# Expanding the Use of Reperfusion Therapy. From GISSI to DANAMI

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*Myocardial reperfusion therapy has revolutionized the management of patients with acute myocardial infarction (AMI), reducing its mortality in as much as 50%. However, due to reasons that vary from region to region, several eligible patients do not receive such treatment. A new strategy, "primary angioplasty after transfer to an intervention center", proved to be promising and to have a great potential, because more patients will be able to benefit from the most efficient form of reperfusion therapy. A new chest pain protocol to be adopted at hospitals without a catheterization laboratory, but with a "program of transfer", has been suggested. In Brazil, some protocols have been established, but none in the public health system. Nevertheless, the Rio de Janeiro branch of the Brazilian Society of Cardiology (SBC/RJ) has developed a model based on new concepts, which, if implemented in major urban centers, can reduce the high mortality rates due to AMI in our country.*

## Introduction

The last 2 decades of the twentieth century witnessed true revolutions in the history of the treatment of acute myocardial infarction (AMI) with elevation in the ST segment. The "first revolution in cardiology" was the appearance of the thrombolytic therapy in 1986, which finally provided the physicians with the opportunity of treating the disease and not only its complications, as shown in the GISSI study [1]. The "second revolution in cardiology" was the introduction of primary angioplasty in the beginning of the 1990s, which, perfected by the stents[2], established itself definitely as the most efficient method of reperfusion[3-7]. Its use, however, is limited to a few hospitals with catheterization laboratories. Finally, in the beginning of the 2000s, the "third revolution in cardiology" occurred with the demonstration that, for certain patients with AMI, primary angioplasty is better than thrombolysis, even if it requires the transfer of patients from the emergency room of a community hospital to another hospital with catheterization laboratory, despite the time spent with transportation[8-11]. Such an important observation has allowed the dissemination of new strategies of health care, which, if used with organization and competence, may considerably widen the chances that patients with AMI receive the best treatment.

## Studies on patient's transfer initiated the "third revolution in cardiology" regarding the approach to AMI

Until recently, the transfer of patients with AMI to a tertiary hospital was contraindicated due to the risks inherent to transfer and the undesirable increase in "delta T". Therefore, the transfer of patients with AMI was limited to "rescue" angioplasties in extremely severe situations. That history began to change with the "Danish Multicenter Randomized Trial on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction" (DANAMI-2)[8]. In that study, 1,572 patients with AMI treated in 24 hospitals in Denmark were randomized to receive either the "accelerated" form of the plasminogen tissue activator or primary angioplasty, even when requiring transfer to one of the 5 centers of angioplasty, as long as that transfer did not take more than 3 hours. The distance traveled by the ambulances ranged from 3 to 150 km (mean, 50 km), and the time required for the transfer ranged from 50 to 85 minutes (mean, 67 minutes). The patients tolerated well the transfer, and neither death nor serious adverse reactions occurred. The study was precociously interrupted, because, when angioplasty was used, a 40% reduction occurred in the incidence of the primary objective of recurring infarction, stroke, or death within 30 days (8.5% versus 14.2%; P=0.002). The study "Primary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis" (PRAGUE-1)[9], carried out in the Czech Republic, randomized 300 patients to compare 3 different types of approach to AMI as follows: group A patients received intravenous streptokinase; group B patients also received streptokinase, but were immediately transferred to another hospital to undergo angioplasty; and group C patients were transferred to another hospital to undergo angioplasty without receiving the thrombolytic agent. The incidence of the primary outcomes (reinfarction, stroke, or death) in the 3 groups were 23%, 15%, and 8%, respectively, (P<0.02), favoring the transfer without previous administration of the thrombolytic agent. On the other hand, PRAGUE-2[10] randomized 850 patients to undergo angioplasty after transfer or thrombolysis, and shed new light on the matter: in addition to confirming the safety of transfer, it showed that transfer was the best option for patients who were tardy in arriving at the hospital, but was not advantageous for those treated within the first 3 hours. That finding was confirmed by the

"Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction" (CAPTIM) study[11], which only showed advantages in transfer for primary angioplasty in regard to prehospital thrombolysis for patients treated after the first 2 hours. The American "Air Primary Angioplasty in Myocardial Infarction" (AIR-PAMI) study[12] was the first to randomize high-risk patients for thrombolysis or angioplasty after transfer, and, although it was precociously interrupted due to the difficulty in selecting patients (138 patients - 32% of the previewed sample), it showed a tendency towards a better evolution for patients of the "angioplasty after transfer" arm (8.4% versus 13.6%; P=0.33).

A recently published meta-analysis[13], including data of the 5 major studies on transfer, has confirmed the favorable results. Although subject to a series of criticisms, which will not be commented here, those studies showed that the transfer of patients with AMI to undergo primary angioplasty is possible, safe, and possibly more effective than thrombolysis for those with more than 3 hours of AMI manifestation, as long as the transfer time does not exceed 2 to 3 hours.

Since then, several articles signed by the most important "opinion makers" of the international cardiology community have been published in the most prestigious medical journals in the United States and Europe, leaving no room for doubts in regard to the impact caused by the results of such studies[14-20]. Eric Topol has even suggested a radical change in the North American health care system for patients with AMI, who would be referred to the closest "center of angioplasty" rather than to the closest emergency hospital, as already happens with patients with traumas, directly referred to a "trauma center"[18]. Several metropolitan areas of that country have adopted a system that integrates community hospitals to a "center of angioplasty" located in the region, which provides primary angioplasty 7 days per week, 24 hours per day, with the return of the patient to the original community hospital within the 24 hours following the procedure. The success of that integrated system may be due to the fact that all those involved are benefited as follows: the "center of angioplasty" or "intervention center" increases its volume of invasive procedures; the community hospital provides its patients with a more efficient treatment, without the need for a great investment; and patients with AMI have access to a better quality treatment, returning to the community hospital some hours after the procedure, continuing their recovery close to their home and family.

## Identifying which patients benefit from transfer for primary angioplasty

The decision to use the thrombolytic agent or to transfer the patient with AMI for primary angioplasty should be based on solid evidence and answer the following question: for which patients will the benefits deriving from the transfer for intervention exceed the disadvantages resulting from the delay in reperfusion? The recently published North American guidelines for the treatment of AMI with an ST elevation[21] help in defining that important question based on the best data currently available in the literature about the issue. The following points should be analyzed before deciding.

**1) Time of hospital admission**: Some studies have shown that patients receiving thrombolytic agents within the first 3 hours of symptom onset had a similar[10] or even better[11] clinical evolution than those treated with primary angioplasty after transfer, as long as they had access to rescue angioplasty, when indicated. The same studies have also shown a significant benefit in transferring those patients who arrived at the emergency service after 3 hours of symptom onset and should be immediately transferred for primary angioplasty, as long as it could be performed within the 12 conventional hours; **2) time of transfer**: similarly to that which happens with the thrombolytic therapy, "time is muscle" also for angioplasty[22]. In the model proposed, it is fundamental that the "center of angioplasty" should be strategically located in regard to the "integrated hospitals" to allow a "door-to-balloon" time up to 60 minutes greater than the time necessary for the beginning of the thrombolytic agent, as recommended[23]. However, unexpected operational situations may occur, causing an extension in that time, independently of the geographical proximity, such as an already occupied catheterization laboratory. Therefore, whenever the time of transfer is very long (maximum of 3 hours), the thrombolytic agent should be preferred; **3) evaluation of the risk of death**: patients with a great hemodynamic instability (cardiogenic shock, acute pulmonary edema) have little chance of surviving if they have no access to primary angioplasty[24-26]; therefore, they should be immediately transferred despite the risks of the transfer. Such risks may be reduced if the transfer is performed in a properly equipped ambulance with a medical team trained for transporting critically ill patients. The Air-Pami study[12] has shown that such patients may be transported with an acceptable margin of safety; **4) failure of the thrombolytic agent**: the thrombolytic agents currently available, specially the most used in Brazil, streptokinase, have a high rate of failure to promote effective reperfusion with TIMI 3 flow[27]. Patients benefit from the transfer for rescue angioplasty[28-29]; **5) electrocardiogram of dubious interpretation**: many patients with AMI do not show the characteristic pattern in the first hours of coronary occlusion. Therefore, patients with typical clinical findings, specially those at higher risk (diabetes, hemodynamic instability, age greater than 75 years, elevated troponin, presence of ventricular arrhythmias) should be transferred to undergo coronary angiography and angioplasty, if indicated, even when ECG is not diagnostic; **6) contraindications to thrombolysis**: the contraindications to the use of thrombolytic agents are numerous[21]. Obviously, such patients need immediate transfer to a "center of angioplasty".

## A new chest pain protocol based on current concepts

Protocols of chest pain have had great acceptance since the studies by Bhar[30], because they make the treatment of patients with chest pain quicker and more efficient, and reduce the probability of diagnostic errors. Classically, hospitals with catheterization laboratory use protocols that recommend primary angioplasty for all patients with AMI with an ST elevation or new LBBB treated within the first 12 hours of evolution. On the other hand, hospitals without a catheterization laboratory use protocols that recommend thrombolysis for all patients without any contraindication. Based on the evidence related to the possibility of transfer, a third model of protocol should be adopted by the hospitals without a catheterization laboratory that can act integrated with a "center of angioplasty". Figure 1 shows a protocol inspired by the suggestions of William O'Neil[31] and the Canadian Cardiovascular Society[32],

both based on the recently published recommendations of the North American guidelines[21]. It is worth noting that that protocol has not proposed the replacement of the thrombolytic therapy by primary angioplasty after transfer, as has been the concern of the conservatives, but makes that option of treatment possible in the cases with precise indication.

## The Brazilian experience. The SIAAC project

Although timidly, the "third revolution of cardiology" has already arrived in Brazil. In São Bernardo do Campo, a "Center for AMI" (Neo Mater Hospital) provides primary angioplasty to several hospitals of the "ABC paulista" region[33]. In the state of Rio de Janeiro, a tertiary hospital of the city of Volta Redonda (Hospital Vita) acts as an "intervention center", providing emergency angioplasty to hospitals of the "Médio Paraíba" region, benefiting a population of almost one million inhabitants. Figure 2 shows the small distances to be traveled by the ambulances after the previous contact between the team of the emergency sector of the "integrated hospital" and that of the catheterization sector of the "intervention center". Information on the results of these pioneering experiences still lacks.

However, the public health system, whose need for improving the quality of the treatment for AMI is greater, has no program of patient's transfer. The "Buscando Soluções para A Subutilização de Terapia Trombolítica no Rio de Janeiro" (BÚSSOLA) study[34]

showed that it is unlikely that a patient with AMI receives any type of reperfusion therapy in most of the emergency services in the city of Rio de Janeiro. Aiming at minimizing this serious situation, the Rio de Janeiro branch of the Brazilian Society of Cardiology (SBC/RJ) has elaborated the SIAAC (Sistema Integrado de Atendimento ao Ataque Cardíaco – Integrated System for Heart Attack Care) Project to involve all public hospitals and emergency services of the capital. In addition to a program of patient's transfer to a "public intervention center", the SIAAC includes several other fundamental measures for supporting the project (chart I). The model suggested by SIAAC, much more comprehensive than a simple "program of transfer", should be adopted by all public and private institutions that want to be part of an "integrated system", because it guarantees high-quality results. Chart II shows the role played by each component of the "system".

## Conclusion

The results of the "studies on transfer" continue to cause reactions worldwide, ranging from a radical disbelief to a dangerous euphoria. It is worth stressing that the success of that strategy depends, to a great extent, on the adoption of strict quality criteria in all points of the process. The superiority of the interventional approach over the conservative one, especially of primary angioplasty over thrombolysis, is known to be only unquestionable when
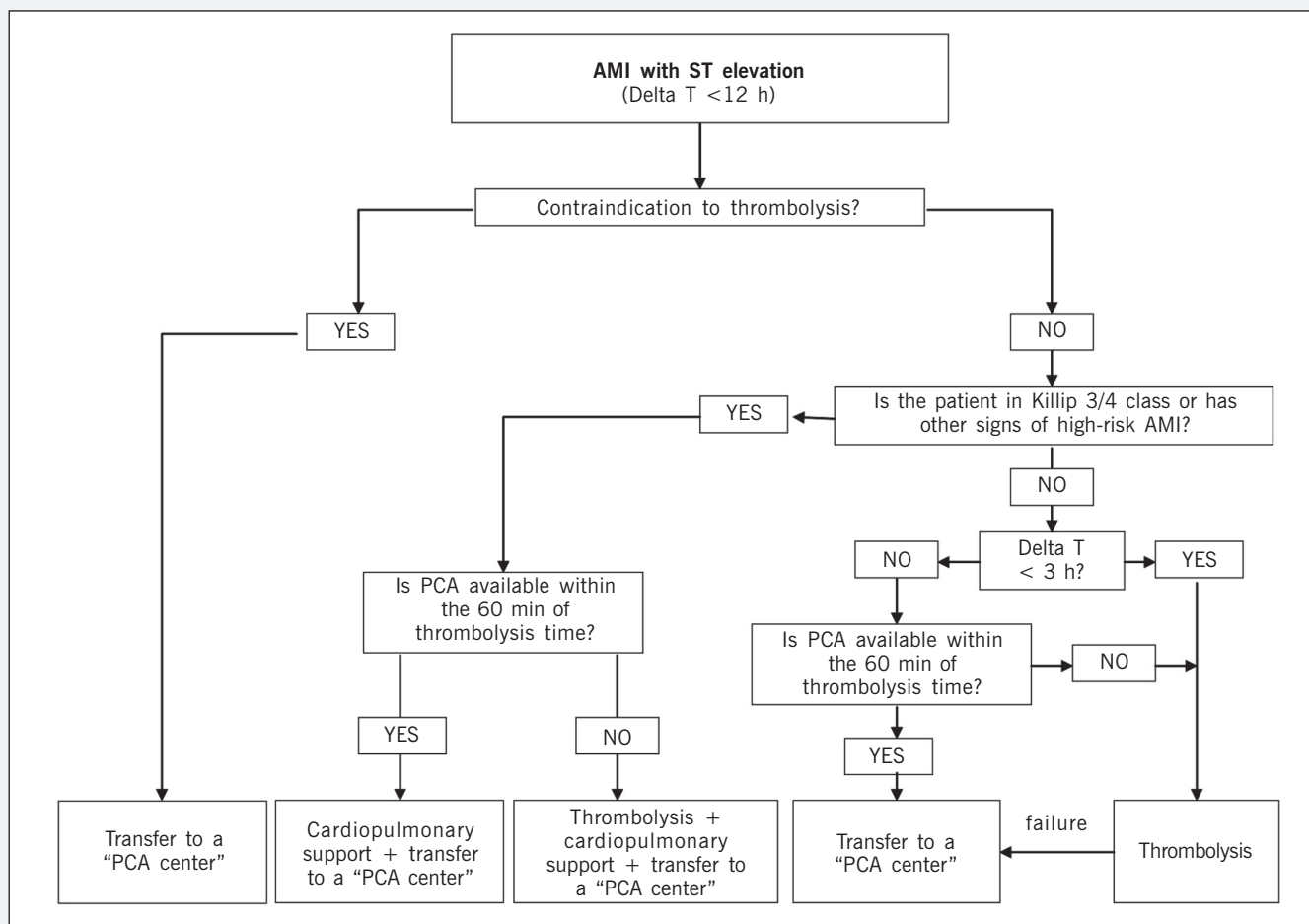


Fig. 1 - Algorithm of the protocol of treatment of AMI with an ST elevation or new LBBB for hospitals without a catheterization laboratory, but participating in a "transfer program" to a center of Percutaneous Coronary Angioplasty (PCA). Adapted from the Canadian Cardiovascular Society (Can J Cardiol 2004; 20: 1075-9).
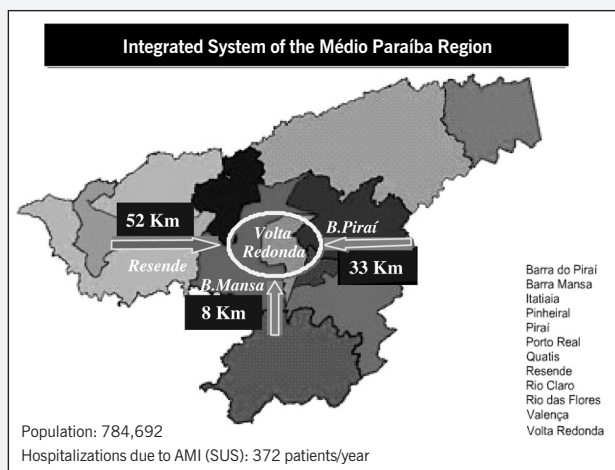
**Integrated System of the Médio Paraíba Region**

52 Km
Resende
*Volta Redonda*
*B.Piraí*
33 Km
*B.Mansa*
8 Km

Barra do Piraí
Barra Mansa
Itatiaia
Pinheiral
Pirai
Porto Real
Quatis
Resende
Rio Claro
Rio das Flores
Valença
Volta Redonda

Population: 784,692
Hospitalizations due to AMI (SUS): 372 patients/year

Fig. 2 – Overview of the "integrated system of the Médio Paraíba region", in the inner region of the State of Rio de Janeiro. Note the short distance between the "integrated hospitals" of the major cities of the region and the "intervention center", an important characteristic for the logistics of the program. The population and the volume of patients benefiting from the project justify its implementation.

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**SIAAC Project - SBC/RJ**
(topics)

- Full-time "public intervention center";
- Public call center for full-time specialized cardiology support;
- Standardized chest pain protocol to be followed by all the elements involved;
- Standardized routines of emergency adjuvant treatment of AMI and other ACS to be followed by all elements involved;
- Program of Training and Continuous Education for all professionals involved in the System;
- Centralized database for processing and analysis of basic information and quality management of the System.

Chart I. The SIAAC Project of the SBC/RJ and its topics.

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**SIAAC Project of the SBC/RJ**
Responsibilities

**"Integrated hospitals"**
- To strictly follow the **"Standardized Chest Pain Protocol"**
- To decide the indication for **emergency coronary angiography**
- To contact and/or consult with the **"intervention center" (teleconsultation)**
- To initiate the treatment following the **"standardized routines of the system"**
- To arrange the transfer of patients to the **"intervention center"**

**"Intervention center"**
- To provide specialized consultancy 24 hours per day
- To provide emergency coronary angiography 24 hours per day
- To perform **"percutaneous coronary intervention"**, when indicated, 24 hours per day
- To maintain the patient in an intensive care unit environment (if possible, coronary unit) until clinical stabilization
- To send the patients back to their original hospital as soon as it is possible and safe

**"Coordinating Committee"**
- To organize the **"Program of Training and Continuous Education"** for all professionals involved
- To maintain a continuous update of the **"Standardized Chest Pain Protocol"**
- To maintain the adequate system of **"Data Collection and Processing"**
- To maintain a strict **"Quality Control System"** (use of "indicators")
- To carry out a permanent **Audit**
- To stimulate high-quality scientific production and to create a single

Chart II. The role played by each component of the system. It is worth noting that the Coordinating Committee should be constituted by representatives of all institutions involved.

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well indicated and performed by experienced professionals, with a significant volume of procedures, and in an adequately equipped environment[35]. The "centers of intervention" should be adequate to the quality criteria defined by the international guidelines and those of the Brazilian Society of Hemodynamics and Interventional Cardiology (Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista - SBHCI)[36] or they will not be part of the "integrated system". Similarly, the emergency services and coronary units, or ICUs, of the hospitals participating should be qualified to receive critically ill coronary patients, to strictly follow the protocols and standard routines based on international and SBC guidelines, and to have adequate equipment and modern laboratory routines, such as the troponin "kit". The correct selection of patients who will benefit from the transfer should be based on a protocol, such as that suggested in figure 1. A recent report of the results of the GRACE registry[37] with more than 28,000 patients with ACS has shown that the advantages of the intervention, so clearly evidenced

in the clinical studies, are lost in the so-called "real world", maybe because strict quality criteria, such as those in the studies, are not adopted. Therefore, the strategy of creating a "coordinating committee of the system" (chart II), comprised by representatives of all hospitals involved, is fundamental for the success of the program. That committee meets periodically with the following objectives: to update the routines, and training and continuous education programs; to evaluate the statistics of the system; to discuss the relevant clinical cases; to evaluate occasional failures and difficulties; and, last but not least, to socialize.

It is worth noting that, no idea, as brilliant as it may be, will be important if it only benefits the richest segment of the population. "Integrated systems for heart attack care" similar to that of SIAAC have a social impact, are economically viable, and are politically attractive. In addition, considering the scientific evidence, it is unacceptable, even from the ethic point of view, that a city like Rio de Janeiro, with more than 5 million inhabitants and the highest mortality rate due to AMI in the country, does not have a single public institution that provides, decently and routinely, the possibility to perform emergency invasive procedures. The situation is aggravated by the fact that, frequently, those procedures are the only means by which a patient's life can be saved, or by which others can be spared from falling victim to the disability resulting from heart failure.

# References

1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986; 1: 397-401.

2. Zhu MM, Feit A, Chadow H et al. Primary stent implantation compared with primary balloon angioplasty for acute myocardial infarction: a meta-analysis of randomized clinical trials. Am J Cardiol 2001; 88: 297–301.

3. Grines CL, Browne KF, Marco J et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction: the Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1993; 328: 673-9.

4. Zijlstra F, de Boer MJ, Hoorntje JC et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993; 328: 680-4.

5. Gibbons RJ, Holmes DR, Reeder GS et al. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction: the Mayo Coronary Care Unit and Catheterization Laboratory Groups. N Engl J Med 1993; 328: 661-85.

6. Weaver WD, Simes RJ, Betriu A et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997; 278: 2093-8.

7. 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.

8. Andersen HR, Nielsen TT, Rasmussen K et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med 2003; 349: 733-72.

9. Widimsky P, Groch L, Zelizko M et al. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory: the PRAGUE study. Eur Heart J 2000; 21: 823-31.

10. Widimsky P, Budesinsky T, Vorac D et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction: final results of the randomized national multicentre trial: PRAGUE-2. Eur Heart J 2003; 24: 94-104.

11. Steg PG, Bonnefoy E, Chabaud S et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. Circulation 2003; 108: 2851-6.

12. Grines CL, Westerhausen DR, Grines LL et al. A randomized trial of transfer for primary angioplasty versus on-site thrombolysis in patients with high-risk myocardial infarction. J Am Coll Cardiol 2002; 39: 1713-19.

13. Dalby M, Bouzamondo A, Lechat P et al. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. Circulation 2003; 108: 1809-14.

14. Topol E J. Current status and future prospects for acute myocardial infarction therapy. Circulation 2003; 108(16 Suppl 1): III 6-13.

15. Jacobs AK. Primary angioplasty for acute myocardial infarction—is it worth the wait? N Engl J Med 2003 Aug 21; 349:798-800.

16. Grines CL, Serruys P, O'Neill WW. Fibrinolytic therapy: is it a treatment of the past? Circulation 2003; 107: 2538-42.

17. Califf RM, Faxon DP. Need for centers to care for patients with acute coronary syndromes. Circulation 2003; 107: 1467-70.

18. Topol EJ, Kereiakes DJ. Regionalization of care for acute ischemic heart disease: a call for specialized centers. Circulation 2003; 107: 1463-6.

19. Weaver WD. All Hospitals are not equals for treatment of patients with acute myocardial infarction. Circulation 2003; 108: 1768-71.

20. Cannon CP. Primary percutaneous coronary intervention for all? JAMA 2002; 287: 1987-9.

21. Antman EM, Anbe DT, Armstrong PW et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2004; 44: 671-719.

22. de Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction. Circulation 2004; 109: 1223-5.

23. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? Am J Cardiol 2003; 92: 824-6.

24. Hochman JS, Sleeper LA, Webb JG et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. N Engl J Med 1999; 341: 625-34.

25. Wu AH, Parsons L, Every NR, Bates ER. Second National Registry of Myocardial Infarction. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). J Am Coll Cardiol 2002; 40: 1389-94.

26. Stone GW, Grines CL, Browne KF et al. Influence of acute myocardial infarction location on in-hospital and late outcome after primary percutaneous transluminal coronary angioplasty versus tissue plasminogen activator therapy. Am J Cardiol 1996; 78: 19-25.

27. The GUSTO angiographics investigators. The effect of tissue plasminogen activator, streptokinase or both in coronary-artery patency, ventricular function and survival after acute myocardial infarction. N Eng J Med 1993; 329: 1615: 22.

28. Schweiger MJ, Cannon CP, Murphy AS et al. Early coronary intervention following pharmacologic therapy for acute myocardial infarction (the combined TIMI 10B-TIMI 14 experience). Am J Cardiol 2001; 88: 831-6.

29. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E. TIMI Study Group. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation 2002; 105: 1909-13.

30. Bahr RD. Chest pain centers: moving toward proactive acute coronary care. Int J Cardiol 2000; 72: 101-10.

31. Simpósio Satelite via Internet com acesso em 7 de outubro de 2004 http://www.theheart.org/viewArticle.do?primaryKey=119817

32. Bogaty P, Buller CE, Dorian P, O'Neill BJ, Armstrong PW. Canadian Cardiovascular Society Working Group. Applying the new STEMI guidelines: 1. Reperfusion in acute ST-segment elevation myocardial infarction. CMAJ 2004; 171: 1039-41.

33. Carvalho LCM, Silva LA, Carneiro R et al. Tratamento do infarto agudo do miocárdio (IAM) no grande ABC. Arq Bras Cardiol 2004; 83(Supl. III): 99.

34. Brasileiro AL. The Bussola study. Final results, conclusions and proposals. Arq Bras Cardiol 2000; 75: 225-34.

35. Magid DJ, Calonge BN, Rumsfeld JS et al. Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. JAMA 2000; 284: 3131-8.

36. Diretriz para a Realização de Exames Diagnósticos e Terapêuticos em Hemodinâmica. Arq Bras Cardiol 2004; 82(Supl. I).

37. BMJ, dói:10.1136/bmj.38335.390718.82 (published 21 January 2005).