Long-term outcomes of patients with acute myocardial infarction presenting to hospitals without catheterization laboratory and randomized to immediate thrombolysis or interhospital transport for primary percutaneous coronary intervention. Five years’ follow-up of the PRAGUE-2 trial

Petr Widimsky1*, Dana Bilkova1, Martin Penicka1, Martin Novak2, Miroslava Lanikova1, Vladimir Porizka3, Ladislav Groch2, Michael Zelizko3, Tomas Budesinsky1, and Michael Aschermann1 on behalf of the PRAGUE Study Group Investigators

1Cardiocenter Vinohrady, Third Faculty of Medicine, Charles University, Srobarova 50, 100 34 Prague 10, Czech Republic; 2Masaryk University, Brno, Czech Republic; and 3IKEM, Prague, Czech Republic

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Aims Randomized trials in ST-elevation myocardial infarction (STEMI) showed improved early outcomes after primary percutaneous coronary intervention (p-PCI) compared with thrombolysis (TL). It is less known whether the early benefit is sustained during the long-term follow-up.

Methods and results The PRAGUE-2 trial enrolled 850 STEMI patients presenting to community hospitals without cath-labs within 12 h of symptom onset. Patients were randomized into the groups 'TL in community hospital' (n = 421) and 'interhospital transfer for p-PCI' (n = 429).

Follow-up data were available in 416 (98.8%) patients in the TL group and 428 (99.8%) in the p-PCI group. At 5 year follow-up, the cumulative incidence of composite endpoint (death from any cause or recurrent infarction or stroke or revascularization) was 53% in TL patients compared with 40% in p-PCI patients (HR 1.8; 95% CI 1.38 –2.33; P<0.001). The respective cumulative incidence of death from any cause was 23 and 19% (HR 1.34; 95% CI 0.99 –1.82; P=0.06), recurrent infarction 19 vs. 12% (HR 1.72; 95% CI 1.15–2.58; P=0.009), stroke 8 vs. 8% (HR 1.65; 95% CI 0.84–2.23; P=0.18), revascularization 51 vs. 34% (HR 1.81; 95% CI 1.21–2.35; P<0.001).

Conclusion The early benefit from the p-PCI strategy (over TL) is sustained during the 5 years’ follow-up. It can be almost exclusively derived from differences in event rate during the first month.

KEYWORDS Myocardial infarction; Primary coronary intervention; Thrombolysis; Interhospital transport; Long-term outcome

Introduction

Reperfusion therapy of acute myocardial infarction (MI) with ST-elevations is currently undergoing major changes in many countries. More than 20 randomized clinical trials have shown that mechanical reperfusion by primary percutaneous coronary intervention (p-PCI) is able to reduce the early risk of death, recurrent infarction, or stroke when compared with pharmacological reperfusion by intravenous thrombolysis (TL).1,2 This benefit was clearly shown during the acute phase (30 day outcome was assessed in most these trials). Whether this benefit is sustained, increased, or decreased in the long-term follow-up after several years is not known. Recent p-PCI registry data from Italy3 showed 20% mortality rate and 5% non-fatal reinfarction rate, and 19% need additional revascularization during a mean follow-up of 51 months. However, patients included in the registry were not transported between hospitals in the acute phase of MI, and no randomized comparison with long-term outcomes after TL was available. Therefore, we compared the 5 years’ outcomes of patients after ST-elevation MI (STEMI), who were randomized in the acute phase to TL in the nearest hospital or interhospital transport for p-PCI.

Methods

Patients and randomization

The PRAGUE-2 trial4 enrolled 850 patients within 12 h after onset of ST-elevation acute MI (for details, see Widimsky et al.5). In brief,
the inclusion criteria for the PRAGUE-2 study were acute MI (ST-elevations >1 mm in at least two leads or a new bundle branch block on initial ECG) within <12 h from the onset of symptoms, distance to PCI centre <120 km, feasibility to begin transport within 30 min after randomization, and signed written informed consent. Exclusion criteria were contraindication to TL (ischaemic stroke within previous 12 months, haemorrhagic stroke at any time, intracranial tumour, active internal bleeding, aortic dissection) and absence of bilateral femoral artery pulsations. All patients presented initially to a community hospital without catheterization facilities and were randomized immediately after the diagnostic presentation initially to a community hospital without catheterization facilities and were randomized immediately after the diagnostic ECG and signing the written informed consent in two groups: TL in the nearest PCI centre for p-PCI (PCI group, n = 429). Patients were enrolled in the PRAGUE-2 trial between September 1999 and January 2002. The current long-term follow-up was completed in February 2006. Thirty day outcome was reported in the original manuscript. The study complied with the Declaration of Helsinki, the locally appointed Ethics Committees approved the research protocol, and written informed consent has been obtained from all patients.

Follow-up

Patients have been followed either at the primary (community) hospital, where they had been originally randomized, or in the PCI centre related to this hospital in the PRAGUE-2 study network. The goal was to see all living patients in person. The information about survival status of patients not responding to invitations were obtained through their general practitioners and family members or from the health insurance databases of deceased patients.

Endpoints

The primary endpoint for this long-term follow-up was a composite of death from any cause or recurrent infarction or stroke, whichever occurred first at any time during the long-term follow-up. Only the first event in each patient was included in this analysis. The secondary endpoint was a composite of death from any cause or recurrent infarction or stroke or revascularization, whichever occurred first at any time during the long-term follow-up. Only the first event in each patient was included in this analysis. Individual components of both combined endpoints have been analysed too. Stroke was defined as any new neurological deficit lasting >24 h. Recurrent infarction was defined as recurrent symptoms of ischaemia with new electrocardiographic changes and a rise in CK-MB. (This definition was done at the time of study protocol designing in 1998 and thus differs from the current definition accepted in 2000.) Revascularization was defined as any coronary revascularization (PCI or bypass surgery) after the acute phase of STEMI. The results were analysed on the basis of any endpoints between randomization and end of the follow-up (hospital stay + follow-up).

Statistical analysis

Data are analysed and presented on the intention-to-treat principle. Specifically, four patients (1%) randomized to the PCI group were not transferred owing to fast clinical deterioration. They all received TL, three of them died, but all four are analysed as an integral part of the PCI group according to their randomization. All patients randomized to TL received this treatment. Data are presented as mean ± standard deviation. Categorical data are presented by counts and percentages. Unpaired Student’s t-test, Fisher’s exact test, or χ² test was used as appropriate. The time to an endpoint event was plotted according to the Kaplan–Meier method, and differences between groups were analysed by the log-rank test and Cox proportional-hazard models. Statistical significance was defined at P < 0.05. Analyses were conducted with the use of SPSS software for Windows (version 13).

Results

Baseline characteristics were similar in the two groups (Table 1). The median duration of follow-up was 55.1 months (IQR 46–62) in the TL group and 55.3 months (IQR 47–62) in the PCI group (P = 0.95). Information about survival status was available in 416 (98.8%) patients in the TL group and 428 (99.8%) in the PCI group (Figure 1). By the end of follow-up, 483 patients had reached the primary endpoint and 188 patients had died. Table 2 shows the summary of cumulative endpoint occurrence by the 5 years’ follow-up. Patients in the TL group had significantly higher incidence of both primary (HR 1.8; 95% CI 1.38–2.33; P < 0.001) and secondary (HR 1.35; 95% CI 1.02–1.70; P = 0.04) endpoints than patients in the PCI group (Figure 2A). The majority of deaths were cardiovascular (91%) in both groups. Furthermore, patients assigned to TL had significantly higher rate of recurrent infarctions (HR 1.72; 95% CI 1.15–2.58; P = 0.009) and additional revascularizations (HR 1.81; 95% CI 1.21–2.35; P < 0.001) than patients assigned to interhospital transport to p-PCI. In contrast, rates of deaths from any cause (Figure 2B) and rates of strokes were similar in both groups. Mortality among patients with anterior infarctions was 32.5% (TL) vs. 28.4% (PCI), and for non-anterior infarct location, 15% (TL) vs. 15.4% (PCI)—differences not significant. The survival among early and late presenters was compared at long-term. Patients randomized within 3 h had a long-term mortality of 19.8% (TL) and 20.9% (PCI; P = 0.11). Long-term mortality of those presenting late (≥3 h after symptom onset) was 32.1% (TL) and 20.7% (PCI; P = 0.03).

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
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<tr>
<td></td>
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<tr>
<td>Number of randomized patients</td>
</tr>
<tr>
<td>Males, n (%)</td>
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<tr>
<td>Age, years (mean ± SD)</td>
</tr>
<tr>
<td>Anterior infarction, n (%)</td>
</tr>
<tr>
<td>Previous infarction, n (%)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Heart failure (Killip ≥1)</td>
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<tr>
<td>Time from pain onset to randomization (min)</td>
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</tbody>
</table>
Table 3 shows the 30 day outcome in both groups. Patients in the TL group had a slightly higher mortality and tended to have more recurrent infarctions and strokes when compared with the PCI group. The rate of re-PCI was significantly higher in patients assigned to TL when compared with PCI ($P = 0.001$). Thus, the initial benefit from transport to p-PCI persisted by the end of follow-up. However, all differences in outcomes in the two groups were derived by the acute benefit from p-PCI, whereas for the next 5 years, the Kaplan–Meier curves run in parallel (Figures 2 and 3).

Furthermore, the late (follow-up) mortality in patients who survived the first month was comparable in both groups (Figure 4). Thus, no delayed benefit can be attributed to the PCI strategy.

Discussion
The present study reports the 5 year outcome of patients enrolled in the PRAGUE-2 study. The main findings can be summarized as follows. (i) In patients with STEMI, the
interhospital transport to the nearest PCI centre for p-PCI is associated with superior long-term outcome when compared with immediate TL in community hospital without catheterization facilities. (ii) The benefit in patients assigned to PCI was driven primarily by lower rate of recurrent infarction and additional revascularizations when compared with patients receiving TL. (iii) The long-term benefit from the p-PCI strategy over TL was almost exclusively derived from differences in event rate during the first month after initial hospitalization. The benefit from p-PCI is largely derived from the fact that mechanical reperfusion is capable of opening substantially more (90%) occluded coronary arteries (cca) in acute MI compared with TL (cca 50–60%). The better infrastructure (personnel, workload, and equipment) of the tertiary cardiac centres may also have an impact to better the results of the PCI group (TL group patients remained in smaller community hospitals).

The long-term outcomes after p-PCI vs. TL are described in only few reports and the information is controversial. The long-term (8 years) follow-up of the original pioneering randomized Zwolle trial showed benefit of p-PCI over TL only in patients with anterior MI. In contrast, outcomes of patients with non-anterior infarct location were similar regardless of the treatment strategy. Moreover, patients with anterior MI treated by p-PCI showed significant incremental benefit from 1 to 8 years, which was in addition to the early benefit observed within the first year. The number of PCI-treated patients with anterior infarction to prevent one death was only five. These findings are in accordance with our data.

A small, single-centre trial randomized 87 elderly (>75 years) patients with ST-elevation acute MI presenting within initial 6 h to either p-PCI or TL. During the mean follow-up of 24 months, both the combined endpoint (death/reinfarction/stroke) and mortality were significantly decreased by the p-PCI strategy when compared with TL (20 vs. 44%, \( P = 0.003 \) and 15 vs. 32%, \( P = 0.04 \), respectively).

The long-term follow-up of the DANAMI-2 trial showed diminished difference in reinfarction rates in the late vs. previously reported early phase, and hence, decrease in initial benefit of p-PCI compared with TL.

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**Table 3** The 30 day outcome

<table>
<thead>
<tr>
<th></th>
<th>TL group (( n = 421 ))</th>
<th>PCI group (( n = 429 ))</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, n %</td>
<td>42 (10)</td>
<td>29 (6.8)</td>
<td>1.53 (0.91–2.32)</td>
<td>0.12</td>
</tr>
<tr>
<td>Death/reinfarction/stroke (n %)</td>
<td>64 (15.2)</td>
<td>36 (8.4)</td>
<td>1.95 (1.24–3.09)</td>
<td>0.003</td>
</tr>
<tr>
<td>Death/reinfarction/stroke/revascularization (n %)</td>
<td>100 (23.8)</td>
<td>61 (14.2)</td>
<td>1.87 (1.29–2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrent infarction (n %)</td>
<td>13 (3.1)</td>
<td>6 (1.4)</td>
<td>2.25 (0.79–7.27)</td>
<td>0.10</td>
</tr>
<tr>
<td>Stroke (n %)</td>
<td>9 (2.1)</td>
<td>1 (0.2)</td>
<td>10.55 (1.45–46.36)</td>
<td>0.03</td>
</tr>
<tr>
<td>(Re-) PCI (n %)</td>
<td>56 (13.3)</td>
<td>29 (6.8)</td>
<td>2.12 (1.29–3.48)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Figure 2** Kaplan–Meier estimates of event-free survival (survival to the combined endpoint).

**Figure 3** Kaplan–Meier estimates of overall survival (survival to death from any cause).

**Figure 4** Late mortality among 30 day survivors (day 31–end of follow-up) on top of early (day 1–30) mortality among all randomized patients.
Our observations are different: the lower rate of reinfarction in the PCI group was not significant in the early phase, but became significant in the long-term. This might be influenced by the fact that clopidogrel was given per protocol also to TL group patients during the first month (for details, see Table 1 in Widimsky et al.4). Strokes showed opposite pattern: significant initial (30 days) excess of strokes in the TL group (Table 3) became non-significant in the long-term follow-up (Table 2).

The fact that detailed information about actual medication at the last study visit was not collected is certainly a methodological limitation of this study. However, it is very unlikely that any differences in medications between the two groups were present 5 years after the initial event. Specifically, clopidogrel was given per protocol to both groups during the initial 30 days and was stopped in nearly all study patients after this period (only bare metal stents—no drug-eluting stents—have been used in the trial). All medications after day 30 were left to the discretion of the patient’s physician. It can be indirectly expected that the overall medication use was close to that observed in the recent CZECH registry (not yet published): aspirin in 93%, statins in 76%, beta-blockers in 78%, and ACE-inhibitors in 59% of patients.

The difference in outcome between early (<3 h) and late (3–12 h) presenters found in this study was not confirmed by a meta-analysis of multiple trials including individual data from the PRAGUE-2 trial.9 The unpublished hour-by-hour subgroup analysis of PRAGUE-2 trial patients found better outcomes with PCI strategy in all subgroups, except the relatively largest third-hour subgroup (specifically, better outcomes were observed with PCI strategy in the first 2 h). Owing to the small size of these ‘hour subgroups’, the differences were not significant and the data not published separately, but only as a part of the earlier-mentioned meta-analysis.9

The European Society of Cardiology declared PCI as a routine treatment for most acute STEMI, preferably as p-PCI. When p-PCI is not available within 90 min after the first medical contact, pre-hospital TL is the best option, but should be followed by rescue PCI or next-day PCI.10

Our observation that the initial benefit from p-PCI is not increased (late mortality was exactly the same in both study arms) during the follow-up strikingly resembles long-term follow-up data after coronary bypass graft surgery.11 Both long-term comparisons (PCI vs. TL as well as coronary artery bypass grafting (CABG) vs. medical therapy) demonstrate the initial benefit of an intervention (PCI and CABG), which is not further increased (or even may tend to diminish) during the very long follow-up periods of 5–10 years. This reflects the fact that both procedures (PCI and CABG) are effective, palliative solutions for an acute problem, but cannot reverse the progression of atherosclerosis. This supports the global treatment approach to coronary atherosclerosis as a chronic disease with acute episodes: mechanical intervention saves lives in the acute phase, but long-term course is more dependent on the complex nature of this disease and the secondary prevention of its consequences.

Thus, patients with acute MI should be treated by effective reperfusion strategies to improve their early outcomes. Yet, meticulous attention should be focused on aggressive secondary prevention to slow the atherosclerosis progression and also to improve the long-term outcomes.

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Conflict of interest: none declared.

Appendix

Full list of co-investigators who contributed to data collection

**PCI centres.** Cardiocenter, University Hospital Vinohrady, Prague: P.W. (principal investigator of the study), D.B. (co-principal investigator of the long-term follow-up), M.P. (significant contribution to data analysis and manuscript preparation), T.B., David Vorač, Jaroslav Dvořák, Jiří Krupička, Libor Lisa, Radovan Jirman, Pavel Gregor, Rudolf Špaček.

Cardiovascular Department I, University Hospital St. Anne, Brno: L.G., Ivan Horňáček, Ota Hlinomaz, Jan Šitá, Libor Němeček, M.N.

Cardiocenter, Hospital Podlesí, Třinec: Maran Branýn, Igor Nykl, Ivo Varvařovský, Jindřich Černý, Marek Richter.

Cardiology Clinic IKEM, Prague: Michal Želízko, Bronislav Janek, Jiří Kettner, Vladimir Karmazín, Vladimir Pöřížka.

Cardiocenter, University Hospital Hradec Králové: Josef Šlasek, Pavel Červinka, Dušan Černohorský, Miroslav Brtko, Vladimír Rozsival, Aleš Herman, Martina Laníkova.

Cardiology Department, Hospital Na Homolce, Prague: Pavel Formánek, Petr Kromíček, Ondřej Aschermann.

Medical Department II, General University Hospital, M.A., Stanislav Šimek, Aleš Linhart, František Holm, Jan Bělohlávek.

**Community hospitals and investigators.**

References

Clinical vignette
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Pathology of explanted ASD occluder
Gerhard Bauriedel1,2*, Dirk Skowasch2, and Matthias Peuster3
1Department of Internal Medicine I/Cardiology, Klinikum Meiningen, Meiningen, Germany; 2Department of Internal Medicine II/Cardiology, University of Bonn, Bonn, Germany; 3Department of Pediatric Cardiology and Pediatric Intensive Care Medicine, University of Rostock, Rostock, Germany
* Corresponding author. E-mail address: g.bauriedel.med1@klinikum-meiningen.de

A 45-year-old woman with previous apoplexia due to paradoxical embolism via atrial septal defect (ASD) received a 28 mm Amplatzer ASD occluder (AGA Medical Corp., USA). The device was explanted by surgery 15 months later when transoesophageal echocardiography documented that a small residual interatrial shunt post-intervention increased continuously.

Macroscopic inspection of the explanted occluder showed large surface areas covered by white glistening tissue of variable thickness and some patches with bare metal nitinol struts (Panel A). In contrast, tissue localized between the occluder discs appeared hyperaemic and prevented complete disc separation (Panel B). Although no wire fraction was observed, detailed electron microscopy gave ample evidence for pit corrosion (Panel C). Immunohistochemistry demonstrated most device areas covered by an endothelial monolayer and collagen-rich fibroelastic tissue that continuously merged into broad fibrous endocardium. This ‘pseudointima’ showed numerous alpha-smooth muscle actin+ cells and signalling of heat shock protein 47 indicative of ongoing collagen synthesis. Cell-rich, vascularized granulation tissue between the wire mesh discs comprised monocyte infiltrates composed of CD68+ macrophages as well as single cells expressing CD34 as hematopoietic progenitor cell marker. Presence of dendritic cells indicated by S100 (Panel D) and fascin was found close to the metal struts, whereas CD3 lymphocyte immunolabelling was sparse throughout all tissue areas. No vegetations or histopathological evidence of acute infection were detected within the specimen.

The explanted Amplatzer ASD occluder demonstrated (i) a partly incomplete endothelial covering, (ii) pit corrosion, and (iii) ongoing inflammation and granulation adjacent to fibroelastic scarring even 15 months after device implantation.