CONTROVERSY

# All Patients Treated with Thrombolytic Agents Should Undergo a Pharmacoinvasive Strategy in the First 24 Hours

## Agonist

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ST-segment elevation myocardial infarction (STEMI) constitutes an important cause of mortality and hospitalization. The therapeutic target in the acute phase of STEMI is achieving rapid and permanent restoration of epicardial blood flow with subsequent improvement in myocardial tissue perfusion. (1) Several studies have demonstrated the superiority of primary percutaneous coronary intervention (PCI) over fibrinolytic therapy (FT) when this strategy can be implemented within a reasonable time. (1, 2) However, in our country most patients seek medical care at centers without PCI facilities. These centers choose to administer early FT to achieve rapid reperfusion, as the administration of FT within 3 hours after symptom onset is a favorable strategy and probably equivalent to primary PCI. (3, 4) Fibrinolytic therapy, however, has limitations, even if the best thrombolytic agent currently available is used (r-TPA accelerated infusion). Approximately 20% of patients do not achieve successful and sustained reperfusion (5) and this percentage increases when another thrombolytic agent with proven lower efficacy, as streptokinase in our environment, is used.

Actually, management of STEMI in low or medium complexity centers presents a therapeutic dilemma demanding a series of prompt decisions concerning the type of reperfusion strategy and eventual transfer of the patient to a center with catheterization laboratory. Although primary PCI is more efficient than FT, the benefit of both strategies is strongly associated with the progression of myocardial ischemia to necrosis. In this sense, a meta-analysis of 23 randomized trials which compared mechanical and pharmacological reperfusion strategies showed that a delay > 62 min abolished the benefit of primary PCI over FT. (6) This phenomenon was also observed in the real world where reperfusion delay ≥ 120 minutes neutralized the benefit of mechanical reperfusion over FT. (7) In addition, patient delay to presentation also has a clinical impact on the time interval to PCI. In patients with late presentation (time from first medical contact to center ≥ 120 minutes), the superiority of primary PCI continues up to 190 minutes, while patients presenting earlier tolerate shorter delays (< 94 minutes). (7) Probably, this might be due to the fact that organized thrombi associated with longer term evolving infarctions are more resistant to fibrinolysis.

The implementation of a pharmacoinvasive strategy or combined reperfusion (FT followed by PCI) could offer the best of each approach, reaching rapid, optimized and stable reperfusion with PCI. Several studies evaluated the role of immediate angiography (< 2 hours) after the administration of FT. (1, 8) The results of this strategy, known as facilitated PCI, were disappointing because of high rates of bleeding and thrombosis due to insufficient antiplatelet therapy. (8) Nowadays, the perioperative pharmacological management of primary PCI has evolved significantly, achieving high levels of antiplatelet effect and low bleeding rates. The use of adjuvant measures as thrombus aspiration and the implantation of thin-strut stents which are less thrombogenic ensure a safe and efficient procedure after FT.

The results of the most recent clinical trials evaluating the role of a routine invasive strategy after FT were characterized by small samples and use of surrogates as primary objectives. (9-13) However, most trials showed improved clinical outcomes with early PCI in high-risk patients. (9, 13)

The GRACIA trial [Grupo de Análisis de la Cardiopatía Isquémica Aguda (Acute Ischemic Cardiomyopathy Working Group)] compared early post-thrombolysis coronary angiography (6 to 24 hours) with ischemia-guided conservative approach in stable patients. (14) In this study, death, reinfarction, or revascularization rate at 12 months were lower with the invasive strategy. (14) The RANSFER-AMI study (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction, n = 1059) showed a significant reduction in the composite of death, reinfarction, recurrent ischemia, or development of congestive heart failure at 30 days compared to a conservative strategy. (13) These findings indicate that patients with STEMI with hemodynamic stability or at higher risk of death benefit from an invasive strategy within 6-12 hours after FT. The benefits lie in the reduction of reinfarction and recurrent ischemia.

The STREAM trial (Strategic Reperfusion Early After Myocardial Infarction), randomized 1892 patients with STEMI ≤ 3 hours after symptom onset and estimated delay to PCI > 60 minutes to two

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reperfusion strategies: pharmacoinvasive strategy (FT followed by PCI) or primary PCI. (15) The primary endpoint occurred in 12.4% of patients in the pharmacoinvasive group and in 14.3% of patients in the primary PCI group (p = 0.21) with greater intracranial bleeding in the pharmacoinvasive group (1.0% vs. 0.2%, p = 0.04). The protocol was amended during the course of the study to reduce the dose of the fibrinolytic agent in aged patients. After the amendment, the rate of intracranial bleeding decreased to 0.5%, similar to that of the primary PCI group. (15) The time delay between symptom onset and start of reperfusion therapy was significantly shorter in the pharmacoinvasive strategy (median 100 minutes vs.178 minutes), allowing longer time to angiography (median 600 vs. 170 minutes). Undoubtedly, one of the advantages of the pharmacoinvasive strategy is that on-site FT aids logistics, providing the health care system with an additional time to organize patient transfer for coronary angiography and final PCI on a non-urgent basis. These findings suggest that the pharmacoinvasive strategy is feasible and has a similar efficacy to that of primary PCI, though the safety of this approach depends on the patient's bleeding risk.

In conclusion, several therapeutic scenarios should be considered in patients with STEMI. Primary PCI is the treatment of choice in patients presenting at tertiary care centers or at medium complexity centers with a transport time delay to a center with PCI capacity < 120 minutes or with contraindications for FT (e.g., high bleeding risk or hemodynamic instability).

The implementation of a pharmacoinvasive strategy seems particularly attractive in patients presenting to a medium complexity center within 3 hours after the onset of symptoms, with high risk of death and low bleeding risk. For those patients presenting later, the efficacy of FT decreases significantly and might not justify its administration due to the risk of bleeding. In these cases, patient transfer for urgent PCI is recommended.

**Conflicts of interest:**
None declared.

## REFERENCES

**1.** O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78-140. http://doi.org/mn9

**2.** Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20. http://doi.org/c7p2r9

**3.** Bainey KR, Senaratne MP. Is the outcomes of early ST-segment resolution after thrombolytic therapy in acute myocardial infarction always favorable? J Electrocardiol 2005;38:354-60. http://doi.org/c2cc4b

**4.** Dong J, Ndrepepa G, Schmitt C, Mehilli J, Schmieder S, Schwaiger M, et al. Early resolution of ST-segment elevation correlates with myocardial salvage assessed by Tc-99m sestamibi scintigraphy in patients with acute myocardial infarction after mechanical or thrombolytic reperfusion therapy. Circulation 2002;105:2946-9. http://doi.org/c6r7pb

**5.** Ellis SG, Da Silva ER, Spaulding CM, Nobuyoshi M, Weiner B, Talley JD. Review of immediate angioplasty after fibrinolytic therapy for acute myocardial infarction: insights from the RESCUE I, RESCUE II, and other contemporary clinical experiences. Am Heart J 2000;139:1046-53. http://doi.org/d79wcj

**6.** Tarantini G, Ramondo A, Napodano M, Bilato C, Buja P, Isabella G, et al. Time delay-adjusted survival benefit of angioplasty over thrombolysis in acute myocardial infarction: influence of time from symptom onset. Ital Heart J 2004;5:844-50.

**7.** Pinto DS, Frederick PD, Chakrabarti AK, Kirtane AJ, Ullman E, Dejam A, et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. Circulation 2011;124:2512-21. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.018549

**8.** Kiernan TJ, Ting HH, Gersh BJ. Facilitated percutaneous coronary intervention: current concepts, promises, and pitfalls. Eur Heart J 2007;28:1545-53. http://doi.org/bhshdd

**9.** Danchin N, Coste P, Ferrieres J, Steg PG, Cottin Y, Blanchard D, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the french registry on acute ST-elevation myocardial infarction (FAST-MI). Circulation 2008;118:268-76. http://doi.org/fv574t

**10.** Bodi V, Rumiz E, Merlos P, Nunez J, Lopez-Lereu MP, Monmeneu JV, et al. One-week and 6-month cardiovascular magnetic resonance outcome of the pharmacoinvasive strategy and primary angioplasty for the reperfusion of ST-segment elevation myocardial infarction. Rev Esp Cardiol 2011;64:111-20.

**11.** Capodanno D, Dangas G. Facilitated/pharmaco-invasive approaches in STEMI. Curr Cardiol Rev 2012;8:177-80. http://doi.org/mpb

**12.** Welsh RC, Armstrong PW. Contemporary pharmacological reperfusion in ST elevation myocardial infarction. Curr Opin Cardiol 2012;27:340-6. http://doi.org/mpc

**13.** Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med 2009;360:2705-18. http://doi.org/b3rtrg

**14.** Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, Vazquez N, Blanco J, Alonso-Briales J, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. Lancet 2004;364:1045-53. http://doi.org/d42t34

**15.** Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med 2013;368:1379-87. http://doi.org/mb9

# Antagonist

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*"In a time of universal deceit - telling the truth is a revolutionary act.."*

Quote attributed to **George Orwell**

## WHAT IS "PHARMACOINVASIVENESS"?

This topic starts with a problem: what do we mean by pharmacoinvasive treatment or strategy?

In principle, common sense indicates that we are

referring to the use of drugs in combination with an invasive treatment. In cardiology practice, it refers to the use of coronary angiography, usually in combination with percutaneous coronary intervention (PCI) of the infarct-related artery, after the use of thrombolytic agents indicated as reperfusion therapy in the setting of acute myocardial infarction (AMI).

In fact, both rescue PCI and facilitated PCI are pharmacoinvasive strategies. But in practice, the term has been restricted to the systematic indication of coronary angiography/PCI after thrombolytic therapy in AMI. This implies that this scheme does not consider the presence or the absence of reperfusion from a non-invasive point of view; in other words, if fibrinolysis was successful or not.

In this controversy I shall refer to the latter definition as it is the one currently used.

## WHAT IS A REINFARCTION?

The term AMI has experienced significant changes over the years. Myocardial infarction, which was the easiest disease to define, has become one of the most complex definitions. The "First Universal Definition of Myocardial Infarction" was developed more than 10 years ago, (1) and was subsequently replaced by a second (2) and recently by a third definition. (3) Among the several reasons for these redefinitions, the emergence of cardiac troponins for the diagnosis of myocardial necrosis, previously defined by increased levels of creatine kinase (CK) and its myocardial isoenzyme (CK-MB), was fundamental for the development of new "universal definitions"

The definition of reinfarction is as complex or even more complex, particularly when it occurs within the first hours after AMI. For this reason, each trial adopts its own definition which is rarely the same. Troponin-based diagnosis of reinfarction has even been suggested despite the lack of consistent evidence. (2) despite the lack of consistent evidence. (2)

## PHARMACOINVASIVE STRATEGY STUDIES IN ACUTE MYOCARDIAL INFARCTION

We shall focus only on the most important studies analyzing the pharmacoinvasive strategy without considering those evaluating invasive strategies, as rescue PCI and "facilitated PCI". We will analyze three different design studies which randomized at least 500 patients: GRACIA-1, CARESS-in-AMI and TRANSFER-AMI. (4-6) We shall also comment the meta-analysis by D'Souza et al. (7)

In the Spanish GRACIA-1 (4) study, 500 patients with ST-segment elevation myocardial infarction (STEMI) treated with recombinant tissue plasminogen activator were randomly assigned to angiography and routine percutaneous intervention within 24 h of thrombolysis, or to an ischemia-guided conservative approach. The primary endpoint was death, reinfarction, or revascularization at 12 months. Revascularization was needed in 84% of patients in the invasive group and in 20% in the conservative group. The primary endpoint occurred in 9% of patients in the first group vs. 21 % in the second group ($p < 0.001$). However, if the indication of new revascularization is excluded, the difference between hard events is no longer statistically significant. Mean time between thrombolysis and PCI in the invasive group was 16.7 hours.

The CARESS-in-AMI (5) trial was a multinational European study that randomized 600 patients with STEMI and high-risk features treated with half-dose reteplase and abciximab to a group of immediate transfer to an interventional center for angiography and PCI, or to a group managed in the local hospital with transfer only in case of absence of clinical signs of reperfusion or clinical deterioration. The primary endpoint was death, reinfarction, or refractory ischemia at 30 days. In the first group, 85.6% of patients received PCI, and rescue PCI was done in 30.3% of patients in the second group. Mean time between thrombolysis and PCI in the invasive group was 135 minutes (2.2 hours). The primary endpoint occurred in 4 .4% of patients in the invasive group vs. 10.7% in the conservative group ($p = 0.004$). This difference was exclusively due to recurrent ischemia, as there were no differences in reinfarction or death. After one year of follow up, there were no statistically significant differences in the primary endpoint ($p = 0.07$).

The TRANSFER-AMI study (6), performed in Canada, randomly assigned 1059 high-risk patients with STEMI treated with tenecteplase at centers that did not have PCI capacity to either a strategy of transfer to another hospital for coronary angiography/PCI within 6 hours after fibrinolysis or standard treatment including transfer for rescue PCI, if required. In this group, coronary angiography within 2 weeks after randomization was recommended. The primary end point of the study was the incidence of death, reinfarction, recurrent ischemia, new or worsening heart failure, or cardiogenic shock at 30 days. Mean time between thrombolysis and PCI in the invasive group was 3.9 hours. PCI was done in 85% of patients in the invasive group and in 67% in the conservative group. The primary endpoint occurred in 11% of patients in the first group vs. 17.2% in the second group ($p = 0.004$). When the events were analyzed separately, no differences were observed in the incidence of death, reinfarction or cardiogenic shock. Again, recurrent ischemia evidenced the most significant difference.

### D'Souza's meta-analysis

In 2011, authors from the city of Manchester, United Kingdom, published a meta-analysis comparing early

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routine PCI with ischemia-guided PCI after thrombolysis in STEMI. (7) The meta-analysis was performed on eight studies published between 2000 and 2010, including the three main studies previously commented, comprising a population of 3195 patients. The primary composite endpoint of reinfarction, death or recurrent ischemia at 30 days was observed in 7.3% of patients in the first group vs. 13.5% in the second group ($p < 0.0001$), at the expense of lower incidence of reinfarction and ischemia. There were no significant differences in the incidence of mortality and severe bleeding. Interestingly, the authors did not find a definite association in the timing of PCI after fibrinolytic therapy and the rate of events.

### How should the results be understood?

Two facts clearly arise from the randomized clinical studies that we have commented. Firstly: the pharmacoinvasive strategy has not proved to prolong life of STEMI patients. Secondly: this therapeutic strategy has a favorable impact on the development of new ischemic events as angina or reinfarction.

Yet, some information provided by these studies should be briefly reviewed. The CARESS-in-AMI trial does not seem practical, as the use of half-dose reteplase plus abciximab is not common in our environment. The use of clopidogrel, which reduces mortality in STEMI in patients treated or not with thrombolytic agents, (8) was different among the groups compared. In the CARESS trial, clopidogrel was used in 57.1% of patients in the conservative group vs. 85.9% in the invasive group ($p < 0.0001$). In the TRANSFER-AMI study, clopidogrel was used in 68.8% and 88.5% of patients, respectively ($p < 0.001$). This treatment bias may benefit the outcomes of the invasive group.

The different studies used fibrin-specific thrombolytic agents: alteplase, reteplase, tenecteplase. Unfortunately, the results of these studies cannot be applied to our environment, where streptokinase is practically the only fibrinolytic agent used in AMI. (9)

## THE PROBLEM OF REINFARCTION

Reinfarction after a STEMI treated with fibrinolytic agents is rare, with an incidence of about 3% to 4% at 30 days and 2% to 3% at 6 months. (10, 11) Unfortunately, predictors of reinfarction are scarce and have low predictive value in clinical practice. Postinfarction angina is probably the strongest predictor; yet, 50% of reinfarctions occur in the absence of predictive factors. (10-12) The conclusive fact is that reinfarction implies adverse outcomes. An analysis of the GUSTO I and GUSTO III databases demonstrated that mortality increased from 3.5% in patients without reinfarction to 11.3% in those with reinfarction (odds ratio 3.5; $p < 0.001$). (11) Therefore, it is difficult to understand how an intervention that reduces the incidence of reinfarction does not have any impact on mortality. This phenomenon might be explained in part by an insufficient sample size or by problems in defining reinfarction. Although the studies that we have commented may individually lack statistical power to demonstrate reduction in mortality, it is also true that both CARESS and TRANSFER studies included high-risk patients requiring a smaller sample size. However, the meta-analysis including all the studies also failed to demonstrate lower mortality with the pharmacoinvasive intervention.

## CONCLUSIONS

The uncertainty about this topic is reflected in the ACC/AHA guidelines published this year which recommends class II (level of evidence B) for the pharmacoinvasive strategy, despite the ideological viewpoint of interventional management of ischemic heart disease advocated in the USA. (13) Class II means that "there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/treatment".

The definite answer to the question: "should all patients treated with thrombolytic agents undergo a pharmacoinvasive strategy within the first 24 hours?" which has originated this controversy, should be no. This does not imply that there are no patients who can benefit from this strategy, always bearing in mind the cost-benefit ratio. Surely there are. The future challenge is to identify them. As an example, the NORDISTEMI study (14) included a small sample of patients living in rural areas of Norway without access to a catheterization laboratory and long transfer delays to tertiary care centers. Probably this type of patients, particularly those at high risk, might benefit from this strategy.

Finally, I recall a phrase that Dr Carlos Bertolasi, the person who taught me how to think in cardiology, once told me: "Nothing is for everybody". Simple and conclusive, this statement is particularly applicable to complex and expensive strategies as the one analyzed today.

### Conflicts of interest

None declared.

## REFERENCES

**1.** The Joint European Society of Cardiology/American College of Cardiology Committee: Myocardial Infarction Redefined A Consensus Document of The Joint European Society of Cardiology/ American College of Cardiology Committee for the Redefinition of Myocardial Infarction. J Am Coll Cardiol 2000;36:959-69. http://doi.org/dm4t3t

**2.** Thygesen K, Alpert J White H, on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: Universal Definition of Myocardial Infarction. J Am Coll Cardiol 2007;50:2173-95. http://doi.org/fhnv5q

**3.** Tygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al: the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction: Third universal definition of myocardial infarction. Circulation 2012;126:2020-35. http://doi.org/d42t34

**4.** Fernández-Avilés F, Alonso JJ, Castro-Beiras A, Vázquez N, Blanco J, Alonso-Briales J, et al, on behalf of the GRACIA (Grupo de Análisis de la Cardiopatía Isquémica Aguda) Group: Routine in-

vasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. Lancet 2004;364:1045-53. http://doi.org/d42t34

**5.** Di Mario C, Dudek D, Piscione F, Mielecki W, Savonitto S, Murena E, et al, on behalf of the CARESS-in-AMI (Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction) Investigators: Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab RE-teplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. Lancet 2008;371:559-68. http://doi.org/dg8j7h

**6.** Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, et al, for the TRANSFER-AMI Trial Investigators: Routine Early Angioplasty after Fibrinolysis for Acute Myocardial Infarction. N Engl J Med 2009;360:2705-18. http://doi.org/b3rtrg

**7.** D'Souza S, Mamas M, Fraser D, et al. Routine early coronary angioplasty versus ischaemia-guided angioplasty after thrombolysis in acute ST-elevation myocardial infarction: a meta-analysis. Eur Heart J 2011;32:972-82. http://doi.org/d4pktj

**8.** COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group: Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-21. http://doi.org/dkdfgd

**9.** Blanco P, Gagliardi J, Higa C y cols., por los Investigadores del Área de Investigación SAC y el Consejo de Emergencias Cardiovasculares de la SAC: Infarto agudo de miocardio. Resultados de la Encuesta SAC 2005 en la República Argentina. Rev Argent Cardiol 2007;75:163-70.

**10.** Volpi A, de Vita C, Franzosi M, et al. Predictors of nonfatal reinfarction in survivors of myocardial infarction after thrombolysis: Results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) Data Base. J Am Coll Cardiol 1994;24:608-15. http://doi.org/dj5g9n

**11.** Hudson M, Granger C, Topol E, et al. Early reinfarction after fibrinolysis: experience from the global utilization of streptokinase and tissue plasminogen activator (alteplase) for occluded coronary arteries (GUSTO I) and global use of strategies to open occluded coronary arteries (GUSTO III) trials. Circulation 2001;104:1229-35. http://doi.org/cjgq7s

**12.** Piombo A, Gagliardi J, Ulmete E, et al. Prognostic value of clinical variables for recurrent ischemic events after acute myocardial infarction. Clin Cardiol 1995;18:157-60. http://doi.org/d6m3bf

**13.** O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e362-e425. http://doi.org/mpd

**14.** Bøhmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and Safety of Immediate Angioplasty Versus Ischemia-Guided Management After Thrombolysis in Acute Myocardial Infarction in Areas With Very Long Transfer Distances. Results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2010;55:102-10. http://doi.org/cqwxf7

## AGONIST'S REPLY

I agree with the antagonist that a high-risk STEMI patient presenting at a rural center represents the ideal case to implement a pharmacoinvasive strategy.

There are two therapeutic options available in our environment for this type of patients: 1) the administration of suboptimal FT, as is the case of streptokinase, without subsequent transfer to a tertiary care center, or 2) transfer for primary PCI with long delay. The first option is associated with low reperfusion rate and high incidence of reinfarction, while the second is associated with high reperfusion rate; however, the long delay reduces the size of myocardium saved. In this scenario, patient's transfer for coronary angiography after suboptimal FT could be even more useful than in the mentioned studies evaluating a pharmacoinvasive strategy, as the need of rescue PCI and the risk of reinfarction could be greater than in those studies.

I also agree that the definition of reinfarction has been modified across the years. However, and independently of its definition, in many occasions reinfarction has devastating consequences, multiplying the risk of cardiovascular mortality (in the DANAMI 2 trial, mortality with reinfarction was 24.3% vs. 6.5%; $p < 0.0001$).

After the administration of nonspecific thrombolytic agents as streptokinase, reinfarction rate is about 4% (more than 6-7% with fibrin-specific thrombolytic agents, which achieve greater reperfusion), while after primary PCI the reinfarction rate is about 2%.

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## ANTAGONIST'S REPLY

Interestingly, I agree with Dr Bettinotti that not all patients treated with thrombolytic agents should undergo a pharmacoinvasive strategy within the first 24 hours. My colleague states so when he says that AMI patients with "high risk of death" benefit from this strategy and only in relation to reinfarction and recurrent ischemia.

The STREAM trial is an interesting study but, in my opinion, does not qualify for this controversy, as it does not compare a pharmacoinvasive strategy with fibrinolysis alone but with another invasive strategy (primary PCI). Even more, it can be only applied to patients with less than 3 hours after symptom onset undergoing prehospital fibrinolysis (which is unavailable in our environment).

I certainly do not agree with the statement that the "low efficacy" of thrombolytic therapy after 3 hours from symptom onset does not justify its use. Thrombolytic agents have proved to be efficient up to 12 hours after symptom onset; yet, their ability to save lives decreases with time. The same happens with primary PCI, although in a lower proportion. For these reasons, I do not agree with the systematic transfer of such patients unless one is completely sure that patient transport will be done respecting the adequate delays. Early thrombolysis is better than late PCI.

Finally, I think that clinical and interventional cardiologists should work together in the future to understand which patients will benefit from "pharmacoinvasive" strategies, particularly in our environment which is obviously very different from the environment where most of the valuable randomized clinical trials have been developed.

There is not a single real world but a huge variety of "real worlds".

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