

## Importance of Time Delay in Selecting Reperfusion Therapy

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In its day, in the 1980s, fibrinolysis represented an important qualitative change in the treatment of acute infarction offering an active therapeutic alternative to the traditional “wait and see” approach.<sup>1,2</sup> Later, in the 1990s, the benefits of pharmacologic reperfusion were surpassed by primary angioplasty.<sup>3</sup> Several randomized studies showed mechanical reperfusion, while reducing the risk of hemorrhage, permits the most efficient, sustained restoration of permeability to the occluded artery and improves the prognosis. In a 22-study meta-analysis, the superiority of primary angioplasty over fibrinolysis was translated into reductions in 30-day mortality (from 7% to 5%;  $P=.0002$ ), reinfarction (from 7% to 3%;  $P=.0003$ ), and hemorrhagic stroke (from 1% to 0.5%;  $P=.0001$ ).<sup>4</sup>

Based on this evidence, clinical practice guidelines for myocardial infarction with ST-segment elevation consider primary angioplasty the treatment of choice if it can be performed within 12 hours of evolution of the symptoms, by an experienced team, and within 90 min of initial contact with a physician.<sup>5,6</sup> The enthusiasm for primary angioplasty led to analysis of its potential in patients admitted to provincial hospitals that lack the equipment to undertake catheterization on site. The DANAMI-2 study<sup>7</sup> showed systematic transfer of patients to tertiary centers was more beneficial than administering fibrinolytic drugs in the admitting hospital, reporting combined incidence of death, reinfarction and ictus fell from 14.2% to 8.5%, ( $P<.002$ ) at 30 days. Despite logistic difficulties, mean ambulance transport time was only 32 min and the time from arrival at the first hospital to angioplasty was <2 hours.

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In the present issue of *Revista Española de Cardiología*, Carrillo et al<sup>8</sup> focus precisely on the issue of transport to primary angioplasty. They analyze the clinical course of a series of patients with acute myocardial infarction who are all candidates for reperfusion. They enrolled 222 patients: 158 attended a tertiary center with a catheterization laboratory and the remaining 64 attended a provincial hospital without one, and therefore needing to be transferred for primary angioplasty. Transfers were rapid and the difference between arrival at the first hospital and angiography was only 13 min (15 min to open artery). In these circumstances, it should surprise no one that the clinical course of the 2 groups was apparently similar: at 1-year follow-up, mortality was 16.5% and 12.5%, respectively ( $P=.459$ ; tertiary center vs provincial hospital) and reinfarction 4.4% and 1.6%, respectively ( $P=.444$ ). This is a non-randomized comparison and baseline characteristics of the populations have little in common, which explains the substantial difference of almost 7 decimal points (20.9% vs 14%) –worryingly, although by chance, in favor of the provincial hospital—for combined death and reinfarction. In any case, the inadequate sample size makes statistical generalization futile. Methodological considerations aside, the authors—to whom we owe important contributions in the field of primary angioplasty<sup>9</sup>—deserve credit for proving that in the local context it is also possible to make efficient patient transfers and achieve a door-to-balloon time (artery open) which, in comparison with the registers,<sup>10-12</sup> is very short. In this context, we should recall that delay in reperfusion times has rekindled the fibrinolysis versus angioplasty debate. Let us consider why.

The time factor has been of transcendental importance in the history of coronary reperfusion. The pioneering GISSI 1 study<sup>1</sup> recognized this when it showed a reduction in mortality close to 50% in patients receiving streptokinase within 1 hour following the onset of symptoms. The slogan “time is muscle” was quickly coined to give urgency to the initiation of treatment in the emergency room. Boersma et al<sup>13</sup> quantified the benefit of fibrinolytic treatment versus a placebo as a function of time, and showed the number of lives saved

per 1000 patients treated was greatest (n=65) in the first hour after infarction, falling gradually in successive hours (n=37 in the second hour and n=26 in the third). Although less than fibrinolysis, primary angioplasty is not impermeable as time passes and the reduction in mortality is also greater in the patients treated earliest.<sup>14</sup> So, we should ask ourselves how long (in minutes or hours) angioplasty can be delayed while maintaining its superiority over fibrinolysis. Recently, the clinical impact of time inherent to angioplasty (resulting from subtracting door-to-needle time from door-to-balloon time) has aroused growing interest. According to Nallamothu and Bates,<sup>15</sup> when the delay reaches 60 min, the superiority of angioplasty over fibrinolysis is nil. Later, Nallamothu et al<sup>16</sup> established a 60-minute limit would only apply to fibrin-specific agents. On analyzing data from 21 random studies, weighted to allow for the size of each individual population, we located the point of equivalence (time of equal efficacy in terms of mortality) at 110 min.<sup>17</sup> Data derived from registers are even more contradictory, putting it at 2-4 hours approximately.<sup>18,19</sup> Pinto et al's study,<sup>19</sup> based on data from 192 509 patients in the NRMI 2, 3, and 4 registers, constitutes the definitive reference. It reports a mean time of equivalence of 114 min, very close to our own, although the wide-ranging population also facilitated the study of patient behavior as a function of age, infarction location, and time of evolution of symptoms. Thus, time of equivalence of both treatments was shown not to be unique and a 40-180 min range, according to the variables analyzed, was found. On the one hand, we find the <65 year-old patient with previous infarction, attending hospital within 2 hours after onset of symptoms, for whom an intrinsic delay of >40 min would be dangerous. On the other, we have the 70 year-old patient, with inferior infarction and >2 hours from onset of symptoms who would still benefit from angioplasty despite the 180-minute delay.

It remains, then, for us to stress the importance, also in the field of reperfusion, of individualized treatment over the "single recipe." This message should preside over both regional planning for treatment of infarction and decision-making for the individual patient. If we are to be consistent, the praiseworthy objective of giving priority to mechanical reperfusion should not exclude a surely substantial number of patients from the benefits of fibrinolysis.

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