Effects of early abciximab administration before primary percutaneous coronary intervention on left ventricular function assessed by cardiac magnetic resonance

Tomasz Rakowski[1], Waldemar Mielecki[1], Agata Brzozowska-Czarnek[2], Artur Dziewierz[1], Zbigniew Siudak[1], Jacek Legutko[1], Łukasz Rzeszutko[1], Andrzej Urbanik[2], Jacek S. Dubiel[1], Dariusz Dudek[3]

[1] 2nd Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland

[2] Department of Radiology, Jagiellonian University Medical College, Krakow, Poland

[3] Department of Interventional Cardiology, Jagiellonian University Medical College, Krakow, Poland

Abstract

Background: It has been shown that early abciximab administration before primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI) improves efficacy of treatment. However, there are no data on the impact of this strategy on left ventricular (LV) function during long-term follow-up.

Aim: To analyse the effects of early abciximab administration in patients with first anterior STEMI treated with pPCI on infarct size and LV function assessed by cardiac magnetic resonance.

Methods: A total of 59 patients with STEMI, <12 hours from the chest pain onset, without cardiogenic shock, admitted to local hospitals without interventional facilities, with anticipated delay to pPCI <90 min were randomly assigned to two study groups: 27 patients received abciximab before transfer to the catheterisation laboratory (early abciximab group), and 32 patients received abciximab in the catheterisation laboratory just before pPCI (late abciximab group). All patients received aspirin and heparin (70 U/kg) before transfer to the cath lab. Clopidogrel loading dose was administered in the cath lab before angiography.

Results: Cardiac magnetic resonance was performed in 14 patients from each study group 1 year after pPCI and revealed a significantly lower LV end-systolic volume index (p=0.003), end-diastolic volume index (p=0.009) and better ejection fraction (p <0.05) in patients who received abciximab early.

Conclusions: Early abciximab administration prior to transfer for pPCI in patients with first anterior STEMI results in a lower degree of LV remodelling and better LV ejection fraction at 1-year follow-up compared to late abciximab administration in the cath lab during pPCI.

Key words: myocardial infarction, abciximab, percutaneous coronary intervention, magnetic resonance

Kardiol Pol 2008; 66: 617-622

Introduction

Abciximab administration during primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI) is recommended in the guidelines [1, 2]. A few meta-analyses have confirmed the beneficial effects of abciximab administration during pPCI [3, 4]. However, the optimal time for administration of abciximab prior to or during the pPCI procedure remains to be defined. The available randomised studies investigating early (prior to transport for the intervention) administration of abciximab showed conflicting results [5-8]. However, there is a growing amount of data suggesting beneficial effects of early abciximab administration over conventional therapy (administration during pPCI). Little is known about the impact of this strategy on left ventricular (LV) function during long-term follow-up.

The purpose of the present study was to evaluate the effects of early administration of abciximab on infarct size and LV function assessed by cardiac magnetic resonance (CMR) at one-year follow-up in a population of patients with a first anterior wall STEMI treated with pPCI.

Methods

Study group

Study design details were described previously [9]. In brief, patients >18 years with acute anterior STEMI (chest

Address for correspondence:
Dariusz Dudek MD, PhD, Department of Interventional Cardiology, CM UJ, ul. Kopernika 17, 31-501 Kraków, tel.: +48 12 424 71 81,
e-mail: mcdudek@cyf-kr.edu.pl

Received: 03 February 2008. **Accepted:** 02 April 2008.

pain >30 min, ST-segment elevation >0.2 mV in at least two adjacent precordial leads) within 12 hours from chest pain onset were enrolled. Patients with previous MI, previous PCI or coronary arterial bypass graft and Killip Class III or IV assessed in a local hospital were excluded.

In local hospitals without interventional facilities with an anticipated transportation time delay to a pPCI centre of less than 90 minutes, patients were randomly assigned to two study groups. In the Early Abciximab (EA) Group, patients received a bolus of abciximab (0.25 mg/kg) and a bolus of heparin (70 U/kg) before transfer. In the Late Abciximab (LA) Group, patients received only a bolus of heparin (70 U/kg). All patients were given aspirin orally (300--500 mg) and received a loading dose of clopidogrel (300 mg) in the cath lab. Patients from the EA group received an intravenous infusion of abciximab (0.125 μg/kg/min), whereas in the LA group a bolus and infusion of abciximab were administered after coronary angiography and prior to pPCI. Baseline and post-PCI angiographic parameters such as TIMI grade, corrected TIMI frame count (cTFC), TIMI myocardial perfusion grade (TMPG), ECG ST-segment resolution, and echocardiography at baseline and at 30-day and 30-day clinical follow-up were analysed. Methods and results were reported previously. In brief, 59 patients were enrolled in the main study (27 patients in the EA group, 32 in the LA group). We found that early abciximab administration resulted in better early infarct related artery (IRA) patency (defined as TIMI 2+3), lower enzymatic infarct size (area under curve CK-MB), better ST-segment resolution in ECG 60 minutes after pPCI and lower LV remodelling in echocardiography after 30 days [9].

Cardiac magnetic resonance

The CMR sub-study was performed in the first 14 consecutive patients from each study group. The exclusion criteria for the CMR study were: death or reinfarction during follow-up, contraindications to CMR, or patient's refusal.

The CMR study was performed using a 1,5T scanner (GE Signa EXCITE) with a TORSOPA coil. Left ventricular volumes, ejection fraction (EF) and infarct size were analysed 12 months after index MI. The end-diastolic and end-systolic volume indices were obtained after dividing volume by body surface area according to the DuBois formula [10].

Left ventricle volumes and LVEF were assessed with cine-CMR using a steady-state free-precession technique (FIESTA) with the following imaging parameters: 20 phases per slice location, FOV 32 × 32 cm; TR 1.6 ms; TE 2.8 ms; FA 20-30°; matrix 256 × 160; NEX 1. 10-14 consecutive slices of 8 mm were planned with a gap of 2 mm in short axis view. Also one horizontal long axis view (four-chamber) was obtained.

Delayed enhancement images were acquired 15-20 min after a double bolus of gadolinium (0.2 mmol/kg) using an inversion recovery gradient-echo sequence with the following imaging parameters: FOV 42 × 42 cm; TR 8 ms; TE 3.8 ms; FA 40-50°, NEX 2; slice thickness 8 mm; gap 2 mm. The inversion time was adjusted individually to null normal myocardium. Slice locations of the delayed enhancement images were copied from the cine images to ensure registration between cine-CMR and infarct measurements.

Dedicated software was used for post-processing (MASS, Medis). End-systolic and end-diastolic volumes were quantified by drawing endocardial and epicardial contours on the short axis series of the cine images, and LVEF was calculated. The volume of delayed enhancement was quantified manually from consecutive short axis slices and was multiplied by 1.05 g/ml to obtain myocardial infarct mass (1 ml = 1.05 g). Infarct size was expressed as the percentage of total LV mass. All analyses were performed by an observer blinded to patients' clinical data and group allocation.

Statistical analysis

Results are expressed as means ± standard deviations or numbers and percentages of patients. Differences between continuous and dichotomous variables were assessed by the Wilcoxon two-sample test, Mann-Whitney U-test and Fisher's exact test where appropriate. The R Spearman method was used to assess correlations between variables. A p value of <0.05 was considered statistically significant.

Results

Twenty-eight patients entered the CMR sub-study. In 14 patients abciximab was given in a local hospital before transportation (EA group), and 14 patients received the drug prior to PPCI in the catheterisation laboratory (LA group). There were no significant differences in clinical and demographic characteristics between these groups (Table I). Patent IRA (TIMI 2+3) at baseline angiography was found in 50% of patients in the EA group and 21.4% in the LA group (NS). The TIMI 3 flow after PCI was found in 92.9% of patients in each group (NS).

The CMR study performed one year after pPCI revealed lower LV end-systolic (36.7±12.7 vs. 59.4±17 ml/m^2; p=0.003) and end-diastolic volume index (76.2±14 vs. 96.4±18 ml/m^2; p=0.009) in the EA group (Figures 1A and 1B). Left ventricular EF was higher in the EA group (47±10 vs. 40±8%; $p<0.05$) (Figure 1C). Delayed enhancement infarct size analysis showed a trend towards lower infarct size in the EA group (12.4±10.8 vs. 16.3±12%; p=0.2) (Figure 1D).

We also analysed the correlation between early IRA patency (TIMI flow grade 2+3 in baseline angiography) and CMR results. A significant correlation was found between patent IRA in baseline angiography and infarct size (r=–0.56; p=0.005), LVEF (r=0.68; p=0.0003), and LV end-systolic volume index (r=–0.4; $p<0.05$).

Table I. Characteristics of the study population

Parameter	Early Group (n=14)	Late Group (n=14)	p
Age [years]	61±11	55±10	NS
Gender male [%]	85.7	92.3	NS
History of CAD [%]	21.4	14.3	NS
Diabetes mellitus [%]	7.2	7.2	NS
Arterial hypertension [%]	42.9	50	NS
Hypercholesterolaemia [%]	28.5	28.5	NS
Smoking [%]	50	42.9	NS
SBP on admission [mmHg]	135±16	135±15	NS
DBP on admission [mmHg]	87±9	87±9	NS
Heart rate on admission [beats per minute]	78±9	77±12	NS
Time from chest pain onset to first balloon inflation [min]	190±64	194±80	NS
Time from chest pain onset to abciximab administration [min]	103±63	185±83	0.019
Time from abciximab administration to first balloon inflation [min]	87±20	10±5	<0.0001

Abbreviations: CAD – coronary artery disease, DBP – diastolic blood pressure, SBP – systolic blood pressure

Discussion

This is the first study investigating the impact of early abciximab administration on LV function and infarct size in long-term follow-up. We found that early administration of abciximab before transportation for PCI in high-risk anterior STEMI patients was associated with better LVEF and reduced LV remodelling in CMR at 1 year. These results emphasise the role of early abciximab administration as an important element of adjunctive pharmacotherapy in patients undergoing pPCI.

Randomised published studies investigating early administration of abciximab provided diverse results. Zorman et al. and the ReoPro BRIDGING study demonstrated a significant advantage of this strategy over administration of abciximab after angiography just before or during pPCI [5, 6]. In contrast, the REOMOBILE and ERAMI studies comparing early and late abciximab administration before pPCI did not show any significant advantages of early administration strategy [7, 8]. A meta-analysis of 6 studies comparing early and late abciximab administration before pPCI in 602 patients showed higher IRA patency rates before pPCI, better ST-segment elevation resolution after pPCI and a trend favouring improved clinical outcome after early abciximab administration [11].

We have previously published results of our study favouring early abciximab administration. We found that early abciximab administration before transfer for pPCI in

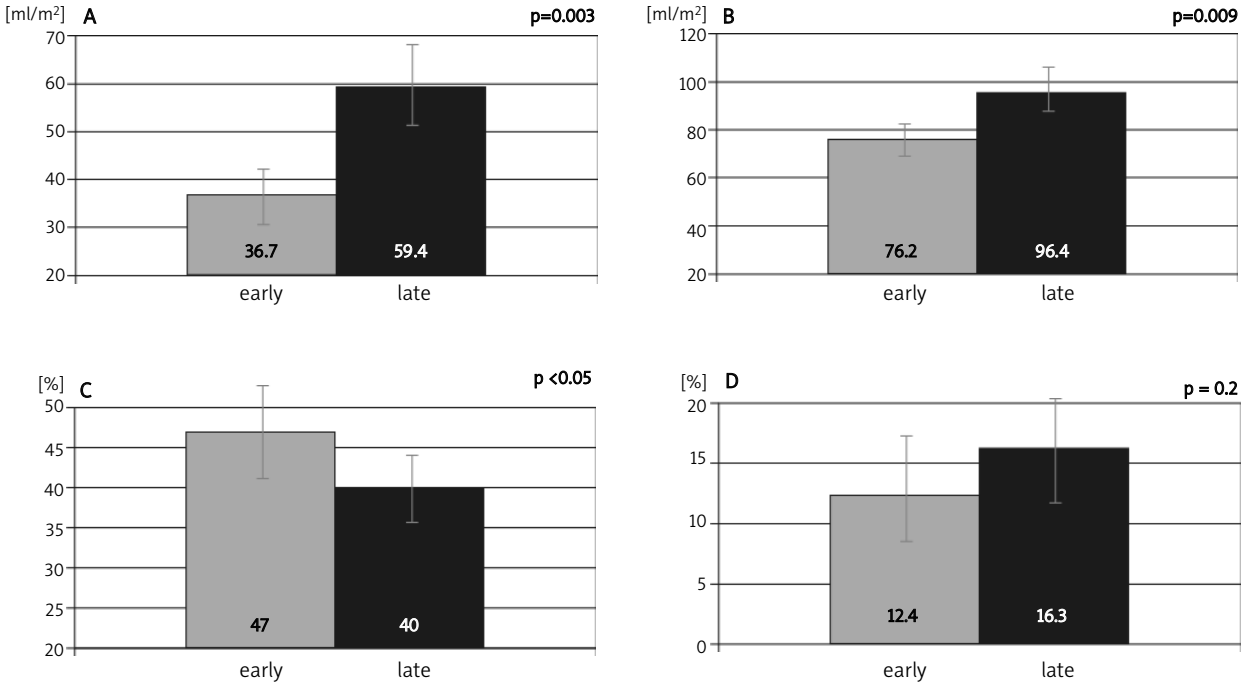

Figure 1. One-year cardiac magnetic resonance results obtained one year after index STEMI. **A.** Left ventricular end-systolic volume index. **B.** Left ventricular end-diastolic volume index. **C.** Left ventricular ejection fraction and **D.** Infarct size (grey bars – early abciximab administration, black bars – late abciximab administration)

high-risk patients with first anterior wall STEMI resulted in more frequent IRA patency before pPCI, better myocardial tissue perfusion after pPCI with lower enzymatic infarct size, and lower degree of LV remodelling in echocardiography during 30-day follow-up [9].

To the best of our knowledge, there is only one published study investigating the effects of early abciximab administration of LV function assessed by SPECT, and another one which used echocardiography, but both analysed short-term outcome. Bellandi et al. randomised 55 patients to early versus late abciximab administration before pPCI and analysed SPECT results at baseline, 7 days and 30 days. Significant differences favouring early abciximab administration were found in 7-day salvage index and 30-day LVEF [12]. In the RELAx AMI trial the same investigators analysed global and regional LV function in echocardiography in 30-day follow-up and better results were found after early abciximab administration [13].

There are no data about the impact of this strategy on LV function and remodelling in long-term follow-up. We observed lower CMR infarct size in the early abciximab group, but this difference did not reach statistical significance. In previously published data lower infarct size after early abciximab administration was observed in short-term follow-up using enzymatic, ECG and SPECT studies but never CMR [12, 13].

In the present study, we enrolled a homogeneous population of patients with a first anterior MI, i.e. a condition in which ischaemic myocardial injury and LV remodelling might have been most extensive. We expected the greatest benefit after early abciximab administration in these high-risk patients. The exclusion of patients with previous MI provided a possibility of evaluating more precisely the effects of this therapy on LV function. We decided to use CMR because this modality offers accurate and highly reproducible assessment of LV function and infarct size. The reproducibility is much better than using other methods and the sample sizes for research studies can be significantly reduced [14].

We have also found a correlation between early IRA patency and CMR infarct size and LV function. Spontaneous IRA patency before pPCI is said to be a favourable prognostic factor [15, 16]. The role of early pharmacological reperfusion is now a matter of debate. A recent meta-analysis of studies on pharmacological facilitation of pPCI with GP IIb/IIIa inhibitors concluded that this approach results in more frequent early IRA patency but it does not translate into additional clinical benefit. However, that study included a heterogeneous patient population with short-term follow-up and the results were not analysed in low- and high-risk subgroups [17]. Early IRA patency restored by abciximab may further improve outcomes in STEMI and overcome a basic limitation of pPCI, i.e. the time delay related to transfer to a hospital with invasive facilities.

All previous studies were underpowered to assess clinical end-points but suggested a benefit of early abciximab administration based on surrogate end-points. Finally, the FINESSE study did not show any clinical benefit of early abciximab administration over standard administration during pPCI, which is in contrast to the large European EUROTRANSFER Registry [18, 19]. The discrepancy between these studies may be caused by differences in patients' risk profile, logistics of patients' enrolment (only 40% of patients with inter-hospital transfer in FINESSE and 100% in EUROTRANSFER) and longer time from chest pain onset to abciximab administration.

Study limitations

The main limitation of our CMR sub-study is the relatively small number of patients enrolled. However, the study population consisted of a highly selected homogeneous population of high-risk STEMI patients and we used CMR, which required a lower sample size. The study was not double blind and placebo controlled, which may have influenced the results. However, CMR results were analysed by a blinded observer. Clopidogrel loading dose was 300 mg and it was administered in the cath lab, but when the study was designed (year 2003--2004) it was a standard therapy.

Conclusions

Early abciximab administration before transfer for pPCI in high-risk patients with first anterior STEMI results in better LVEF and lower degree of LV remodelling after one-year follow-up.

Acknowledgements

This work was supported by a grant from the State Committee for Scientific Research, Poland.

References

1. Van de Werf F, Ardissino D, Betriu A, et al; Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003; 24: 28-66.
2. 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 (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation* 2004; 110: 588-636.
3. De Luca G, Suryapranata H, Stone GW, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *JAMA* 2005; 293: 1759-65.
4. Montalescot G, Antoniucci D, Kastrati A, et al. Abciximab in primary coronary stenting of ST-elevation myocardial infarction:

a European meta-analysis on individual patients' data with long-term follow-up. *Eur Heart J* 2007; 28: 443-9.
5. Zorman S, Zorman D, Noc M. Effects of abciximab pretreatment in patients with acute myocardial infarction undergoing primary angioplasty. *Am J Cardiol* 2002; 90: 533-6.
6. Gyöngyösi M, Domanovits H, Benzer W, et al. ReoPro-BRIDGING Study Group. Use of abciximab prior to primary angioplasty in STEMI results in early recanalization of the infarct-related artery and improved myocardial tissue reperfusion – results of the Austrian multi-centre randomized ReoPro-BRIDGING Study. *Eur Heart J* 2004; 25: 2125-33.
7. Gabriel HM, Oliveira JA, da Silva PC, et al. Early administration of abciximab bolus in the emergency department improves angiographic outcome after primary PCI as assessed by TIMI frame count: results of the early ReoPro administration in myocardial infarction (ERAMI) trial. *Catheter Cardiovasc Interv* 2006; 68: 218-24.
8. Arntz HR, Schroder JF, Pels K, et al. Prehospital versus periprocedural administration of abciximab in STEMI: early and late results from the randomised REOMOBILE-study. *Eur Heart J* 2003; 24 (abstract suppl.): 268.
9. Rakowski T, Zalewski J, Legutko J, et al. Early abciximab administration before primary percutaneous coronary intervention improves infarct-related artery patency and left ventricular function in high-risk patients with anterior wall myocardial infarction: a randomized study. *Am Heart J* 2007; 153: 360-5.
10. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 1916; 17: 863-71.
11. Godicke J, Flather M, Noc M, et al. Early versus periprocedural administration of abciximab for primary angioplasty: a pooled analysis of 6 studies. *Am Heart J* 2005; 150: 1015.
12. Bellandi F, Maioli M, Leoncini M, et al. Early abciximab administration in acute myocardial infarction treated with primary coronary intervention. *Int J Cardiol* 2006; 108: 36-42.
13. Maioli M, Bellandi F, Leoncini M, et al. Randomized early versus late abciximab in acute myocardial infarction treated with primary coronary intervention (RELAx-AMI Trial). *J Am Coll Cardiol* 2007; 49: 1517-24.
14. Bellenger NG, Davies LC, Francis JM, et al. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2000; 2: 271-8.
15. Stone GW, Cox D, Garcia E, et al. Normal flow (TIMI 3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. *Circulation* 2001; 104: 636-41.
16. De Luca G, Ernst N, Zijlstra F, et al. Preprocedural TIMI flow and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol* 2004; 43: 1363-7.
17. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet* 2006; 367: 579-88.
18. FINESSE trial results presented by Dr Stephen Ellis on September 3rd 2007 at European Society of Cardiology Congress in Vienna. ttp://webcasts.prous.com/esc2007/article.asp?CID=YY&CLID =2&AID =349#; return%20false; (assessed November 30th, 2007).
19. Dudek D, Siudak Z, Janzon M, et al. Patients transferred for primary PCI display reduced mortality when treatment with abciximab was started early compared with abciximab given in the cathlab. Results from the EUROTRANSFER Registry. *Eur Heart J* 2007; 28: 384 (abstract).

Wpływ wczesnego podania abciksimabu przed zabiegami pierwotnej angioplastyki wieńcowej na funkcję lewej komory serca ocenianą w badaniu sercowego rezonansu magnetycznego

Tomasz Rakowski[1], Waldemar Mielecki[1], Agata Brzozowska-Czarnek[2], Artur Dziewierz[1], Zbigniew Siudak[1], Jacek Legutko[1], Łukasz Rzeszutko[1], Andrzej Urbanik[2], Jacek S. Dubiel[1], Dariusz Dudek[3]

[1] II Klinika Kardiologii, Instytut Kardiologii, *Collegium Medicum*, Uniwersytet Jagielloński, Kraków

[2] Katedra Radiologii, *Collegium Medicum*, Uniwersytet Jagielloński, Kraków

[3] Zakład Hemodynamiki i Angiokardiografii, Instytut Kardiologii, *Collegium Medicum*, Uniwersytet Jagielloński, Kraków

Streszczenie

Wstęp: Istnieją przesłanki, iż wczesne podanie abciksimabu przed zabiegiem pierwotnej przezskórnej angioplastyki wieńcowej (pPCI) w zawale serca z uniesieniem odcinka ST (STEMI) poprawia wyniki leczenia, aczkolwiek brakuje danych dotyczących wpływu takiej terapii na funkcję lewej komory (LV) w obserwacji odległej.

Cel: Celem badania była ocena wpływu wczesnego podania abciksimabu u chorych z pierwszym STEMI ściany przedniej leczonych zabiegami pPCI na wielkość obszaru zawału oraz funkcję LV ocenianą w badaniu rezonansu magnetycznego w obserwacji odległej.

Metodyka: Do badania włączono 59 chorych z pierwszym STEMI ściany przedniej bez objawów wstrząsu kardiogennego, do 12 godz. od początku bólu zawałowego, którzy zostali przyjęci do szpitali rejonowych ze spodziewanym opóźnieniem do zabiegu pPCI mniejszym niż 90 min. Chorzy zostali losowo przydzieleni do dwóch grup – 27 otrzymało abciksimab przed transportem do pracowni hemodynamiki (grupa wczesnego podania abciksimabu), a 32 otrzymało abciksimab w pracowni hemodynamiki przed zabiegiem pPCI (grupa późnego podania abciksimabu). Wszyscy chorzy otrzymali w szpitalu rejonowym kwas acetylosalicylowy oraz heparynę niefrakcjonowaną (70 U/kg). Dawkę nasycającą klopidogrelu podawano w pracowni hemodynamiki przed angiografią.

Wyniki: Charakterystyka wyjściowa chorych była zbliżona w obu grupach. Badanie rezonansu magnetycznego serca zostało wykonane u 28 osób (po 14 w każdej z grup) po roku i wykazało istotnie niższy indeks końcowoskurczowej objętości LV (36,7±12 *vs* 59,4±17 ml/m^2; p=0,003), końcoworozkurczowej objętości LV (76,2±14 *vs* 96,4±18 ml/m^2; p=0,009) oraz lepszą frakcję wyrzutową LV (LVEF) (47±10 *vs* 40±8%; p <0,05) w grupie wczesnego podania abciksimabu.

Wnioski: Wczesne podanie abciksimabu przed transportem do pracowni wykonującej zabieg pPCI u chorych z pierwszym STEMI ściany przedniej skutkuje mniejszym remodelingiem oraz lepszą LVEF w obserwacji rocznej w porównaniu z podaniem abciksimabu podczas zabiegu pPCI.

Kardiol Pol 2008; 66: 617-622

Adres do korespondencji:

dr hab. n. med. Dariusz Dudek, Zakład Hemodynamiki i Angiokardiologii CM UJ, ul. Kopernika 17, 31-501 Kraków, tel.: +48 12 424 71 81, e-mail: mcdudek@cyf-kr.edu.pl

Praca wpłynęła: 03.02.2008. **Zaakceptowana do druku:** 02.04.2008.