Emerging primary percutaneous coronary intervention as the dominant reperfusion strategy for myocardial infarction in Europe

Avrupa'da primer perkütan koroner girişimin miyokard infarktüsünde ana reperfüzyon stratejisi olarak gelişimi

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Randomized trials have confirmed the superiority of primary percutaneous coronary intervention (p-PCI) over thrombolysis as the reperfusion therapy for ST-elevation myocardial infarction. The Czech Republic, where two of these trials were performed, developed a network of PCI centers and satellite hospitals throughout the country, enabling 93% of the reperfusion therapy to be p-PCI in 2003, with thrombolysis accounting for only 7%. In other European countries, however, the p-PCI-to-thrombolysis ratio largely varies between 80:20 and 1:99. In this article, the infrastructure and logistics of the achievement in the Czech Republic are described.

Key words: Angioplasty, transluminal, percutaneous coronary; Europe; Czech Republic; myocardial infarction/drug therapy; myocardial revascularization; patient transfer; thrombolytic therapy.

Randomize çalışmalar, ST-yükselmeli miyokard infarktüsünü için reperfüzyon tedavisinde primer perkütan koroner girişimin (p-PKG) trombolize karşı üstünlüğünü göstermiş bulunuyor. Bu çalışmalardan ikisinin yapıldığı Çek Cumhuriyeti'nde, ülke çapındaki PKG merkezleri ve bunlara bağlı uydu hastanelerden oluşan bir ağ sayesinde, 2003 yılındaki reperfüzyon tedavilerinin %93'ü p-PKG ile yapılmış, tromboliz oranı %7'ye kadar gerilemiştir. Diğer Avrupa ülkelerinde bunun oranı büyük ölçüde değişkenlik göstermektedir (80:20 ile 1:99). Bu makalede, Çek Cumhuriyeti'ndeki başarıyı hazırlayan altyapı ve lojistik hakkında bilgi verildi.

Anahtar sözcükler: Anjiyoplasti, transluminal, perkütan koroner; Avrupa; Çek Cumhuriyeti; miyokard infarktüsü/ilaç tedavisi; miyokard revaskülarizasyonu; hasta transferi; trombolitik tedavi.

Percutaneous transluminal coronary angioplasty (PTCA) was introduced by Andreas Gruntzig[1] in Zurich in 1977. Few years later this method was used for the first time to treat acute myocardial infarction.[2] It took additional 10 years to demonstrate in randomized trials the superiority of angioplasty over thrombolysis in the setting of acute ST-elevation myocardial infarction.[3-5] It is hard to understand why it took another 10 years before primary percutaneous coronary intervention (p-PCI, term used in the current stent era) started to become a widely used reperfusion modality. The aim of this review is to summarize the evolution of catheter-based reperfusion therapy, analyze the current situation with p-PCI in Europe, and discuss its future venues. More details will be given about the situation in the Czech Republic in which the use of p-PCI has reached the highest frequency throughout the world.

Primary PCI *versus* thrombolysis in PCI centers

The first trials published in 1993[3-5] compared immediate p-PCI with immediate thrombolysis in patients admitted to PCI centers. A meta-analysis of 10 randomized trials was published in 1997.[6] In these trials, both treatments were started with similar delays. Percutaneous coronary intervention significantly decreased 30-day mortality, reinfarction, and stroke rates compared to thrombolysis. A more recent meta-analysis[7] that enrolled 18 trials of this type (plus 5 other trials with interhospital transport) confirmed these findings (Fig. 1). The data from this meta-analysis can be translated into events that were prevented by

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the use of p-PCI instead of thrombolysis: per each 1,000 patients treated by p-PCI 20 lives were saved, 10 strokes and 40 reinfarctions were prevented.

Interhospital transport for p-PCI *versus* thrombolysis in the nearest hospital

Between 1997 and 2002, five randomized trials investigated which reperfusion therapy was most effective.[8-12] Another trial compared direct transfer to p-PCI *versus* prehospital thrombolysis followed by transfer to a PCI center.[13] Of these, two trials ("LIMI" in the Netherlands and "PRAGUE-1" in the Czech Republic) had a similar design. Patients with ST-elevation myocardial infarction, who initially presented to a small community hospital without PCI facilities were randomized in the emergency room into one of the three groups: immediate thrombolysis and stay in the hospital, immediate thrombolysis with immediate transport to a PCI center with thrombolysis infusion running (facilitated PCI), or immediate transport for primary PCI (p-PCI). The findings favoring p-PCI are summarized in Fig. 2. This superiority of transportation strategy (p-PCI) over thrombolysis in the nearest hospital was confirmed by two larger trials ("DANAMI-2" in Denmark and "PRAGUE-2" in the Czech Republic) and one small trial ("Air-PAMI"). The latter three trials did not include facilitated PCI.

One of the most important findings of DANAMI-2 and PRAGUE-2 trials was that, contrary to the widely accepted notion, immediate transport for p-PCI was not associated with a significant delay in reperfusion. Indeed, the delay was minimal: given the assumption that thrombolysis opens the artery 60 minutes after the beginning of infusion, the delay in reperfusion in transported patients was only 32 minutes in the PRAGUE-2 study while there was no delay in the DANAMI-2 study (Fig. 3).

The CAPTIM trial also provided evidence that favored the strategy of collecting all ST-elevation

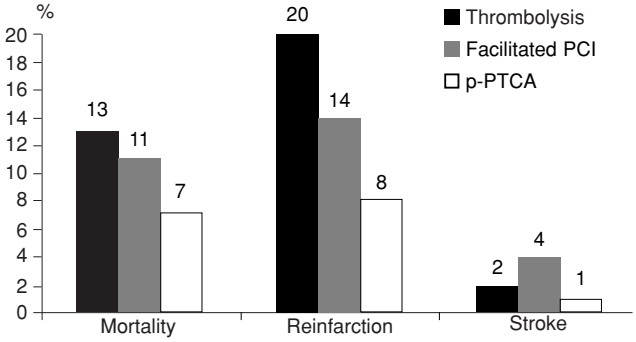

Fig. 2. Results of the LIMI and PRAGUE-1 trials.

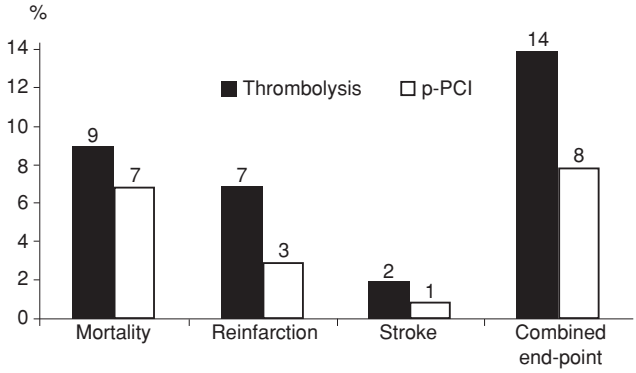

Fig. 1. A meta-analysis of 23 randomized trials comparing p-PCI and thrombolysis. Illustration of events within 30 days.[7]

patients at PCI centers. This is the only trial in which no patient was admitted to small community hospitals - all were transferred to PCI centers with or without prehospital thrombolysis.[13] That is why the results of this trial are somewhat different from the other five trials: prehospital thrombolysis followed by admission to a PCI center (with facilitated or rescue PCI in one-third of the patients) is a better option than thrombolysis in a small community hospital without a cardiac cath-lab.

The development of p-PCI services in the Czech Republic

In a country with a population of 10.5 million, six interventional cardiologists performed about 200 elective PTCA procedures per year in 1989 and 1990. After the political and economic change, the new health care system allowed to perform as many PCIs as the hospitals were physically capable. A corollary of this change was that, between 1991 and 2003, the number of hospitals with cath-labs increased from 5 to 21, and the number of all PCIs per million inhabitants increased from 30 to 1978, with an increase in the number of primary PCIs from 0 to 652 (Fig. 4). These tremendous changes were allowed by the improvements in the economy and health care system. However, this still could not be possible without the immense enthusiasm of Czech interventional cardiologists and nurses.

Almost all interventional cardiologists in this country are young (most below 40 years of age). A fact which contributes much to their enthusiasm: they do not object or show unwillingness to emergencies occurring at night or during weekends. The recent critical words of Dr. Menko-Jan DeBoer, the president of the Netherlands Society of Cardiology, *"Cardiologist and not logistics is the problem for p-PCI development"* do not apply to Czech interven-

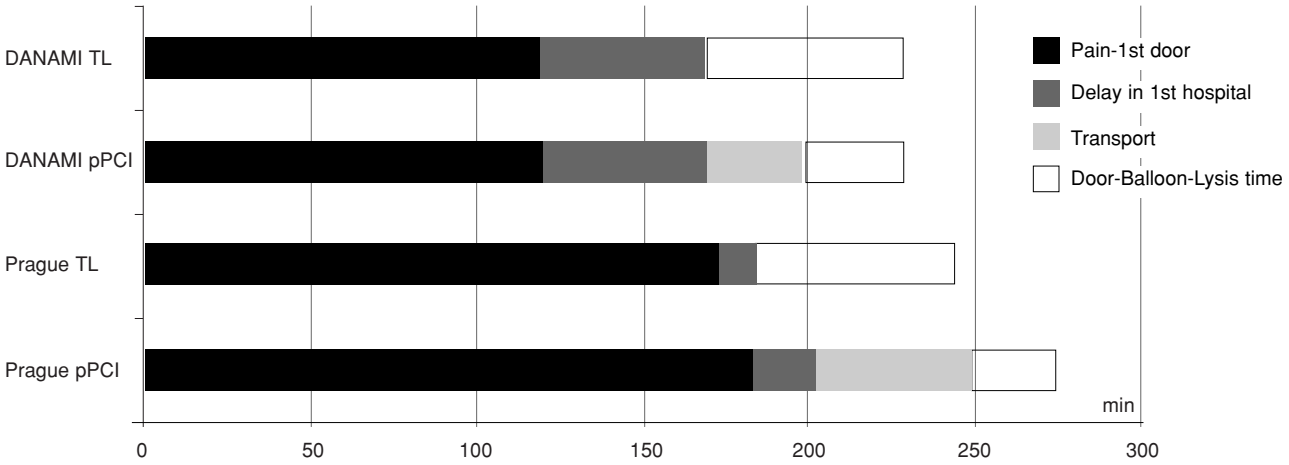

Fig. 3. Time to reperfusion in the PRAGUE-2 and DANAMI-2 trials. In the thrombolytic arm it is assumed that reperfusion occurs 60 minutes after the beginning of infusion. TL: Immediate thrombolysis and stay in the hospital.

tional cardiologists. Finally, the very effective Czech emergency medical system (Záchranná služba) should be acknowledged for a very good participation in these revolutionary changes.

Organization of p-PCI services in the Czech Republic in 2004

The PRAGUE-1 and PRAGUE-2 trials triggered great enthusiasm in favor of the PCI strategy not only among cardiologists in PCI centers, but also among internists or cardiologists in small community hospitals. In fact, one of the two reasons for premature discontinuation of the PRAGUE-2 trials was the growing reluctance of physicians in small hospitals to randomize the patients: they were so much convinced by the improvement provided by PCI that they no longer wanted to refer their patients to streptokinase treatment.

Another important contribution of the PRAGUE trials was that the infrastructure, logistics, and all the personnel in half of the country were highly organized to run this strategy as fast as possible to minimize time intervals.

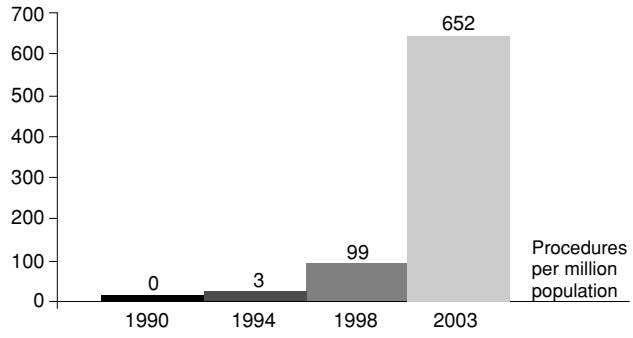

Fig. 4. The evolution of p-PCI procedures in the Czech Republic.

The guidelines of the Czech Society of Cardiology for the treatment of ST-elevation acute myocardial infarction[14] recommend to use p-PCI as the default reperfusion strategy for all the patients with only one exception: patients presenting within three hours after symptom onset to a place with more than 90-minute transport time to catheterization laboratory (early presenters in remote areas).

The Czech Republic has a population of 10.3 million, of which about 60% live in or around the cities with PCI centers. This means that about 40% of the population do not have access to a PCI center in the city where they live. There are 21 hospitals with catheterization laboratories and PCI facilities, 19 of which provide full primary PCI service 24 hours per day throughout a year. The number of inhabitants per primary PCI center is 540,000. With an estimated 700 reperfusion-treated ST-elevation infarctions per one million inhabitants, this gives a mean theoretical maximal workload of 378 primary PCIs/center/year. The real number in 2003 was 326 primary PCIs/center/year. Considering that 70 interventional cardiologists are qualified for PCI, the mean "infarction workload" is 93 primary PCIs/cardiologist/year.

The registry of all hospitalized patients with acute myocardial infarction is available only in one region (South Bohemia with capital České Budějovice, population 680,000, infarctions registered at 7 hospitals) where a total of 599 hospital admissions for ST elevation/Q-wave myocardial infarction took place in

2003. Of those who underwent reperfusion therapy, 93% were treated with p-PCI, and only 7% with thrombolysis (Fig. 5 includes all patients, including those who did not receive reperfusion, mostly for coming after 12 hours). In the Prague region, it is very likely that PCI accounts for 100% of reperfusion and thrombolysis is probably not used at all. The situation is similar in the Brno region. For the rest of the country, the PCI to thrombolysis ratio varies from 75:25 to 95:5.

How a typical Czech patient with ST-elevation infarction is treated?

A patient with chest pain dials an emergency number (155). An emergency ambulance (in most regions with 12-lead ECG) takes the patient. ECG reveals typical ST elevations. The patient receives intravenous Aspegic and heparin (bolus of 5,000-10,000 U) and the emergency physician calls the nearest PCI center. While the patient is transferred, the cath-lab prepares to receive the patient and an interventional cardiologist hastens to the cath-lab usually in simultaneity with the patient's arrival. On arrival, the patient is taken directly to the cath-lab. In the presence of a diagnostic prehospital ECG, the first in-hospital examination is coronary angiography. The time from a prehospital ECG to arrival at the cath-lab varies depending on the distance, but it is less than 60 minutes in the vast majority of patients. The door-balloon time is around 30 minutes. Hence, most patients are reperfused within 90 minutes of the diagnosis. We strictly insist on not taking the patient to interim places (general emergency unit, chest pain unit, coronary care unit, etc.) and on keeping the direct line from the ambulance (helicopter) to the cath-lab. Placing a patient on a CCU bed will cause at least a 20-minute delay.

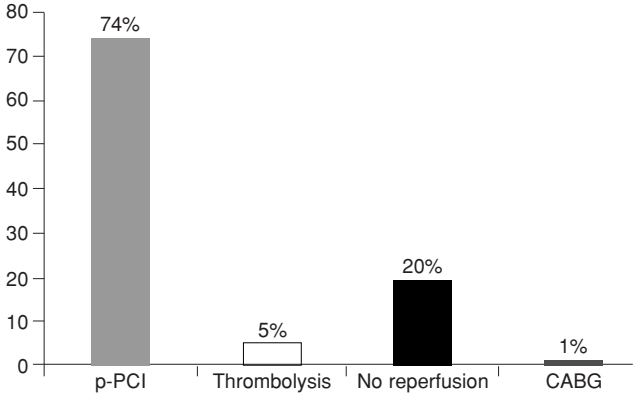

Fig. 5. Distribution of reperfusion therapies for ST-elevation/Q-wave myocardial infarction in South Bohemian region in 2003. CABG: Coronary artery bypass graft.

After the PCI procedure, the patient is kept in the PCI center until the site of the groin puncture is safe (usually 24 hours), after which he/she is transported to his/her regional community hospital to stay for a few days. In cases in which a prehospital ECG is not available during transport, the patient is taken to the nearest hospital to have an ECG recording. If ST elevation is observed on ECG, the patient is then transferred by the same ambulance to a PCI center.

This management must be implemented under military-like discipline, the key part of which is the golden 30-minute rule which covers the following:

– The prehospital ECG should be recorded and interpreted in less than 30 minutes of the patient's initial call for help.

– The patient should be brought directly to the cath-lab ideally in less than 30 minutes after the initial ECG recording.

– An interventional cardiologist must begin the procedure in less than 30 minutes after receiving the emergency message on his/her mobile phone (the use of "beepers" is not recommended, because they cause delays due to the uncertainty of the physician's immediate availability).

– The first balloon inflation is usually completed in less than 30 minutes after the patient's arrival at the cath-lab.

The discipline of all the team members (emergency ambulance, cath-lab personnel, CCU personnel) is essential. The extraordinary flexibility required in the daily work of a cath-lab is something which may be psychologically difficult to implement in conservative environments of "older-generation" cardiologists or nurses. It should be accepted that modern interventional cardiology has moved from a "plastic surgery-like" discipline (nicely planned elective procedures performed on a cooperative patient) to a "trauma surgery-like" one (sudden, unexpected emergency patients disturbing the planned cath-lab program and frequently not cooperating at all; some elderly patients trying to walk down from the cath-lab table in the middle of the procedure, others vomiting, etc.).

Europe in 2004

Thanks to the DANAMI and PRAGUE trials, the Czech Republic and Denmark have become the two European countries having the most developed primary PCI services, and the use of thrombolysis has been widely disparaged to such an extent that, in the Czech Republic, streptokinase has been withdrawn by the producer from the market.

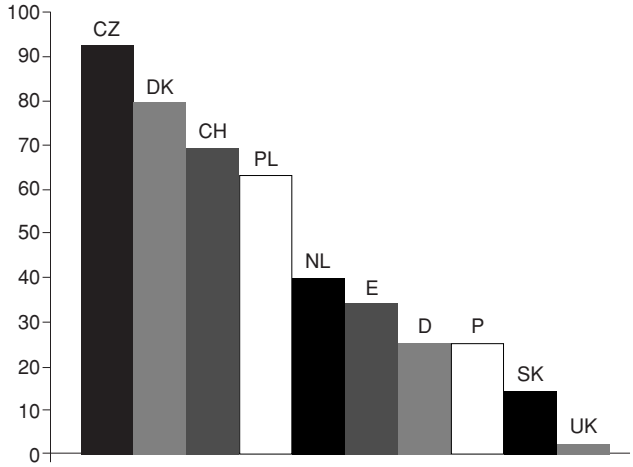

Fig. 6. Approximate ratios of p-PCI to reperfusion in the treatment of ST-elevation myocardial infarction in some European countries. CZ: Czech Republic; DK: Denmark; CH: Switzerland; PL: Poland; NL: Netherlands; E: Spain; D: Germany; P: Portugal; SK: Slovakia UK: United Kingdom.

Based on estimates of interventional cardiologists from several European countries, Fig. 6 shows an approximate overview on the relative ratio of primary PCI- *versus* thrombolysis-treated patients. Although the precise data (especially on thrombolysis) are not available in some of these countries, they somewhat may help us understand the current situation.

Switzerland has established a very good network of PCI services covering the country and this is reflected in a high rate of p-PCI use. The high estimate for Poland may not be applicable to the whole country because the data have been provided by Dr. Dudek from the Krakow area where PCI is very well developed. The Netherlands and Spain are two countries with enormous variability, the use of p-PCI for reperfusion being almost 100% in some regions and 10-20% in others. Not surprisingly, the lowest p-PCI use is in the United Kingdom, but an ongoing dramatic change is seen in the attitude of this country to p-PCI. Finally, no data are available from the remaining European countries, although it seems that the p-PCI use varies between clear dominance (very likely for Belgium, Slovenia, Norway?) and almost none (very likely for some countries of the former Soviet Union, maybe also Ireland?).

Most European countries have quite an eligible infrastructure for conversion to p-PCI procedures, with an adequate number of cath-labs and interventional cardiologists, and the health care systems do reimburse for the p-PCI procedures. However, the main limitation for a more widespread use of p-PCI almost virtually lies in the conservative minds of some cardiologists.

Future perspectives

Despite our robust attitude favoring p-PCI against thrombolysis, the future may include combination strategy ("reperfusion mosaic"). In the near future, the vast majority (if not all) of acute myocardial infarction patients will be transported to PCI centers and performed coronary angiography/PCI as soon as possible. Some (early presenters, long transport distances) will certainly benefit from early (prehospital) thrombolysis. Moreover, "adjunctive thrombolysis" during PCI might be re-introduced for individuals with a large intracoronary thrombus visible at the initial coronary angiogram, a concept that warrants to be tested in the near future due to the failure of distal protection devices.

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