Primary percutaneous coronary intervention (PCI) is a better reperfusion therapy for ST-segment elevation acute myocardial infarction than in-hospital fibrinolytic therapy when it is performed soon after the onset of symptoms by an experienced team. Both the American and the European guidelines for the management of ST-segment elevation acute myocardial infarction recommend that the procedure should be done within 90 minutes of presentation.\(^1\,^2\) Although delays in the delivery of both fibrinolytic therapy and primary PCI are associated with increased mortality rates, an extra (unavoidable) delay of up to 60 minutes is considered to be acceptable for primary PCI because this reperfusion treatment is associated with higher potency rates of the infarct vessel and better survival when compared with fibrinolytic therapy. This “PCI-related delay” is usually presented as the “door-to-balloon” time minus the “door-to-needle” time. The guidelines recommend a “door-to-needle” time of 30 minutes and, as mentioned above, the recommended “door-to-balloon” time is 90 minutes, resulting in an acceptable “PCI-related delay” of 60 minutes. A recent reanalysis by the Primary Coronary Angioplasty versus Thrombolysis (PCAT)-2 Investigators of the delay times in 22 randomized studies that have compared primary PCI with in-hospital fibrinolysis suggests that a survival benefit of primary PCI could still be present with PCI-related delays of up to 2 hours.\(^3\)

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From the aforementioned studies, one could conclude that the selection of a reperfusion strategy is predominantly determined by time delays, namely the presentation delay (should be less than 12 hours) and the PCI-related delay (should be less than 1 or perhaps 2 hours). In this issue of *Circulation*, new data from the large National Registries of Myocardial Infarction (NRMI) 2, 3, and 4 are reported.\(^1\) They indicate that when selecting a reperfusion treatment, not only the time delays but also the baseline characteristics of the patients presenting with an ST-segment elevation acute myocardial infarction should be taken into account. In the study, Pinto et al analyzed data from 192,509 patients, treated between June 1994 and August 2003 at 645 hospitals in the United States. For each hospital, the median PCI-related delay was calculated by subtracting the median “door-to-needle” time from the median “door-to-balloon” time at each hospital. Hospitals had to treat at least 10 patients with fibrinolitics and at least 10 patients with primary PCI. For patients transferred from another hospital, the reference time was the arrival time at the first hospital. Hospitals were divided into 4 categories of increasing PCI-related delays: \(<60, 60 to 89, 90 to 120, and \(>120 \) minutes. For each of the 4 categories, hospital and patient characteristics were analyzed. Statistical models were used to assess the overall relationship between PCI-related delays, selected reperfusion treatment, and in-hospital mortality, with adjustments for patient and hospital characteristics. The effect of the PCI-related delay in specific subgroups of patients stratified by the well-known risk factors age (\(<65\) years versus \(>65\) years), infarct location (anterior versus non anterior), and time from symptom onset to hospital arrival (\(\leq2\) hours versus \(>2\) hours) was also examined. Of the study population, 36% were transferred patients, 60% were younger than 65 years, 65% presented to the (first) hospital within 2 hours after symptom onset, 36% had an anterior infarction, and 34% were treated with primary PCI versus 66% with fibrinolitics.

A first remarkable finding is that there was a gradual increase in the proportion of transferred patients with increasing “door-to-balloon” times (and therefore increasing PCI-related delays), although in randomized studies “door-to-balloon” times were much shorter for transferred patients because the catherization laboratory in the interventional hospital was alerted in advance.\(^5\,^6\) Hospitals with long “door-to-balloon” times also performed fewer primary PCIs, although the prehospital delay and the baseline risk of their patients were similar to those coming to hospitals with a short “door-to-balloon” time. These results strongly suggest that outside the context of a clinical trial, early communication with the catherization laboratory does not always take place or at least does not always result in a (fast) intervention.

In the total study population, there was a 10% increase in the relative risk of in-hospital death with every 30-minute increase in the PCI-related delay. The survival benefit of primary PCI over fibrinolytic therapy was lost when the PCI-related delay was 114 minutes (= in-hospital mortality equipoise), a time delay very similar to the 30-day mortality equipoise of 110 minutes calculated from the randomized trials\(^7\) and in agreement with the findings of the PCAT-2 Investigators.\(^3\) Most important, the PCI-related delay beyond which the survival benefit of primary PCI was lost varied considerably, depending on the patients’ characteristics. The shortest mortality equipoise (less than 1 hour) was found in patients \(<65\) years of age presenting with an anterior infarction within 2 hours after symptom onset and the longest (almost 3 hours) in patients \(>65\) years of age with a nonanterior infarction presenting more than 2 hours after symptom onset. The explanation of these findings is relatively simple: The larger the amount of ischemic but viable myocardial tissue, the easier to dissolve the occlusive thrombus and the lower the risk for bleeding complications (intracranial hemorrhage and other), the more likely fibrinolytic therapy is
going to be beneficial, and the more unlikely a delayed primary PCI will be superior to fibrinolytic therapy. Because of the relatively small number of patients and the much shorter delay times, a possible impact of patients’ characteristics on the mortality equipoise could not be demonstrated in the randomized trials.3,7

There are several limitations to this large registry-type study, as outlined by the investigators, and caution is certainly needed when interpreting these data. It is well known that the exact time of symptom onset is very often unclear, and treatment times reported for patients who need emergency care may lack precision. Thus, not the exact time intervals reported in Figure 4 of the report but the overall picture of a variable impact of the PCI-related delay on survival, depending on baseline risk and time of presentation, is the key message of the study. Furthermore, as discussed by the authors and indicated above, PCI-related delay times also reflect the quality of care at a particular hospital and the efficiency of the health care organization in a particular region. Therefore, the poor outcomes associated with a long PCI-related delay are not because of the long delay time alone but also because of the overall quality of care offered to the patients. Notwithstanding these obvious limitations, the study results do reflect daily clinical practice in a large number of hospitals and should help clinicians working in community hospitals or ambulance systems in managing patients for whom the selection of a reperfusion treatment is difficult. Let us illustrate this by comparing 2 patients with an ST-segment elevation acute myocardial infarction presenting to a community hospital. The first patient is a man of 55 years with a negative medical history presenting with ST-segment elevations of >3 mm in the precordial leads within 90 minutes after onset of symptoms. Many clinicians transfer this patient to a tertiary care hospital for primary PCI. According to the findings of the study by Pinto et al, such a reperfusion strategy can only be superior to fibrinolytic therapy given immediately on arrival in the community hospital if the primary PCI after transfer to the tertiary care hospital can be performed within less than 1 hour after arrival in the community hospital. In daily clinical practice, such a short PCI-related delay is achievable in only a minority of cases. The second patient is an elderly woman of 75 years with a history of hypertension, presenting more than 5 hours after the onset of an inferior infarction with ST-segment elevations of 1 mm in the inferior leads. The risk/benefit ratio of immediate fibrinolysis in this patient is unfavorable when compared with primary PCI, even if the latter is performed with a delay of a couple of hours. The benefit of primary PCI in this patient is probably also small.

The findings of the Pinto et al study must also be taken into account when designing new reperfusion studies. So far, trials that have compared primary PCI with facilitated PCI with full-dose fibrinolytics, glycoprotein IIb/IIIa inhibitors, or combination therapy of half-dose fibrinolytic plus a glycoprotein IIb/IIIa inhibitor have failed to show a clinical benefit although infract artery patency rates before the PCI were significantly higher in the facilitated PCI arm.8,9 Among the many possible explanations for these negative results, the inclusion of patients who could hardly get any of the benefit of a pre-PCI pharmacologic reperfusion treatment but only suffer from its bleeding complications is certainly an important one. New trials of prehospital (ambulance) administration of fibrinolytic therapy are currently being considered. The findings of this large NRMI analysis by Pinto and colleagues certainly need to be taken into account when designing the protocol.

Disclosures

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References


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