Mini Review

Interventional Cardiology

Pharmaco-invasive PCI for STEMI-What are the outcomes?

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Received date: 22-Jul-2024, Manuscript No. FMIC-24-142858;
Editor assigned: 24-Jul-2024, PreQC No. FMIC-24-142858 (PQ);
Reviewed date: 08-Aug-2024, QC No. FMIC-24-142858;
Revised date: 15-Aug-2024, Manuscript No. FMIC-24-142858 (R);
Published date: 23-Aug-2024, DOI: 10.37532/1755-5310.2024.16(4).878

Summary

As pharmaco-invasive Percutaneous Coronary Intervention (PCI) remains an important treatment modality for patients with ST-Elevation Myocardial Infarction (STEMI), this review aims to explore the evidence base for pharmaco-invasive strategies, and contrasts clinical outcomes to those of patients undergoing primary PCI.

Fibrinolytic therapy, due to geographic and resource considerations, will continue to be widely administered in patients with STEMI despite timely primary PCI being the preferred reperfusion strategy. This is because, for a significant proportion of patients, the anticipated time from First Medical Contact (FMC) to initial device time is likely to be greater than 90 minutes (or greater than 120 minutes according to some guidelines) if primary PCI were to be performed, despite increasing pre-hospital identification of STEMI. Such patients should be considered for pharmaco-invasive strategies, which have undergone modifications over the last decade, including (selective) half-dose fibrinolytic therapy, increased radial artery access, the liberal utilization of both rescue PCI and early in-hospital angiography, and, if indicated, PCI.

We recently reported that patients with STEMI presenting within 12 hours of symptom onset who received a pharmaco-invasive strategy (48%) had a lower 3-year mortality rate than those who underwent primary PCI (6.2% vs. 11.1%; p<0.001), though this was largely attributable to the high (20.2%) mortality rate of those patients who received (late) primary PCI at greater than 120 minutes from FMC. However, 1-year mortality rates for timely primary PCI (less than 120 minutes from FMC) and a pharmaco-invasive strategy, both in our study and in other registries and randomized trials, have been reported to be similar, generally 4%-6%, supporting the use of this strategy in appropriate patients.

Keywords: Rescue PCI • Fibrinolytic therapy • Myocardial infarction • Primary PCI

Introduction

In patients with STEMI, early reperfusion of the Infarct-Related Artery (IRA) restores oxygenation and metabolic substrates to myocytes [1]. In patients presenting within 12 hours of symptom-onset with STEMI, mortality is reduced by pharmacologic reperfusion with fibrinolytic, anti-platelet, and anti-thrombotic therapies [2]. Furthermore, primary Percutaneous Coronary Intervention (PCI) reduces the rates of re-infarction, stroke, and mortality compared to fibrinolytic therapy [3], and therefore many centres have adopted primary PCI as their reperfusion strategy of choice [4]. However, despite recent suggestions that thrombolysis has "lost its mojo" [5], for a variety of reasons including geographic location and resource considerations, a significant proportion of patients with STEMI are likely to be administered fibrinolytic therapy for the foreseeable future [4]. In this review, pharmaco-invasive

PCI in the treatment of STEMI is outlined and clinical outcomes are contrasted with those after primary PCI.

Pre-hospital fibrinolytic therapy

As fibrinolytic therapy can be administered outside specialist centres by non-medical personnel facilitating earlier treatment of patients with STEMI, compared to fibrinolytic administration after hospital arrival, mortality rates are lower [6,7]. In the French USIC registry, for example, patients receiving pre-hospital fibrinolytics had better survival rates than those undergoing primary PCI [8]. Two decades of data from the FAST MI registry found survival rates with pre-hospital fibrinolytic use tended to be higher than those with primary PCI [8].

The initial Randomized Clinical Trial (RCT) in the setting of pre-hospital fibrinolytic use was the Comparison of Angioplasty and Pre-Hospital Thrombolysis in Myocardial infarction (CAPTIM), which randomized patients to receive pre-hospital fibrinolytics or primary PCI [9]. In CAPTIM, patients presenting <2 hours after symptom-onset had reduced cardiogenic shock, compared to patients undergoing primary PCI [10]. In particular, the rates were 26% and 60% of rescue PCI and PCI in-hospital respectively. These procedural rates after fibrinolytic therapy are probably necessary to achieve outcomes as good as or possibly better than those achieved with primary PCI. The CAPTIM trial, however, was not included in the landmark Lancet 2003 meta-analysis of 22 RCTs by Keeley et al., [3], comparing fibrinolytics to primary PCI, and had several important differences to those included in this meta-analysis [3], including much higher rescue PCI and angiography rates. Also, in the Assessment of the Safety and Efficacy of New Treatment strategy-4 trial (ASSENT-4), the subgroup of 320 patients receiving pre-hospital fibrinolysis had a 30-day mortality of 3.1% compared to 3.7% for those randomized in the ambulance to receive primary PCI [11]. Thus, in patients presenting early (<2-3 hours) after symptom-onset, pre-hospital fibrinolytic with a policy of liberal utilization of both rescue PCI and in-hospital PCI can achieve mortality rates of ~4%, which are similar to those achieved by contemporary primary PCI [12].

Rescue PCI

A key component of a pharmaco-invasive strategy is rescue PCI, which should be performed when pharmacological reperfusion therapies are likely to have failed. This is usually assessed by the degree of recovery of ST-segment elevation (or depression in leads V2-3) on the 12-lead ECG 60-90 min after fibrinolytic administration [13,14]. ST recovery of >70% has been associated with a 90%-95% probability of achieving a patent IRA [13,14]. Single lead ST-segment measurements are as good as multi-lead ST measurements [1,15], while being less complex and easier to calculate at the bedside and predict the success of pharmacologic reperfusion. However, ST recovery is an imperfect discriminator between TIMI grade 2 and TIMI grade 3 flow, with up to 50% of patients with persistent ST elevation having a patent IRA at the time of angiography [16]. Thus the failure of ST recovery often indicates failure of 'tissue reperfusion'. Microvascular reperfusion failure is associated with more myocyte necrosis and late mortality [1].

The utility of rescue angioplasty after fibrinolytic treatment for STEMI received conceptual support from a meta-analysis in 2000, showing patients with TIMI 0-1 flow had better outcomes after rescue PCI than with conservative therapy [17]. A later meta-analysis of 5 small RCTs comparing rescue PCI to various conservative strategies, which included <1000 patients in total, reported better outcomes and a trend towards lower mortality associated with rescue PCI [18]. At Liverpool Hospital, (Sydney, Australia) we have found that among consecutive patients undergoing rescue angioplasty, ~90% after Tenecteplase and with >70% glycoprotein IIb/IIIa antagonist use, there was a 6-month mortality of 4% in those without cardiogenic shock; similar mortality to that reported for primary PCI [19]. However, this management led to a ~10% transfusion rate, especially as angiography was almost entirely *via* femoral artery access [19]. Such bleeding concerns have led to clinician hesitancy about the performance of early post-lysis angiography and PCI, including rescue PCI [19,20]. However, with the widespread use of radial artery access, compared with femoral access, lower rates of transfusion have been reported. Also, in contemporary studies of pharmaco-invasive strategies the previously reported bleeding rates, compared to those associated with primary PCI, no longer occur [21].

'Scheduled' angiography and intervention

The current European PCI guidelines recommend routine early coronary angiography (at 3-24 hours), and PCI if appropriate, in patients after successful thrombolytic therapy [22,23]. In registry studies of fibrinolytic-treated patients from Western Europe, high rates of in-hospital angiography and PCI are reported [8]. In Australian practice following STEMI, 87% of patients underwent in-hospital angiography, with 65% having PCI [19].

The Randomized Clinical Trial (RCT) basis for a pharmaco-invasive strategy in STEMI came initially from the CAPTIM and WEST trials, to which the Strategic Reperfusion Early After Myocardial Infarction trial (STREAM-1) and recently STREAM-2 have added evidence [9,24,25]. Key features of these trials, which in total randomized 3,649 patients, at variance with those trials cited in the Keeley et al., meta-analysis had high rates of both rescue PCI (>25% of patients receiving fibrinolytics) and in-hospital angiography (>80%) and, if clinically indicated, PCI [3].

The STREAM-1 trial randomized 1,892 patients to either a pharmaco-invasive strategy or primary PCI, thus contributing over 50% of the patients with STEMI randomized to either of these

two reperfusion strategies [24]. Overall, there were no differences in clinical outcomes at one year between the two reperfusion strategies. A key feature of this trial was the reduction in the dose of fibrinolytic to half-dose for those aged 75 or over [24]. This resulted in no subsequent intracranial hemorrhages, a concern the data and safety monitoring committee had identified in the elderly age group in the early phase of the trial. Subsequently, STREAM-2 has shown that this half-dose of fibrinolytic can be applied to those aged 60 years or older with no apparent reduction in efficacy as measured by ST-segment recovery at 90 minutes [25].

One-year mortality rates with pharmaco-invasive strategies are generally 4%-6%, similar to timely primary PCI, and are shown in Table 1. These data come from STREAM-1 and registry data from Alberta (Canada), France, Norway and ourselves [21,24,26-28]. Indeed, recent registries from France and Norway reported better outcomes among patients who underwent pharmaco-invasive PCI compared to late primary PCI [29,30]. We recently reported that pharmaco-invasive PCI was associated with significantly lower mortality compared to primary PCI, in part because of higher mortality among patients undergoing primary PCI at greater than 120 minutes after first medical contact [21]. Also, our lowest mortality was in those who had scheduled PCI, a finding similar to that reported from STREAM-1 among those undergoing scheduled angiography [24].

Table 1: One-year mortality rates following STEMI in patients who were treated with a pharmaco-invasive strategy vs primary PCI.

Study	Pharmaco-invasive strategy	Primary PCI
STREAM 1 [24]	5.90%	6.70%
FAST-MI* [29]	2.50%	2.50%
Norwegian Myocardial Infarction Registry (NORMI)* [30]	4%	4.50%
Liverpool, Sydney [21]	4.30%	3.80%
Vital heart registry+ [30]	3.20%	8.40%

Note: (*) Mortality estimated from Kaplan-Meier Curves; (+) Patients receiving primary PCI beyond recommended timeframes were not excluded.

Conclusion

As many patients with STEMI are still treated with fibrinolytic therapy for a variety of reasons, particularly in the pre-hospital setting, a pharmaco-invasive strategy with the need for which involves plus urgent transfer to a PCI centre in all patients with the need for rescue PCI determined at 60-90 minutes following fibrinolytics. Those who have reperfused pharmacologically should undergo early (3-24 hrs) angiography and if appropriate PCI. As pharmaco-invasive strategies achieve similar mortality rates to timely primary PCI, and given our recent report on the mortality hazard of 'late' primary PCI, this approach to the treatment of STEMI patients should be used when the FMC to first device times are likely to be >120 minutes..

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