



# Inferior ST-Elevation Myocardial Infarction Presenting When Urgent Primary Percutaneous Coronary Intervention Is Unavailable: Should We Adhere to Current Guidelines?

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## Abstract

The pivotal studies that led to the recommendations for emergent reperfusion therapy for ST-elevation myocardial infarction (STEMI) were conducted for the most part over 25 years ago. At that time, contemporary standard treatments including aspirin, statin, and even anticoagulation were not commonly used. The 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines and the 2017 European Society of Cardiology guidelines give a class I recommendation (with the level of evidence A) for primary percutaneous coronary intervention (pPCI) in patients with STEMI and ischemic symptoms of less than 12 h. However, if the patient presents to a hospital without pPCI capacity, and it is anticipated that pPCI cannot be performed within 120 min of first medical contact, fibrinolytic therapy is indicated (if there are no contraindications) (class I indication, level of evidence A). Our review of the pertinent literature shows that the current recommendation for inferior STEMI is based on the level of evidence lower than A. We can consider level B even C, supporting the recommendation for fibrinolytic therapy if pPCI is not available for inferior STEMI.

**Keywords** Fibrinolytic therapy · Guidelines · Reperfusion therapy · ST-elevation myocardial infarction

In the book “Sapiens, a brief history of humankind, Yuval Noah Harari discusses the Scientific Revolution and the importance of the concept of “Ignoramus”: The willingness to

admit ignorance: Modern science is based on the Latin injunction Ignoramus—“we do not know.” It assumes that we do not know everything. Even more critically, it accepts that the things that we think we know could be proven wrong as we gain more knowledge. No concept, idea, or theory is sacred and beyond challenge” [1]. We have to accept that as our knowledge accumulates, old data, paradigms, and practice guidelines could become irrelevant or insufficient.

The clinician is encouraged to follow clinical guidelines. In fact, following guidelines is considered a measure of “quality of care”. However, we should be reminded that guidelines are simply that and not rigid rules. They intend to assist us in the management of the patient who fits the guideline criteria and is not intended to cover all possible clinical scenarios and combinations. Ultimately, the clinician must decide the best treatment for an individual patient, based on knowing the guidelines and (as much as possible), the actual data, and especially the pivotal clinical trials that led to the guideline recommendations. We need to acknowledge that as data accumulate, additional therapies and modalities become standard of care and the old studies might become less relevant to current practice.

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Pivotal studies that led to recommendations for emergent reperfusion therapy for ST-elevation myocardial infarction (STEMI) were conducted for the most part over 25 years ago. At that time, contemporary standard treatments including aspirin, statin, and even anticoagulation were not commonly used. In addition, coronary angiography after fibrinolytic therapy was not routinely performed either prior to rescue PCI or during hospitalization and, if so, was almost invariably via femoral access. There was a debate on whether fibrinolytic therapy should be given to all comers with suspected myocardial infarction or only to certain subgroups. This uncertainty was due in part because electrocardiographic criteria for trial entry varied [2] and not all trials limited inclusion to patients with ST-segment elevation [2]. In that regard, there was a question of whether fibrinolytic therapy is beneficial in patients with inferior myocardial infarction. Subsequently, when primary percutaneous coronary interventions (pPCI) largely replaced fibrinolytic therapy, this question was essentially “swept under the rug,” as pPCI was shown to be more efficacious and safer than fibrinolytic therapy [3, 4]. However, in cases where pPCI is not feasible, the issue of the value of fibrinolytic therapy in inferior STEMI may still be relevant, as illustrated in the following case.

## Two Hypothetical Patients Are Described to Illustrate the Topic

### Hypothetical Case 1

A 76-year-old woman presents with 3–4 h of chest pain to a non-pPCI-capable hospital in the middle of a snowstorm. She has a history of gastrointestinal bleeding 5 years prior after taking the nonsteroidal anti-inflammatory drug for knee pain. However, she has not experienced any bleeding or heartburn since. Blood pressure is 130/90 mmHg and heart rate 60 bpm. Physical examination is unremarkable. ECG shows sinus rhythm at 60 bpm; ST elevation in the inferior leads with reciprocal ST depression and T wave inversion in I and aVL (Fig. 1) compatible with inferior STEMI.

According to current guidelines, chewable aspirin and clopidogrel should be administered [4]. Both European and American guidelines recommend transfer to a pPCI-capable facility if it can be performed within 120 min [3, 4]. There is, however, a raging snowstorm. Transporting the patient is

considered unsafe, and the expected arrival time to the pPCI-capable facility is estimated to be greater than 120 min (could take a few days).

### Hypothetical Case 2

A 77-year-old man presents with 5 h of chest pain to a tertiary hospital with an on-site catheterization laboratory. He reports having fever malaise and cough for the last few days. He is hemodynamically stable, and ECG shows sinus rhythm at 72 bpm, ST elevation in the inferior leads. Due to the current COVID-19 pandemic, the hospital decided to use intravenous thrombolytic therapy instead of pPCI as a policy to minimize exposure, especially as the patient is hemodynamically stable and could have COVID-19 infection.

The 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines and the 2017 European Society of Cardiology guidelines give a class I recommendation (with the level of evidence A) for pPCI in patients with STEMI and ischemic symptoms of less than 12 h [3, 4]. However, if the patient presents to a hospital without pPCI capacity, and it is anticipated that pPCI cannot be performed within 120 min of first medical contact, fibrinolytic therapy is recommended (if there are no contraindications) (class I indication, level of evidence A) [3, 4]. Remote history of gastrointestinal bleeding without active peptic ulcer is not considered a contraindication for thrombolytic therapy [3].

Whether or not the patient receives thrombolytic therapy, the patient should be transferred to a hospital with PCI facility when transportation becomes available, unless the patient is completely asymptomatic and more than 48 h passed from symptoms' onset [4].

## Discussion

By providing a critical appraisal of the available knowledge base, we are questioning whether there is truly a level of evidence A for fibrinolytic therapy in inferior STEMI. The following studies provide evidence that underpins the current guideline recommendations for treatment of inferior STEMI:

Several randomized trials have compared outcomes of fibrinolytic therapy vs. no reperfusion therapy in patients presenting with suspected myocardial infarction (see below).

**Fig. 1** Presenting ECG showing sinus rhythm ~ 60 bpm with ST elevation in the inferior leads and reciprocal ST depression in I and aVL



Extrapolation from these early studies to our current practice is problematic, insofar as the use of aspirin, P2Y<sub>12</sub> inhibitors, anticoagulation, beta-blockers, and statins was not routine at the time these studies were conducted. In the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) trial, only 13–14.7% of the 11,806 enrolled patients received anti-platelet agents and 8.3% beta-blockers [5]. Among patients presenting within 12 h of symptom onset, streptokinase significantly reduced in-hospital mortality in anterior, but not inferior, STEMI [5]. The Second International Study of Infarct Survival (ISIS-2) randomized 17,187 patients within 24 h of onset of symptoms to streptokinase versus placebo and aspirin versus placebo [6]. Streptokinase reduced mortality in patients with anterior STEMI, but only produced a trend toward reduced mortality in patients with inferior STEMI. Furthermore, the beneficial effect of streptokinase was time dependent [6]. There is no report on the interaction between time and efficacy among the subgroup with inferior STEMI. Moreover, the study compared the overall effects of streptokinase versus placebo among the groups that received or did not receive aspirin. There is no comparison between the aspirin alone and streptokinase + aspirin treatments in inferior STEMI [6]. In this study, aspirin alone had the same effect as streptokinase on mortality and the effect of the combination was greater than aspirin alone or streptokinase alone.

The Urochinas per via Sistemica nell'Infarto Miocardico (USIM) study reported increased mortality with urokinase in patients with inferior myocardial infarction (5.81% vs. 3.20%;  $p = 0.04$ ); however, only a quarter of the patients received anti-platelet therapy and 9–10% received beta-blockers [7].

The Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) trial [8], the APSAC Intervention Mortality Study (AIMS) [9], the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) trial [10], the Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur (EMERAS) trial [11], and the Late Assessment of Thrombolytic Efficacy (LATE) study [12] did not report on patient subgroup analysis based on infarct location or on concomitant use of other medications so the value of the use of fibrinolytic therapy in inferior STEMI cannot be ascertained.

The abovementioned earliest trials, that included more than 1000 patients per trial, were summarized by the Fibrinolytic Therapy Trialists Collaborative Group in 1994 [13]. Subgroup analysis showed that fibrinolytic therapy reduced 35-day mortality among patients with ST elevation in the anterior leads or “other” leads but failed to reach statistical significance among patients with ST elevation in the inferior leads (11% proportional reduction; 95% CI –24% to +5%;  $p = 0.08$ ) [13]. Personal communication from the FTT collaborative group that is quoted by a 1995 letter to the editor suggested that mortality was reduced by 13% from 8.1 to 7.1% (95% CI 24% to 0% reduction for patients with inferior infarction randomized within 12 h of onset of symptoms), while the

reduction in mortality was 14% from 7.6 to 6.6% (95% CI 27% to 0% reduction) for patients treated within 6 h [14]. However, this analysis has not been directly published and was not part of the primary or secondary endpoints analysis and, thus, should be considered only as hypothesis generating. No other endpoints, such as heart failure, are provided. One later study and a review did not report on outcomes of the subgroup with inferior STEMI separately [15, 16].

The studies that reported on outcomes of patients with inferior infarct used non-fibrin-specific agents (streptokinase or urokinase), while later studies have shown the advantage of fibrin-specific agents (tenecteplase (TNK), tissue plasminogen activator (tPA), or single-strand PA (reteplase)) [4]. These latter studies did not tease out outcomes of inferior vs anterior STEMIs. According to the guidelines, a half-dose of TNK-tPA should be considered in patients older than 75 years [4]; this dose has not been tested versus no reperfusion therapy in patients with inferior STEMI. Moreover, we do not have sufficient data from randomized trials for the effects of fibrin-specific agents on top of aspirin loading (and clopidogrel), as they are now considered standard of care [4].

Guidelines specify that level A evidence or “estimate of certainty of treatment effect A” should be based on either data derived from multiple randomized clinical trials or meta-analyses [3, 4]. Level B is based on evidence from a single randomized trial or nonrandomized trial, whereas level C is based only on expert opinion, case studies, or registries [3, 4]. Thus, based on these definitions, the level of evidence supporting fibrinolytic therapy for inferior STEMI should, in our opinion, be downgraded to C, LD (limited data), or EO (expert opinion).

In all comer STEMIs, i.e., combining anterior, lateral, and inferior locations, pPCI is associated with reduced mortality compared with fibrinolytic therapy, if pPCI can be performed within 120 min of first medical encounter [17–19]. If the delay is > 120 min, no beneficial effects of pPCI over fibrinolytic therapy have been observed [17–19]. However, most of the studies comparing fibrinolytic therapy to primary angioplasty in STEMI did not report on outcomes of inferior STEMI separately [20–28]. Although the GUSTO IIB [22] and the Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) [29] reported similar advantage of pPCI over fibrinolytic therapy in patients with anterior and non-anterior STEMI, they did not specifically analyze inferior STEMI. Also, those patients randomized to fibrinolysis had a very low rescue PCI rate of 2–3% in the DANAMI-2 study, whereas in STREAM rescue PCI was ~30%, questioning the applicability DANAMI-2 to current practice. The Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI), on the other hand, did report the advantage of pPCI over fibrinolytic therapy in patients with inferior STEMI [30]. However, in the Strategic

**Table 1** Definitions of the levels of Estimate of Certainty (Precision) of Treatment Effect. 2013 ACCF/AHA STEMI Guidelines [3]

|  |
|--|
| Level A: Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses.   |
| Level B: Limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies.      |
| Level C: Very limited populations evaluated. Only consensus opinion of experts, case studies, or standard of care. |
| Definitions of the Levels of Evidence. 2017 ESC STEMI Guidelines [4]   |
| Level A: Data derived from multiple randomized clinical trials or meta-analyses.                                   |
| Level B: Data derived from a single randomized clinical trial or large nonrandomized studies.                      |
| Level C: Consensus of opinion of experts and/or small studies, retrospective studies, registries.                  |

Reperfusion Early after Myocardial Infarction (STREAM) study, the relative risk of the primary end point (death from any cause, shock, congestive heart failure, or reinfarction up to 30 days) favored fibrinolysis over pPCI for patients with inferior STEMI and was neutral for anterior STEMI [17]. Moreover, Dobrzycki et al. found no advantage for transfer for pPCI over fibrinolysis in patients arriving at hospitals without pPCI facility in patients with non-anterior STEMI [31]. Even a pooled analysis of 22 randomized clinical trials comparing pPCI and in-hospital fibrinolysis in STEMI patients showed that there was no significant advantage of pPCI on mortality in patients with non-anterior, in contrast to anterior, STEMI [32] Tables 1 and 2.

Compared with anterior wall STEMI, inferior STEMI has in general a more favorable prognosis [33]. However, certain patients (those with advanced atrioventricular block, right ventricular involvement, or precordial ST depression) are at higher risk. Moreover, certain ECG patterns, such as terminal QRS distortion in the leads with ST elevation [34], or ST

depression mainly in V4-V6 [35–37] is associated with increased mortality. However, the efficacy of either fibrinolytic therapy or pPCI in reducing mortality in patients with these ECG patterns of inferior STEMI has not been studied. Therefore, recommending specific therapies for special ECG patterns of inferior STEMI cannot be based on scientific evidence.

One may argue that fibrinolysis added to “standard of care” provides additional benefits besides short-term mortality, such as limitation of infarct size, prevention of remodeling, and the development of heart failure or even long-term mortality benefit [14, 38]. However, there is no direct evidence that these benefits outweigh the potential risks associated with fibrinolysis in patients with inferior STEMI without high-risk features [39].

One may also argue that we need to concentrate on the primary endpoints of the original studies and any use of secondary endpoints or subgroup analyses should be considered only as hypothesis generating. Yet, using the exact same data, we accepted that fibrinolysis is not beneficial, and even considered harmful, in patients presenting without ST elevation or with isolated ST depression [3, 4].

In conclusion, the justification of reperfusion therapy for patients presenting with inferior STEMI is based on the overall benefit of reperfusion therapy in patients with STEMI; however, we do not have data to justify level of evidence A for fibrinolytic therapy in inferior STEMI. As reperfusion therapy for inferior STEMI (including fibrinolytic therapy if pPCI is not available) has become a “standard of care,” it would be challenging (if not impossible) to conduct a randomized study comparing reperfusion therapy to no reperfusion therapy in these patients. Furthermore, the rationale to treat all STEMI, the same is intuitively attractive.

Taken together, our review of the pertinent literature shows that the current recommendation for inferior STEMI is based on the level of evidence lower than A. We can consider level B (if we accepted the personal communication from the FTT

**Table 2** Summary of the clinical trials evaluating the effects of fibrinolytic therapy versus no reperfusion therapy

| Study  | Reference | Total number of patients | Number of patients with inferior MI | Time frame | Inclusion criteria                      | Fibrinolytic agent | Finding   |
|--------|-----------|--------------------------|-------------------------------------|------------|---|--------------------|---|
| GISSI  | [4]       | 11,712                   | 4005                                | 12 h       | Chest pain + ST elevation or depression | Streptokinase      | Streptokinase significantly reduced in-hospital mortality in anterior, but not inferior MI.   |
| ISIS-2 | [5]       | 17,187                   | 4188                                | 24 h       | Suspected MI. No ECG criteria           | Streptokinase      | Streptokinase reduced mortality in patients with anterior, but MI, but only produced a trend toward reduced mortality in patients with inferior MI. |
| USIM   | [6]       | 2201                     | 1041                                | 4 h        | Chest pain + ST elevation or depression | Urokinase          | Increased mortality with urokinase in patients with inferior MI.  |

collaborative group quoted in a letter [13]) or C. As such, clinicians should exert judgment in balancing the potential benefits versus risks in the individual patient presenting with suspected inferior STEMI when pPCI cannot be performed within 120 min of the first medical contact. As the use of fibrinolytic therapy is associated with increased risk of bleeding (intra-cranial hemorrhage in particular), the use of fibrinolysis for uncomplicated inferior STEMI without high-risk features (and with high potential bleeding risk) should probably not be a class I (benefits>>>risks) indication. A class IIa (benefit>>risks, it is reasonable to perform) recommendation seems more appropriate. To be clear, we do not recommend against giving thrombolytic therapy in this case (class III indication), we just pointing out that per the definitions, set in the Guidelines documents does not support the current class I indication. We thus propose that any guideline revision in the future be more specific, stratifying the weight of its recommendations according to infarct location.

Due to the COVID-19 pandemic, many Medical Centers decided to use thrombolytic therapy instead of primary PCI for STEMI. This could be preferentially used for “low-risk” patients, including inferior STEMI. Thus, the question of the beneficial effects of thrombolytic therapy in uncomplicated inferior STEMI has become even more relevant.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Statement** N/A.

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