Application in daily clinical practice
Introduction

Acute ST-elevation myocardial infarction (STEMI) is a condition strongly related to cardiac arrest, with estimates of up to 90% of cardiac arrests being preceded by STEMI (1). The overall survival rate of out-of-hospital cardiac arrest is approximately 5-10% (1); therefore, the main objective in the management of STEMI has been to treat the greatest number of patients possible with early reperfusion therapy, indiscriminate of treatment option (2). The use of the fastest available reperfusion therapy within 3 hours after symptom onset has been proven to decrease in-hospital mortality (3). Despite international guideline recommendations, the overall proportion of eligible patients that receive any form of treatment still tends to remain low (2). Previous studies have found that up to one third of eligible patients with STEMI or left bundle branch block (LBBB) remain untreated, findings that resemble those reported in the 2\textsuperscript{nd} Euro Heart Survey, where over 30% of the patients with STEMI underwent no reperfusion therapy (2). Time delays in treatment delivery have also remained largely unchanged, with a median of 2.5 to 3 hours for primary PCI (4). Accordingly, pharmacologic reperfusion (thrombolytic therapy) might be an option especially for patients with a short delay (2-3 hours) from onset of symptoms until first medical contact if primary PCI cannot be offered within 90-120 minutes and if no contraindications are present (5, 6).

Guideline Recommendations

The American College of Cardiologists, in association with the American Heart Association (ACC/AHA) (5) and the European Society of Cardiology (ESC) (6) recommend reperfusion therapy in patients with STEMI by use of primary percutaneous intervention (PPCI) within 90 to 120 minutes after first medical contact (FMC), i.e. diagnosis of STEMI by use of 12-lead ECG and symptoms by a physician or well-trained paramedic. Favourable outcome can be expected when treatment starts within 2-3 hours of symptom onset (7). Thrombolytic therapy (TT) is preferred for patients when PPCI cannot be delivered within 90 to 120 minutes of FMC by an experienced team if no contraindications for pharmacologic reperfusion are present (5, 6). TT should be initiated within 30 minutes of FMC. Best outcome with TT can be expected in patients treated within 3-4 hours of symptom onset, in big infarctions, and in patients with low bleeding risk (usually the younger below 75 years of age); but from a clinical data point of view, it is efficacious (versus no reperfusion) up to 12 hours of symptom onset and also in the elderly (8, 9).
Concomitant Medications

In the management of AMI, guidelines have always recommended use of concomitant medications to help achieve and maintain therapeutic effects and offer greater benefits in terms of long-term mortality.

Antiplatelet therapy

After plaque rupture, thrombus formation involves activation of the coagulation cascade, formation of fibrin strands and platelet activation (10). When a fibrinolytic agent is used for thrombus dissolution, local production of thrombin is paradoxically increased, causing a pro-thrombotic phase in which the risk of thrombus formation and re-occlusion of the infarct artery is high (10).

An initial dose of chewable aspirin (150-325 mg) is recommended for all patients with STEMI providing they are not allergic to aspirin. Thereafter, aspirin should be continued at a dose of 75-100 mg daily (5, 6).

In order to reduce the risk of thrombus formation, guidelines recommend the addition of clopidogrel in the acute phase: when PPCI is planned, a (300-600 mg loading dose followed by 75 mg daily maintenance dose for up to 12 months is recommended. In patients with STEMI and phar-
cologenic reperfusion, a loading dose of 300 mg for patients under 75 years is recommended, while older patients should only receive 75 mg/day from the beginning. Long-term maintenance of dual antiplatelet therapy (aspirin+clopidogrel) is recommended for all STEMI patients up to 12 months. However, if CABG or other major surgery is planned, clopidogrel should be withheld for 5-7 days prior to the procedure, while aspirin should be maintained if possible (5, 6).

Gastric protection with proton pump inhibitors

Recently, there has been discussion whether the concomitant use of proton pump inhibitors (PPI) in patients on dual antiplatelet therapy, as recommended by international experts (11), might negatively influence clinical outcome (12). One explanation for a reduced action of clopidogrel under concomitant PPI use is that drug absorption is enhanced in an acidic environment, and therefore the use of a PPI or other antacids may potentially diminish or slow drug absorption. Another hypothesis is that PPIs might inhibit the hepatic isoenzyme CYP2C19 and consecutively prevent the metabolism of the pro-drug clopidogrel to its active metabolites through competition for the same substrate (13). A recent trial (14) and a recent meta-analysis (15), however, have proven that the use of PPIs is safe and that co-morbidities and a higher risk profile seem to be responsible for a worse clinical outcome in patients under PPIs.

Platelet glycoprotein (GP) IIb/IIIa inhibitors

GP IIb/IIIa inhibitors are recommended for use in STEMI patients who are referred for PPCI (5, 6). Abciximab is preferred over small molecules (eptifibatide, tirofiban) based on a higher efficacy and more clinical data (5, 6). In the recent ESC guidelines, the early use (in the organisation phase for PPCI) is, however, not recommended based on the only prospective randomised trial (FINESSE), which was negative (6). However, there is meanwhile evidence for the benefit of early use of abciximab based on meta-analyses (16, 17), the EUROTRANSFER registry (18) and post-hoc investigations of a huge prospective trial (19). These data were not fully known when the recent ESC guidelines were published and it is expected that future updated guidelines will reflect this new information.

The use of GP IIb/IIIa blockers adjuvant to TT was beneficial in pilot trials, when used early before the catheter laboratory by demonstrating a higher TIMI-3 flow rate in the infarct-related artery in the first diagnostic angiogram (20, 21). After FINESSE, however, this strategy has been abandoned because it was not effective but led to higher bleeding complications (22).
Anticoagulant therapy

In patients with STEMI and a conservative strategy, the guidelines prefer the use of fondaparinux or the low molecular weight heparin enoxaparin during the period of hospitalisation (5, 6).

Administration of unfractionated heparin (UFH) is now standard practice with PPCI. UFH is usually given as an i.v. bolus (70-100 mg/kg body weight or 40-60 mg/kg if given together with a GP IIb/IIIa inhibitor). While fondaparinux is not recommended in patients referred for PPCI (6, 23), bivalirudin has recently been shown to be effective and safe (HORIZONS trial) (24) and will enter future guidelines. The role of enoxaparin as adjuvant antithrombin during PPCI is currently under investigation (ATOLL trial).

In STEMI patients treated with TT, enoxaparin, unfractionated heparin as well as fondaparinux are potential options for adjuvant anticoagulation (5, 6). The ExTRACT trial with 20,506 patients used a reduced dose of enoxaparin in the elderly (> 75 years) and those with renal impairment, with the result that although there was a significant increase in non-cerebral bleeding, the overall net benefit with regard to mortality, ICH, or non-fatal infarction was in favour of enoxaparin (25).

In the OASIS-6 trial, the factor Xa inhibitor, fondaparinux, was compared to heparin or placebo (if heparin was contra-indicated) in STEMI patients. The trial concluded that fondaparinux was associated with a 17% relative risk reduction in mortality and reinfarction in patients that underwent thrombolysis (23). Thus, fondaparinux (2.5 mg i.v. bolus followed by 2.5 mg daily s.c for up to 8 days) can be given as an adjunctive therapy in patients with STEMI as long as PPCI is not the treatment of choice (5). Direct thrombin inhibitors, such as bivalirudin, are at present not recommended in patients undergoing fibrinolysis (5).

Practical Considerations

Current trial results and international guideline recommendations emphasise treatment strategies to reduce total ischaemic time (defined as the time from onset of symptoms to reperfusion of the infarct-related artery) with the fastest available, safest, and most efficacious reperfusion strategy (5, 6). Early reperfusion of an occluded infarct-related artery has been associated with increased myocardial blood flow restoration, decreased risk of myocardial necrosis, improved myocardial salvage, and improved clinical outcomes, irrespective of the therapy applied (26). Early treatment strategies include development of mobile coronary care units, with trained staff in the diagnosis and management of STEMI, to reduce transport and hospital time delays (27), and usually only can be offered in well organised systems of care (networks). More information about STEMI networks is provided in chapter 7.
Baseline characteristics of patients with different reperfusion strategies

Younger subjects with fresh infarctions are more frequently submitted to TT (preferably pre-hospital lysis, PHT) than the elderly (8). Elderly patients tend to have co-morbidities (hypertension, diabetes) and a higher risk of poor outcomes according to Killip class, TIMI risk scores and TIMI risk index (25). Regardless of the chosen reperfusion therapy, variables such as age, haemodynamic indicators on admission, high heart rate, heart failure, and site of first treatment have been reported as independent variables for adverse in-hospital mortality (27). In patients receiving TT, higher age, haemodynamic indicators on admission, increased heart rate, heart failure, time delay until administration of TT, and non-optimal in-hospital management have been significantly associated with greater in-hospital mortality (27). Older age and presence of co-morbidities (history of peripheral vascular disease, anterior location of infarction, presence of diabetes mellitus, history of congestive heart failure, and history of renal failure) have also been reported as independent predictors of increased 1-year mortality (8) in patients with STEMI independent of the kind of reperfusion strategy. Women also present with higher mortality rates, and gender seems to be related to presence of a higher risk profile (age, incidence of shock, and time to treatment) (3).

<table>
<thead>
<tr>
<th>Variables</th>
<th>P</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>&lt;0.001</td>
<td>54.21</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>11.05</td>
</tr>
<tr>
<td>Pain to reperfusion time</td>
<td>0.05</td>
<td>1.23</td>
</tr>
<tr>
<td>Infarct location</td>
<td>0.036</td>
<td>0.474</td>
</tr>
<tr>
<td>Gender</td>
<td>0.855</td>
<td>0.932</td>
</tr>
</tbody>
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Table 1: Multivariable Analysis of Predictors of Mortality


In addition, patients without reperfusion therapy have a typical profile of clinical characteristics, which is different from that of patients with either type of reperfusion treatment (28): they are usually older with a higher risk profile, as documented by a higher GRACE risk score, while patients treated with TT or PPCI have a comparable GRACE score (28).

Despite age group variances, lower in-hospital mortality is obtained in patients who receive pre-hospital thrombolysis (PHT). Mathew et al. reported significantly lower in-hospital mortality for the PHT group compared to the
in-hospital thrombolysis (IHT) group (Fig 2) (27/326: 8% vs. 55/424: 13%, \( P=0.04 \)) in their STEMI cohort (27). Trials have shown that both in-hospital mortality and 1-year mortality are dependent on time delays (3, 8).

Figure 2: Impact of pre-hospital care in patients with acute myocardial infarction compared with those first managed in-hospital (27)

Special Groups

Recent trials have shown that survival benefits with PPCI over fibrinolysis seem to be lost after determination of door-to-balloon minus door-to-needle (DB-DN) times (29). Excellent outcomes with TT have been reported when used in properly selected subgroups of patients (28), making consideration of patient characteristics, as well as system delays, as well as benefits and limitations of the reperfusion therapy an important part of the selection procedure (29). Therefore, the international guidelines recommend selection of optimal reperfusion strategy, based not only on anticipated door-to-balloon – door-to-needle (DB-DN) time, but also on patient characteristics (6, 30). Baseline characteristics for STEMI patients referred for any reperfusion strategy tend to be similar in most trials. Subjects seem to be more often males, between 55 and 75 years of age, hypertensive, diabetic, and with a previous history of MI (31). Higher age and female gender seem to be independent variables adding up to higher mortality rates in patients with STEMI.
STEMI is a condition frequently seen in older patients (≥ 75 yrs); in general, STEMI is more frequent in patients between 40 and 70 years of age, but with growing populations and longer life spans, the incidence is increasing in the seventh and eight decades, making the elderly the fastest growing segment of the STEMI patient population (25). Trials have reported that more than one half of the mortality rates can be attributed to this group of patients, due to the high frequency of complications, such as heart failure, stroke, and re-infarction (25). Elderly patients are also associated with a higher risk of adverse events related to treatment (i.e. bleeding) (25). Fox et al. reported that after STEMI, higher rates of reinfarction and stroke are present, especially in the early phase (within the first 4 days following STEMI), with an increased mortality risk during the first 2 weeks (31). For patients receiving TT, significant univariate predictors of in-hospital mortality have been identified in several trials, including older age (≥ 75 years), female gender, non-smoking status, non-ST-elevation myocardial infarction, haemodynamic indicators (admission heart rate, Killip class II & III and hypotension), initial hospital admission and longer delay time (call to fibrinolytic therapy) (27). In contrast, younger patients (< 60 yrs) have reported lower in-hospital mortality when compared to other age groups (3).

With respect to PPCI, time delays with longer DB-DN times as recommended have also been independently associated with mortality in patients with STEMI: Pinto et al described how the survival advantage of PPCI over TT decreases 0.15% as DB-DN times increase in patients with STEMI, for every 10-minute delay in the overall study population (29). But this rate of loss of survival advantage varied depending on patient characteristics. According to survival advantage related to time delays and age, patients younger than 65 years tended to lose the survival advantage with PPCI after 71 minutes of delay (vs. 155 minutes in those ≥ 65 years) (Table 2) (29). These authors were also able to show how mortality advantage with PCI was greater in younger patients, who presented with anterior MI treated within 2 hours of symptom onset, but only when performed within 40 minutes (29). In older subjects, not only was the survival advantage with PPCI present after greater delay (115 minutes) but it also showed equal advantage to fibrinolysis therapy, mainly because of the higher risk of ICH in this specific population treated with TT (29).
Table 2: Relationship of Prehospital Delay, Age, and Infarct Location to the Loss of PCI-Related Mortality Benefit

<table>
<thead>
<tr>
<th>Time, min (No. of patients)*</th>
<th>Symptom Duration ≤120 min</th>
<th>Symptom Duration &gt;120 min</th>
<th>Age &lt;65 y</th>
<th>Age ≥65 y</th>
<th>Anterior Infarction</th>
<th>Non-anterior Infarction</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>94 (n=125,737)</td>
<td>190 (n=66,772)</td>
<td>71</td>
<td>155</td>
<td>115 (n=69,331)</td>
<td>112 (n=123,178)</td>
</tr>
<tr>
<td>P†</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Times represent PCI-related delay (DB-DN time) at which mortality with PCI and fibrinolysis were equal, stratified by symptom duration, age, or location of infarct. To ensure a stable estimate of the mortality difference when primary PCI and fibrinolysis were compared in these subgroups, hospitals were excluded if fewer than 10 STEMI patients were treated with either PCI or fibrinolysis in each category.

† P values for the interaction of treatment with fibrinolysis and DB-DN time.

Female gender has been described in several trials as an independent risk factor for STEMI and higher mortality in STEMI patients. Gender and increasing age have been reported as independent predictors (univariate analysis) of higher in-hospital mortality rates in both reperfusion groups (3). Results from the Vienna STEMI registry reported a non-significant almost doubled mortality rate in the female cohort compared to males in the group submitted to PPCI (P=0.18) (3). Likewise with TT, mortality rates were almost 3 times higher in women than in men (P<0.005) (3).

The importance of timing

The benefits of reperfusion on morbidity and mortality in patients with STEMI are more dependent on the time to reperfusion than on the type of reperfusion. The French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI) demonstrated that over the last 10 years, with the development and optimisation of STEMI treatment networks and treatment, mortality significantly declined in France. TT was administered early and was followed in 96% of cases by coronary angiography with 84% receiving subsequent coronary intervention (28), data, which were similar to that of the VIENNA STEMI network (%). The outcomes in-hospital mortality, 30-day mortality, and 1-year mortality, were comparable in patients receiving TT (with consecutive angiogram and revascularisation) or PPCI, although some difference was seen in 30-day mortality when reperfusion treatment was initiated more than 6 hours after symptom onset: within 6 hours of symptom onset, 30-day mortality was 4.4% with TT and 4.5% with PPCI (P=0.92); in those treated later than 6 hours, 30-day mortality was 7.7% versus 5.7% respectively (P=0.58) (28).
In both the CAPTIM trial (32, 33) and the Vienna STEMI Registry (3), PHT was associated with a lower incidence of mortality compared to PPCI in STEMI patients treated within 2 hours of symptom onset. Interestingly, patients referred for PHT displayed signs of cardiogenic shock less often when they reached the hospital than non-pretreated patients (3). After 2 hours, PPCI was more beneficial with regard to mortality (3, 32, 33).

In real-life terms, this means that patients with infarctions in the very early phase (within 2 hours of symptom onset) need to receive reperfusion therapy as soon as possible after the onset of symptoms. Ideally, this is performed at the first point of contact, which again re-emphasises the importance of implementing optimal STEMI management networks to ensure rapid recognition and initiation of treatment. PHT followed by coronary angiography and PCI if necessary seems to be a practical, logical, and successful solution in a well-organised system of care, if PPCI cannot be offered within the given time frame.

**Practicalities and difficulties (see also chapter on Networks)**

Pre-hospital care offers potential benefit to patients with STEMI, especially when it is readily available and can be delivered by trained healthcare professionals (26). Rapid and accurate recognition and management of STEMI not only improves outcomes, but also reduces transportation and hospital delay times, which also improves mortality rates for STEMI patients (27).

PHT has been shown to reduce the time to treatment by 0.5-1 hour in comparison to IHT (4), while in patients without any type of reperfusion therapy, time to treatment delays remain rather high (8). Comparing reperfusion strategies, TT usually offers shorter mean time delays than PPCI. Time to first call was significantly longer in patients with PPCI (median 75 vs. 60 minutes, P=0.001), as well as time to initiation of reperfusion therapy, as reported in the FAST-MI results (28). Other trials have shown that about half of the patients (50.5%) treated with TT receive therapy within 2 hours after symptom onset, while only 14.6% of the patients receiving PPCI can be treated within 2 hours of symptom onset (3).

**Reduced overall mortality**

Mortality rates are significantly reduced with early treatment strategies, especially for those receiving pre-hospital management. Mathew et al reported an absolute risk reduction of 14% in mortality for patients first seen and managed by the MCCU in comparison to those first managed in-hospital (OR for PH 0.497, 95% CI 0.2-1.01, P=0.051) (27). Greater 1-year survival rates are also higher in patients treated with PHT (94.7% vs. 91.8%) than for those undergoing PPCI (1). PHT is also associated with lower 1-year (RR, 0.49; 95% CI, 0.24 to 1.00; P=0.05) and in-hospital mortalities (3.3%) (8). Overall
causes of death tend to be similar for patients with thrombolysis and PPCI, and no greater differences in in-hospital complications have been seen between those treated with thrombolysis and those undergoing PPCI (28). In-hospital mortality was the highest in patients without reperfusion therapy (9.5%) (28).

**Difficulties related to pre-hospital thrombolysis**

Trials have reported frequent use of rescue PCI performed within 1 day of admission in a higher proportion of patients treated with PHT (37%) compared with those who received in-hospital thrombolysis (18%), primary PCI (0.7%), or no reperfusion therapy (12%) (8). In addition, the risk of intracranial haemorrhage (ICH) with TT, especially in elderly patients, is higher which limits its use in this population (34). This risk of ICH, at least in part, can be associated with the adjuvant antithrombotic therapy and has been reported not only for UFH but also for direct thrombin inhibitors and LMWH (34).

**Conclusion**

In the management of STEMI patients, early access to reperfusion strategies has been consistently shown to significantly decrease morbidity and mortality rates in the overall population (3). This requires that STEMI be rapidly recognised and treated. Time delays and patient characteristics should be taken into consideration when choosing reperfusion strategies as well as concomitant therapies. In particular, prehospital thrombolysis has been associated with reduced time delays in STEMI management (27).
References


