should be avoided.

There are several limitations of the facilitated PCI trials and meta-analysis. Firstly, FINESSE was not included in the meta-analysis, and thus more than half of the patients in the analysis came from the ASSENT-4 trial. Of the 17 trials, 9 used only glycoprotein IIb/IIIa inhibitors and no fibrinolytic, and of the remaining 8 fibrinolytic trials (except ASSENT-4), most of them were small and used balloon angioplasty without coronary stents. Another important limitation to these trials is the absence of up-front clopidogrel loading at the time of fibrinolysis. Fibrinolytic therapy increases platelet activation and aggregation, and without clopidogrel loading, PCI performed early after fibrinolysis may be predisposed toward thrombotic complications [61].

Most patients enrolled in the facilitated PCI studies underwent PCI within 120 min of fibrinolysis. Secondary analyses of the ASSENT-4 and FINESSE study suggested that there may be a subgroup of patients (such as high-risk patients who presented early to non-PCI hospitals) that could benefit from facilitated PCI [62, 63]. However there is no large dataset to support this, and facilitated PCI is not currently recommended in guidelines.

5.3.3 Pharmacoinvasive

The pharmacoinvasive strategy applies to STEMI patients who are treated with fibrinolysis at a non-PCI center. It involves transferring patients to a PCI center right after fibrinolysis (without waiting to see if reperfusion is successful), followed by routine early PCI. For those patients who successfully reperfuse with

fibrinolytic therapy, early PCI prevents recurrent ischemia and reinfarction. In the case of failed reperfusion or clinical instability, the patient undergoes emergent PCI on arrival to the PCI center. Figure 5.3 is a checklist for the use of a pharmacoinvasive strategy.

A number of studies have compared routine early PCI after fibrinolysis with an ischemia-driven conservative strategy or delayed PCI [64–68]. The initial studies

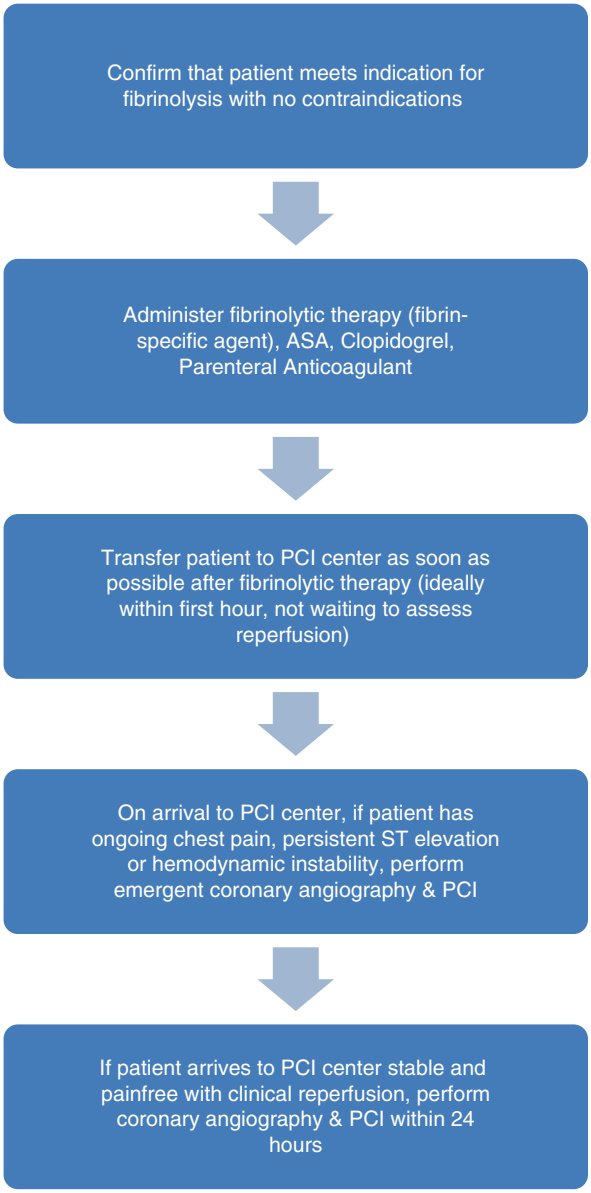

Fig. 5.3 Flow diagram for pharmacoinvasive strategy

were done prior to the use of coronary stents and antiplatelet agents that help maintain infarct artery patency and showed increased rates of emergency bypass surgery and higher mortality when PCI was performed routinely within 24 h of fibrinolysis [69]. Studies that were performed using contemporary PCI techniques (including coronary stenting) and pharmacotherapy have shown improved outcomes with routine early PCI after fibrinolysis [70].

The largest such randomized trial, TRANSFER-AMI (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction), randomized 1059 high-risk patients who received fibrinolytic therapy to either usual care (including rescue PCI for failed fibrinolytic therapy) or urgent transfer to a PCI-capable hospital for a routine early PCI within 6 h after fibrinolytic therapy [71]. The primary endpoint—a composite of death, reinfarction, recurrent ischemia, new or worsening heart failure, or cardiogenic shock within 30 days—was reached in 17.2% of patients in the usual care group and 11.0% of patients assigned to an early invasive strategy (RR 0.64, 95% CI 0.47–0.87, $p = 0.004$). A meta-analysis of seven contemporary trials comparing a pharmacoinvasive strategy to ischemia-driven (or delayed) PCI after fibrinolytic therapy (Figure 5.1) demonstrated a significant reduction in death or MI at 6 months to 1 year in the pharmacoinvasive group, with no difference in stroke or major bleeding (Fig. 5.4) [72].

Real-world data from a prospective registry involving a rural population served by a large regional health network demonstrated the safety and efficacy of a pharmacoinvasive strategy. Two thousand six hundred twenty-four consecutive patients presenting with STEMI to a non-PCI-capable hospital, more than 60 miles from the nearest PCI center, received aspirin, clopidogrel, unfractionated heparin, and half-dose fibrinolysis and were transferred for PCI. When outcomes were compared to STEMI patients presenting directly to PCI centers for primary PCI, there were no significant differences in 30-day mortality (5.5% vs. 5.6%, $p = 0.94$), stroke (1.1% vs. 1.3%, $P = 0.66$), major bleeding (1.5% vs. 1.8%, $p = 0.65$), or reinfarction (1.2% vs. 2.5%, $p = 0.088$) despite a longer door-to-balloon time [73]. An analysis of the FAST-MI also showed no difference in

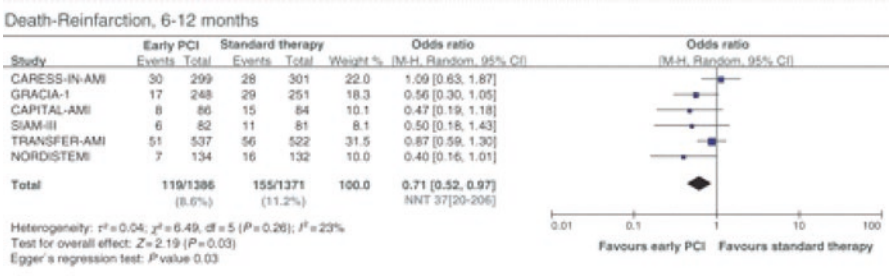

Fig. 5.4 Clinical endpoints at 6–12 months when comparing early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction. Taken from a meta-analysis by Borgia et al. [72]

risk-adjusted mortality at 1 year with primary PCI compared to a pharmacoinvasive strategy [74].

The STREAM trial was an international, multicenter randomized trial comparing a pharmacoinvasive strategy to primary PCI in 1892 STEMI patients presenting within 3 h from symptom onset but who were unable to undergo PPCI in less than 1 h after first medical contact [75]. The primary outcome was a composite of death, reinfarction, shock, or congestive heart failure. There was no significant difference in the composite primary endpoint between the two groups, 12.4% in the fibrinolysis group versus 14.3% in the primary PCI group (p = 0.21, 95% CI 0.68–1.09). There was a higher rate of intracranial hemorrhage in the fibrinolysis group (1.0% vs. 0.2%, p = 0.004). However, after a protocol amendment to decrease the fibrinolytic dose by half in patients ≥75 years of age, there was no longer any significant difference in rates of intracranial hemorrhage between groups (0.5% vs. 0.3%, p = 0.45). It is important to note that almost one third of patients experienced a PPCI delay of less than 1 h and the average time from first medical contact to balloon inflation was 117 min. As such, the results of the STREAM trial may not be applicable to patients who cannot undergo primary PCI within 120 min of first medical contact.

Based on the results of contemporary pharmacoinvasive trials, current guidelines recommend transfer to a PCI-capable hospital after fibrinolysis "even when hemodynamically stable and with clinical evidence of successful reperfusion," to undergo coronary angiography and revascularization within 24 h after fibrinolysis (Class IIa, Level of Evidence B) [17, 18].

5.4 Antiplatelet Therapy as Adjunct to Fibrinolysis

Current guidelines recommend adjunctive antiplatelet therapy in the setting of fibrinolysis in the form of aspirin 162–325 mg as well as clopidogrel 300 mg (for patients <75 years of age) or 75 mg (for patients >75 years of age) (Class I, Level of Evidence A) [17, 18]. The largest trial studying the use of dual antiplatelet therapy was the CLARITY-TIMI 28 trial [53], published in 2005. In CLARITY, the authors randomized 3491 patients presenting within 12 h of onset of STEMI who were planned for fibrinolysis with adjunctive anticoagulant and aspirin to either clopidogrel (300 mg loading dose followed by 75 mg daily) or placebo. The primary endpoint was a composite of occluded IRA on angiography, death prior to angiography, or recurrent MI prior to angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent MI by day 8. The primary safety endpoint was TIMI major bleeding. The primary endpoint occurred in 21.7% of the placebo group versus 15.0% in the clopidogrel group (OR 0.64, 95% CI 0.53–0.76, p < 0.001), an absolute reduction of 6.7%. There was no difference in the rate of TIMI major bleeding.

In the modern era of primary PCI, two novel oral P2Y12 inhibitors have been studied for use in acute coronary syndrome in conjunction with aspirin as part of a dual antiplatelet strategy, namely, prasugrel and ticagrelor [76, 77]. The safety

of combining these more potent P2Y12 inhibitors with fibrinolytic therapy is not known. The TREAT trial randomized 3800 STEMI patients treated with fibrinolytic therapy to ticagrelor or clopidogrel. The primary endpoint is major bleeding. Enrollment was recently completed, and the results of this trial are anticipated in 2018.

More recently, cangrelor, an intravenous, fast-acting, and rapidly reversible P2Y12 inhibitor, has become available for use in the setting of primary PCI, but has not been studied as part of a pharmacoinvasive or fibrinolytic strategy [78].

5.5 Optimal Timing of PCI After Fibrinolytic Therapy

While the current guidelines recommend coronary angiography within 24 h after fibrinolysis as part of a pharmacoinvasive strategy, they discourage performing angiography less than 2–3 h after fibrinolysis, based in part on the adverse outcomes seen in the facilitated PCI trials. However, there remains uncertainty regarding the optimal timing of angiography after fibrinolysis. In TRANSFER-AMI, the median time from randomization to first balloon inflation was 3.2 h, with an interquartile range of 2.5–4.2 h [71]. A meta-analysis evaluating the timing of PCI after fibrinolysis found higher rates of recurrent ischemia and a trend to higher reinfarction when angiography was performed >4 h after fibrinolysis [79].

Conclusions

Fibrinolysis remains a mainstay of STEMI treatment throughout the world and is the initial reperfusion strategy of choice when primary PCI cannot be performed with a first medical contact to balloon time less than 120 min. Fibrin-specific fibrinolytic agents should be used, combined with clopidogrel and parenteral anticoagulant therapy. Patients should be transferred to PCI centers right after receiving fibrinolytic therapy and undergo coronary angiography and revascularization within 24 h. Regional STEMI networks should provide both primary PCI and pharmacoinvasive strategy, based on anticipated first medical contact to balloon times.

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