Pregledni rad / Review article

Farmakoinvazivna strategija i njeno mjesto u zbrinjavanju bolesnika s akutnim infarktom miokarda s elevacijom ST-segmenta

Pharmacoinvasive strategy and its role in the management of patients with acute ST-segment elevation myocardial infarction

Đeiti Prvulović*
Opća bolnica "Dr. Josip Benčević", Slavonski Brod, Hrvatska
General Hospital "Dr. Josip Benčević", Slavonski Brod, Croatia

SAŽETAK: Učinkovita, rana i brza reperfuzijska terapija je najvažniji cilj u liječenju bolesnika s akutnim infarktom s elevacijom ST-segmenta (STEMI). Pravovremeno učinjena primarna perkutana koronarna intervencija (pPCI) je nesumnjivo strategija izbora u liječenju STEMI i u posljednjih desetak godina pPCI kao način revaskularizacijske strategije je zamijenila fibrinolitičku terapiju. Mnoga klinička istraživanja su pokazala da bolesnike liječene fibrinolizom treba rutinski premjestiti u invazivni kardiološki centar radi elektivne perkutane koronarne intervencije (PCI) unutar 24 sata te da ovakva rana invazivna strategija dovodi do stabilizacije ciljne lezije i manje pojavnosti rekurentne ishemije. Najnovije Smjernice Europskog kardiološkog društva za zbrinjavanje bolesnika sa STEMI farmakoinvazivnoj strategiji daju klasu I indikacija.

U ovom preglednom članku su prikazana najvažnija klinička istraživanja o farmakoinvazivnoj strategiji i mjesto ovog načina liječenja STEMI. Ovakav način reperfuzije dovodi do značajnog smanjenja reinfarkta i rekurentne ishemije bez povišenog rizika od krvarenja te bi implementiranje ove strategije u regionalne protokole zbrinjavanja bolesnika sa STEMI povećalo broj bolesnika kojima je pružena pravilna i pravodobna primjena reperfuzijske terapije.

KLJUČNE RIJEČI: farmakoinvazivna strategija, fibrinoliza, primarna perkutana koronarna intervencija, infarkt miokarda

SUMMARY: Effective, early and rapid reperfusion therapy is the most important goal in the treatment of patients with acute ST-segment elevation myocardial infarction (STEMI). Timely performed primary percutaneous coronary intervention (pPCI) is undoubtedly the strategy of choice in the treatment of STEMI and in the last decade pPCI has replaced fibrinolytic therapy as a way revascularization strategy. Many clinical studies have shown that patients treated with fibrinolysis should be routinely moved to the invasive cardiology center for elective percutaneous coronary intervention (PCI) within 24 hours and that this early invasive strategy leads to a stabilization of the target lesion and lowers the incidence of recurrent ischemia. The latest European Society of Cardiology Guidelines for the management of patients with STEMI award the Class I indication to the pharmacoinvasive strategy.

This review article presents the most important clinical research on pharmacoinvasive strategy and importance of this method of treatment of STEMI. This method of reperfusion leads to a significant reduction in reinfarction and recurrent ischemia without increased risk of bleeding and implementing this strategy in regional protocols for the management of patients with STEMI would increase the number of patients who are to receive proper and timely reperfusion therapy.

KEYWORDS: pharmacoinvasive strategy, fibrinolysis, primary percutaneous coronary intervention, myocardial infarction.

CITATION: Cardiol Croat. 2013;8(12):414-423.

Uvod

Akutni infarkt miokarda s elevacijom ST-segmenta (STEMI) predstavlja jedno od najčešćih i najvažnijih hitnih stanja u medicini za koje dobra organizacija medicinske skrbi ima odlučujući utjecaj na rezultate liječenja bolesnika. Učinkovita, rana i brza reperfuzijska terapija je najvažniji cilj u

Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is one of the most common and most significant emergencies in medicine where the good organization of medical care has a decisive impact on the results of the treatment of patients. Effective, early and rapid reperfusion therapy is the

liječenju bolesnika sa STEMI, a dobra organizacija mreže primarne perkutane koronarne intervencije (pPCI) ima najvažnije mjesto u pružanju optimalne zdravstvene skrbi bolesnika u akutnoj fazi infarkta miokarda.

U preglednom članku o akutnom koronarnom sindromu (ACS) objavljenom u ovom broju ovog časopisa[1] autori naglašavaju važnost brzog transporta STEMI bolesnika bez nepotrebnih kašnjenja do bolnice koja ima mogućnost izvođenja pPCI te ističu kako je u svakodnevnoj kliničkoj praksi izrazito teško postići ciljno vrijeme od 2 sata koje preporučuju važeće smjernice. Kao značajan doprinos ovoj temi, autori citiraju istraživanje *Rollanda i sur*[2] u kojem je dokazano da je kraće vrijeme od početka simptoma do pPCI povezano sa smanjenim dugoročnim mortalitetom te je naglašena važnost smanjivanja svake od komponenata koje mogu utjecati na kašnjenje u pružanju pravovremene pPCI kod bolesnika sa STEMI. Kao jedan od glavnih razloga nepotrebnih kašnjenja naveden je prijem bolesnika u hitne prijeme bolnica, umjesto direktnog transporta kolima hitne pomoći.

Suvremena kardiološka literatura navodi i mnoge druge značajke koje su važne u organiziranu regionalnih mreža pPCI koje omogućavaju bržu dostupnost reperfuzijske terapije bolesniku sa STEMI.

Cilj ovog preglednog članka je usredotočiti pozornost na farmakoinvazivni pristup kao jednu od komponenti unutar kompleksnog sustava zbrinjavanja bolesnika sa STEMI, prikazati najvažnija klinička istraživanja o farmakoinvazivnoj strategiji i mjesto ovog načina liječenja STEMI u suvremenim smjernicama, uz pokušaj da prihvaćanja koncepta farmakoinvazivnog pristupa i njegovo inkorporiranje u sustav organizirane lokalne mreže pPCI dovede do promjene paradigme o univerzalnoj prednosti pPCI u liječenju svih bolesnika sa STEMI te tako omogući pružanje pravilne i pravodobne reperfuzijske terapije što većem broju bolesnika.

Usporedba primarne perkutane koronarne intervencije s fibrinolitičkom terapijom

Metoda pPCI predstavlja izbor liječenja bolesnika sa STEMI. U posljednjih deset godina pPCI kao način revaskularizacijske strategije zamijenila je fibrinolitičku terapiju. Najveći izazov u organiziranju mreže pPCI je omogućiti njenu dostupnost unutar vremenskih okvira koje diktiraju aktualne smjernice, što je radi raznih strukturnih poteškoća često neizvodivo.

Čvrsti dokazi potkrepljuju favoriziranje PCI kao metode izbora za postizanje reperfuzije u STEMI. Najčešće citirana je metaanaliza *Keeley i sur*[3] koja je uključila 23 randomizirana istraživanja (RCT prema engl. randomized clinical trials) o usporedbi fibrinolize i pPCI u STEMI. Metoda pPCI u odnosu na fibrinolitičku terapiju značajno smanjuje ukupnu kratkoročnu smrtnost (7% naspram 9%), nefatalni reinfarkt (3% naspram 7%), moždani udar (1% naspram 2%) te u zajednički ishod od smrti, nefatalnog reinfarkta te moždanog udara (8% naspram 14%), a bolji rezultati pPCI su perzistirali i na dugoročnom praćenju.

Huyn i sur[4] su 2009. objavili noviju metaanalizu usporedbe pPCI i fibrinolitičke terapije koja osim 23 RCT uključuje i 32 opservacijske studije. Opservacijske studije obuhvaćaju puno veći broj bolesnika i time su sveobuhvatnije i realnije predstavljaju svakodnevnu praksu. U citiranoj metaanalizi u analiziranim opservacijskim studijama je bilo uključeno 180.877 bolesnika, a u 23 randomizirana klinička istraživa-

most important goal in the treatment of patients with STEMI, while the good organization of the primary percutaneous coronary intervention (pPCI) network has the most important role in providing optimal health care to patients in the acute phase of myocardial infarction.

In the review article on acute coronary syndrome (ACS) published in this issue of this journal[1] authors emphasize the importance of quick transport of STEMI patients without unnecessary delay to a hospital that is capable of performing pPCI and emphasize that in everyday clinical practice it is extremely difficult to achieve the target time of 2 hours as recommended by applicable guidelines. A significant contribution to this topic is given by the authors who cite the trial of *Rolland and et al*[2] in which they proved that a shorter time from the onset of symptoms to pPCI is associated with reduced long-term mortality and emphasized the importance of reducing each of the components that can affect the delay in providing timely pPCI in patients with STEMI. As one of the main reasons of unnecessary delays is that the patients are admitted to the emergency departments of hospitals, instead of direct emergency medical service transportation.

Modern cardiology literature also mentions many other features that are important in organizing regional pPCI networks that allow faster access to reperfusion therapy in patients with STEMI.

The aim of this review article is to draw attention to the pharmacoinvasive approach as one of the components within a complex system of management of patients for STEMI, show the most important clinical trials on pharmacoinvasive strategy and importance of this treatment modality of STEMI in contemporary guidelines, with an attempt to cause the acceptance of the concept of pharmacoinvasive approach and its incorporation into system of organized local pPCI network to change the paradigm on universal benefit of pPCI in the treatment of all patients with STEMI, thus enabling the provision of proper and timely reperfusion therapy to as many patients as possible.

Comparison of primary percutaneous coronary intervention with fibrinolytic therapy

The method pPCI represents the treatment of choice for patients with STEMI. In the last ten years pPCI as a revascularization strategy has replaced the fibrinolytic therapy. The greatest challenge in organizing the pPCI network is to make it available within the time frame specified by current guidelines, which is often not feasible due to a variety of structural problems.

Strong evidence supports favoring PCI as the method of choice for achieving reperfusion in STEMI. The meta-analysis of *Keeley et al*[3] included 23 randomized clinical trials (RCT) on comparison of fibronolysis and pPCI in STEMI. The pPCI method compared to fibrinolytic therapy significantly reduces the overall short-term mortality (7% vs. 9%), nonfatal reinfarction (3% vs. 7%), stroke (1% vs. 2%), and the common outcome of death, nonfatal reinfarction and stroke (8% versus 14%), while better results of pPCI persisted in long-term follow-up.

In 2009, *Huyn et al*[4] publicized more recent meta-analysis of comparison of pPCI and fibrinolytic therapy that in addition to 23 RCT also included 32 observational studies. Observational studies include a much larger number of patients and are thus more comprehensive and more realistically represent the daily practice. The cited meta-analysis, that is, the analyzed observational studies included 180,877 patients in 23 randomized clinical trials included a total of 8140

nja ukupno 8.140 bolesnika. Važnost uključivanja opservacijskih istraživanja u ovu metaanalizu leži i u činjenici da su randomizirana istraživanja provedena od strane vrhunskih interventinih kardiologa u vrhunskim centrima, u njih se uključuju bolesnici koji su mlađi i imaju manje komorbiditeta nego bolesnici uključeni u registre koji uključuju i podatke za bolesnike kojima je pPCI rađena i od strane operatera i centara s manjim volumenom i potencijalno lošijim ishodima. I u ovoj metaanalizi je pPCI u usporedbi s fibrinolitičkom terapijom povezana s kratkoročnim smanjenjem smrtnosti, ponovnog infarkta i moždanog udara i u RCT i u opservacijskim studijama. Dugoročno smanjenje ponovnog infarkta i smrtnosti dokazano je samo u RCT, a u opservacijskim studijama nije bilo razlike u dugoročnom smanjenju smrtnosti i reinfarciranja između pPCI i fibrinolitičke terapije.

Postoje podaci u literaturi da fibrinolitička terapija primijenjena u ranoj fazi STEMI unutar 2 sata od početka bolova može imati i bolje kliničke rezultate od pPCI. U studiji ASSENT 3 približno 25% bolesnika koji su dobili fibrinolitičku terapiju unutar prvog sata od početka tegoba nisu imali nekrozu miokarda mjerenjem vrijednosti kardiospefičnih enzima, što je je nazvano "abortiranim" infarktom miokarda[5,6]. U studiji PRAGUE-2 registriran je trend koji favorizira fibrinolitičku terapiju u odnosu na pPCI, ukoliko je bila primijenjena unutar 3 sata od početka simptoma[7], a identičan trend je primijećen i u bečkom STEMI registru[8]. Hospitalna smrtnost u bolesnika liječenih fibrinolitičkom terapijom koja je primijenjena unutar 2 sata od početka simptoma u odnosu na bolesnike liječene pPCI iznosila je 5,1% naspram 7,8%. U studiji CAPTIM kod bolesnika kod kojih je fibrinolitička terapija primijenjena prehospitalno unutar 2 sata od početka simptoma registrirana je manja smrtnost nakon 30 dana, nego kod bolesnika randomiziranih na pPCI (2,2% naspram 5,7%)[9].

Što jest, a što nije farmakoinvazivni pristup?

Liječenje metodom perkutane koronarne intervencije (PCI) nakon fibrinolitičke terapije u STEMI može se obavljati u različitim kliničkim situacijama, izrazi koji se koriste u literaturi su često zbunjujući i u slučaju da nisu jasno definirani mogu otežati razumijevanje rezultata istraživanja u kojima se koriste. Stoga je važno definirati ove situacije, njihove indikacije i po čemu se razlikuju od farmakoinvazivne strategije. Kliničke situacije koje treba razlikovati od farmakoinvazivnog pristupa uključuju rescue PCI, facilitiranu PCI te kasnu PCI učinjenu nakon više od 24 sata od primijenjene fibrinolitičke terapije, bilo da je ona rađena rutinski ili nakon spontane ili dokumentirane ishemije.

Dauerman i Sobel[10] su prvi upotrijebili izraz "farmakoinvazivna rekanalizacija" koja se definira kao farmakološka reperfuzija fibrinolitičkom terapijom nakon koje slijedi odgođena koronarografija i PCI. Danas farmakoinvazivna strategija predstavlja vrstu reperfuzijske terapije koja uključuje inicijalnu primjenu pune doze fibrinolitičke terapije nakon koje slijedi rutinska invazivna obrada i po potrebi PCI u vremenskom intervalu od 3 do 24 sata nakon primjene fibrinolitičkog lijeka.

Rescue PCI je intervencija učinjena obično 60 do 120 minuta nakon neuspješne fibrinolitičke terapije u bolesnika s perzistiranjem simptoma, znakovima oštećenja miokarda ili okludiranom koronarnom krvnom žilom. Uspješnost rekanalizacije fibrinolitičkom terapijoim se ne može pouzdano procijeniti neinvazivnim metodama, ali općenito prihvaćene indikacije za rescue PCI su rezolucija ST-segmenta za manje

patients. The importance of the inclusion of observational studies in this meta-analysis lies in the fact that randomized trials were conducted by top interventional cardiologists in top centers, they also include patients who are younger and have less comorbidities than patients included in the registries that also include data for patients who underwent pPCI by operators and in lower volume centers and with potentially worse outcomes. pPCI is in comparison with fibrinolytic therapy in this meta-analysis also associated with a short-term reduction in mortality, reinfarction and stroke both in RCTs and observational studies. Long-term reduction in reinfarction and mortality has been proven only in RCT, and there was no difference in long-term reduction in mortality and reinfarction between pPCI and fibrinolytic therapy in observational studies.

There are data in the literature that fibrinolytic therapy administered in the early stage of STEMI within 2 hours from the onset of pains may have better clinical results than pPCI. The study 3 ASSENT shows that approximately 25% of patients who received fibrinolytic therapy within the first hour from the onset of the discomforts did not have myocardial necrosis by measuring the values of cardiac specific enzymes, which is referred to as "aborted" myocardial infarction[5,6]. The study PRAGUE 2 reported a trend that prefers fibrinolytic therapy rather than pPCI, if it is used within 3 hours from the onset of symptoms[7], and the identical trend has been noticed in the Vienna STEMI registry[8]. In-hospital mortality in patients treated with thrombolytic therapy, which is administered within 2 hours from the onset of symptoms compared to patients treated by pPCI was 5.1% versus 7.8%. The study CAPTIM in patients in whom fibrinolytic therapy was used prehospitally within 2 hours from the onset of symptoms reported a lower mortality after 30 days than in patients randomized to pPCI (2.2% vs. 5.7%)[9].

What is and what is not a pharmacoinvasive approach?

The treatment by using the method of percutaneous coronary intervention (PCI) after fibrinolytic therapy in STEMI may be performed in a variety of clinical situations. The terms used in the literature are often confusing and in case when they are not clearly defined they can make it difficult to understand the results of the trials in which they are used. It is therefore important to define these situations, their indications and how they differ from pharmacoinvasive strategy. Clinical situations that should be distinguished from the pharmacoinvasive approach include rescue PCI, facilitated PCI and delayed PCI performed after more than 24 hours following the fibrinolytic therapy, no matter whether it was done routinely or after spontaneous or documented ischemia.

Dauerman and Sobel[10] were the first who used the term "pharmacoinvasive recanalization" which is defined as a pharmacological reperfusion with fibrinolytic therapy to be followed by delayed coronary angiography and PCI. Today, pharmacoinvasive strategy is a kind of reperfusion therapy involving initial application of the full dose of fibrinolytic therapy followed by routine invasive treatment and, if necessary, PCI in the time interval from 3 to 24 hours after administration of the fibrinolytic drug.

Rescue PCI is the intervention usually performed between 60 and 120 minutes after unsuccessful fibrinolytic therapy in patients with persisting symptoms and signs of myocardial damage or occluded coronary blood vessel. There are no reliable non-invasive methods for the reliable assessment of the success of recanalization by administering fibrinolytic

od 50% 90 minuta nakon fibrinolitičke terapije u odvodu u kojem je inicijalno registrirana najviša elevacija te bolesnici koji nakon fibrinolitičke terapije imaju perzistirajuće simptome, razviju kardiogeni šok, hemodinamsku ili električnu nestabilnost. Dvije metaanalize potvrđuju opravdanost PCI u ovim indikacijama[11,12].

Posebno je važno razlikovati farmakoinvazivni pristup od tzv. facilitirane PCI. Ovaj izraz se odnosi se na strategiju u kojoj je unaprijed planirana PCI neposredno nakon inicijalne primjene farmakološke terapije s ciljem poboljšanja koronarne prohodnosti prije zahvata. Primijenjena terapija uključuje punu ili polovičnu dozu fibrinolitika ili inhibitora glikoproteina IIb/IIIa, kao i kombinacije tih dvaju skupina lijekova. Brojne kliničke studije su pokazale da uprkos većoj prohodnosti infarktom zahvaćene arterije na dijagnostičkoj koronarografiji u skupini bolesnika koji su prije intervencije dobivali neki od navedenih lijekova, uredan protok kroz infarciranu žilu se postigao u jednakoj učestalosti kod bolesnika koji su bili randomizirani na facilitiranu PCI u odnosu na bolesnike randomizirane na pPCI. Suprotno očekivanjima, pokazalo se da ovakav pristup čak šteti bolesnicima i to ne samo zbog višeg rizika od krvarenja što se moglo očekivati, nego i od značajno višeg rizika od ishemijskih komplikacija. *Keeley i sur*[13] su objavili pregled koje je obuhvatio 17 kliničkih istraživanja koja su uspoređivala facilitiranu PCI naspram pPCI, od čega devet s inhibitorima glikoproteina IIb/IIIa, šest s fibrinoliticima i dva s kombinacijom fibrinolitika i inhibitora glikoproteina IIb/IIIa. Facilitirana PCI je dovela do povećanja kratkoročnog mortaliteta za 38%, reinfarkta za 83%, rekurentne ishemije koja je zahtjevala hitnu revaskularizaciju za 218% i za 48% porast velikih krvarenja. Objašnjenja ovih nepovoljnih kliničkih događanja su vjerojatno u tome da PCI rađena vrlo rano nakon fibrinolize pogoršava krvarenja i na ubodnom mjestu i intrakranijska krvarenja, reperfuzijsku ozljedu miokarda, krvarenja u sam miokard, a porast ishemijskih komplikacija se objašnjava dokazima da fibrinolitička terapija potiče aktivaciju trombocita i time povećava rizik rekurentne ishemije i reinfarkta[14].

Najvažnija klinička istraživanja na području farmakoinvazivne strategije

SIAM-3

Ukupno 197 bolesnika sa STEMI koji su dobili fibrinolitičku terapiju reteplazom bilo je randomizirano na dva pristupa: grupu koja je transferirana unutar šest sati nakon trombolize radi invazivne obrade i PCI (medijan 3,5 sata) i na grupu kojoj je rađena elektivna PCI nakon dva tjedna[15]. Grupa s ranim invazivnim pristupom imala je značajno manje nepovoljnih kardijalnih događanja nego grupa liječena konzervativnijim pristupom. Nakon šest mjeseci u grupi s ranim invazivnim pristupom bilo je značajno smanjenje zajedničkog primarnog cilja koju su činili ukupna smrtnost, reinfarkt, revaskularizacija, rekurentni ishemijski događaji (25,6% naspram 50,6%; p=0,001), a ova razlika je prvenstveno uzrokovana smanjenjem ishemijskih događanja (4,9% naspram 28,4%; p=0,001), više nego smanjenjem smrtnosti i reinfarkta (7,3% naspram 13,6%; p=0,146). Kako su svi bolesnici bili invazivno liječeni nakon dva tjedna, ova studija nije ispitivala ulogu selektivnog invazivnog pristupa te više daje odgovor o koristi ranog invazivnog pristupa u bolesnika liječenih fibrinolitičkom terapijom.

therapy, but the generally accepted indications for rescue PCI are ST-segment resolution by less than 50% 90 minutes after fibrinolytic therapy in the discharge where the highest elevation was initially registered and the patients who following the fibrinolytic therapy have persistent symptoms develop cardiogenic shock, hemodynamic or electrical instability. The two meta-analyses confirm the justification of PCI in these indications[11,12].

It is particularly important to distinguish between the pharmacoinvasive approach and the so-called facilitated PCI. This term refers to a strategy where PCI was planned in advance immediately after the initial administration of pharmacological therapy aimed at improvement of coronary patency before the procedure. The administered therapy includes a full or a half-dose fibrinolytic drugs and glycoprotein IIb/IIIa inhibitors, as well as the combinations of these two classes of drugs. Numerous clinical studies have shown that despite the greater myocardial infarct related artery patency in the diagnostic coronary angiography in a group of patients who received some of these drugs before the intervention, the orderly flow through the infarcted vessel was achieved in the same incidence in patients who were randomized to facilitated PCI compared to patients randomized to pPCI. Contrary to the expectations, it was proved that this approach even harmed patients not only due to a higher risk of bleeding as expected, but also due to a significantly higher risk of ischemic complications. *Keeley et al*[13] have published a review including 17 clinical trials that compared the facilitated PCI versus pPCI, of which nine with glycoprotein IIb/IIIa inhibitors, six with fibrinolytic drugs and two with a combination of fibrinolytic drugs and glycoprotein IIb/IIIa inhibitors. The facilitated PCI has led to an increase in short-term mortality by 38%, reinfarction by 83%, recurrent ischemia which required urgent revascularization by 218 % and an increase in major bleeding 48%. The explanations for these adverse clinical events are probably that PCI performed very soon after fibrinolysis worsens bleeding both at the injection site and intracranial hemorrhage, myocardial reperfusion injury, bleeding in the myocardium itself, while the increase in ischemic complications is explained by the evidence that fibrinolytic therapy stimulates platelet activation thereby increasing the risk of recurrent ischemia and reinfarction[14].

The most important clinical trials in the field of pharmacoinvasive strategy

SIAM-3

A total of 197 patients with STEMI who received fibrinolytic therapy by reteplase were randomized to two arms: a group that was transferred within six hours after thrombolysis for invasive treatment and PCI (median 3.5 hours) and a group that underwent elective PCI after two weeks[15]. The group with early invasive approach had a significantly fewer adverse cardiac events than the group treated by conservative therapy. After six months, the group with early invasive approach recorded a significant reduction in joint primary endpoint composite of total mortality, reinfarction, revascularization, recurrent ischemic events (25.6% vs. 50.6%; p=0.001), and this difference is primarily caused by a reduction of ischemic events (4.9% vs. 28.4%; p = 0.001) more than by reduction in mortality and reinfarction (7.3% vs. 13.6%; p=0.146). Since all patients were invasively treated after two weeks, this study did not examine the role of selective invasive approach and it rather gives the answer concerning the benefits of early invasive approach in patients treated with fibrinolytic therapy.

GRACIA-1

U studiji GRACIA-1[16] 500 bolesnika sa STEMI liječenih fibrinolitičkom terapijom bilo je randomizirano na rutinsku invazivnu strategiju unutar 24 sata nakon fibrinolize i na grupu bolesnika kod kojih je PCI rađena u slučaju dokumentirane ishemije (konzervativni pristup). U konzervativno liječenoj skupini koronarografija je učinjena u 21% bolesnika. U invazivnoj skupini je revaskularizirano 83% bolesnika, a u konzervativnoj 20%. Zajednički primarni cilj su koji su činili ukupna smrtnost, reinfarkt i revaskularizacija nakon 12 mjeseci praćenja se javio u 21% bolesnika u konzervativnoj, a u 9% u invazivnoj skupini bolesnika (p=0,0008), prvenstveno poradi razlike u revaskularizacijskim procedurama između dvije skupine. Postojao je trend prema smanjenju mortaliteta i reinfakta, ali bez postizanja statističkog značaja. Ova studija podržava ranu neselektivnu intervenciju u bolesnika liječenih fibrinolitičkom terapijom.

CAPITAL-AMI

U ovoj je studiji 170 bolesnika liječenih fibrinolitičkom terapijom bilo randomizirano na rutinsku PCI bez odlaganja i na skupinu bolesnika kod koje je rađena ili rescue PCI ili PCI koja je bila klinički indicirana[17]. U konzervatvno liječenoj skupini 67% bolesnika je upućeno na invazivnu obradu, a u 50% bolesnika iz ove skupine je učinjena i PCI, uključujući i 14% rescue PCI. Zajednički primarni cilj koji su činili ukupna smrtnost, reinfarkt, rekurentna nestabilna ishemija i moždani udar nakon 6 mjeseci praćenja je smanjen primjenom farmakoinvazivne strategije (24,4% naspram 11,6%; p=0,04), i to zbog rekurentne ishemije koja je uključivala i reinfarkt (20,7% naspram 8,1%; p=0,03).

WEST

U studiji su 304 bolesnika randomizirana u 3 skupine: samo fibrinoliza (n=100), fibrinoliza i PCI unutar 24 sata (n=104) i pPCI (n=100)[18]. U 60% bolesnika u skupini koja je liječena fibrinolizom učinjena je revaskularizacija tijekom iste hospitalizacije, od toga 14% kao rescue PCI. Nije bilo značajne razlike u zajedničkom primarnom cilju (mortalitet, reinfarkt, srčano popuštanje, kardiogeni šok, refraktorna ishemija, ventrikularne aritmije). Bolesnici liječeni fibrinolizom imali su statistički značajno veći mortalitet i reinfarkt (13%) u odnosu na bolesnike liječene farmakoinvazivnim pristupom (6,7%) i pPCI (4%). Kako u posljednje dvije skupine nije postojala statistički značajna razlika u učestalosti mortaliteta i reinfarkta, autori su zaključili da farmakoinvazivni pristup predstavlja izvrstan način liječenja koji se ne razlikuje od pPCI učinjene pravovremeno u centrima visokog volumena.

CARESS-AMI

U ovoj studiji je 600 bolesnika nakon što su primili pola doze reteplaze, abciximab, heparin i acetilsalicilatnu kiselinu randomizirano na farmakoinvazivni pristup koji je uključivao neposredan transport u tercijarni centar radi PCI te na grupu koja je ostajala u lokalnoj bolnici i transportirana u tercijarni centar u slučaju perzistentne elevacije ST-segmenta ili kliničkog pogoršanja[19]. U konzervativno liječenoj skupini bolesnika koronarografija je učinjena u 36% bolesnika, a PCI u 30%. Primarni cilj (kombinacija smrti, reinfarkta i refrakterne ishemije) nakon 30 dana praćenja registriran je u 13 pacijenata (4,4%) u farmakoinvazivnoj skupini naspram 32 bolesnika (10,7%) u konzervatnoj skupini. (p=0,005), kao posljedica smanjenja refraktorne ishemije. Glavni nedostatak

GRACIA-1

In the trial GRACIA-1[16] 500 STEMI patients treated with fibrinolytic therapy were randomized to routine invasive strategy within 24 hours after fibrinolysis and to the group of patients who underwent PCI in case of documented ischemia (conservative approach). In the conservatively treated group of patients, coronary angiography was performed in 21% of patients. 83% of patients were revascularized in the invasive group, and 20% in the conservative group. Common primary endpoint composite of all-cause mortality, reinfarction and revascularization after 12 months of follow-up was found in 21% of patients in a conservative, and in 9% of patients in the invasive group (p=0,0008), primarily due to a difference in revascularization procedures between the two groups. There was a downward trend of mortality and reinfarction, but without reaching statistical significance. This study supports an early non-selective intervention in patients treated with fibrinolytic therapy.

CAPITAL-AMI

In this study, 170 patients treated with fibrinolytic therapy were randomized to routine PCI without delay and to a group of patients who underwent either rescue PCI or PCI, which was clinically indicated[17]. In conservatively treated group, 67 % of patients were referred to invasive treatment, and 50% of patients in this group underwent PCI, including 14% that underwent rescue PCI. Common primary endpoint composite of all-cause mortality, reinfarction, recurrent unstable ischemia and stroke at 6 months follow-up was reduced by applying pharmacoinvasive strategy (24.4% vs. 11.6%; p = 0.04), due to recurrent ischemia that also involved reinfarction (20.7% vs. 8.1%; p = 0.03).

WEST

In this study 304 patients were randomized to 3 groups: only fibrinolysis (n=100), fibrinolysis and PCI within 24 hours (n=104) and pPCI (n=100)[18]. 60% of patients in the group treated with fibrinolysis underwent revascularization during the same hospitalization, of whom 14% underwent rescue PCI. There was no significant difference in the common primary endpoint (mortality, reinfarction, heart failure, cardiogenic shock, refractory ischemia, ventricular arrhythmias). Patients treated with fibrinolysis had significantly higher mortality and reinfarction (13%) compared to the patients treated by pharmacoinvasive approach (6.7%) and pPCI (4%). Since in the last two groups there was no statistically significant difference in the incidence of mortality and reinfarction, the authors concluded that the pharmacoinvasive approach provides an excellent method of treatment that is not different from pPCI performed promptly in high volume centers.

CARESS-AMI

In this study, 600 patients after having received a half-dose of reteplase, abciximab, heparin and acetylsalicylic acid were randomized to pharmacoinvasive approach that included a direct transport to a tertiary center for PCI, and to a group that stayed at a local hospital and was transported to a tertiary center in case of persistent ST-segment elevation or clinical impairment[19]. In the conservatively treated group of patients, coronary angiography was performed in 36% and PCI in 30% of patients. The primary endpoint (a combination of death, reinfarction and refractory ischaemia) at 30 days follow-up was registered in 13 patients (4.4%) in pharamacoinvasive group versus 32 patients (10.7%) in the conservative

studije je u činjenici da je primijenjena polovična doza fibrinolitika u kombinaciji s inhibitorom GP IIb/IIIa i heparinom, što nije klasična fibrinolitička terapija.

TRANSFER AMI

U ovoj studiji su 528 bolesnika randomizirani na ranu PCI unutar 4 sata nakon fibrinolitičke terapije (rana farmakoinvazivna strategija) i 511 bolesnika na "standardni" način liječena koji je definiran kao rescue PCI u slučaju neuspjele fibrinolize i uz preporuku da se koronarografija učini u svih bolesnika unutar 2 tjedna[20]. Koronarografija i PCI su učinjene u 99% (medijan 2,8h) i 85% bolesnika (medijan 3,2h) u skupini s ranim farmakoinvazivnim pristupom te u 89% (median 32,5h) i 67% bolesnika (median 21,9h) u standardnoj skupini. Primarni zajednički ishod (kombinacija smrti, reinfarkta, kongestivnog srčanog popuštanja, teške rekurentne ishemije i šoka) nakon 30 dana praćenja javio se u 11,0% bolesnika liječenih ranim invazivnim pristupom, a 17,2% u "standarno" liječenoj skupini (p=0,004) i to radi smanjenja rekurentne ishemije i reinfarkta. Radi dizajna studije je vrlo veliki postotak od 89% uključenih bolesnika u standardnoj grupi invazivno obrađen, što je značajno više od broja koji oslikava svakodnevnu rutinsku praksu[21] te u osnovi ovo istraživanje uspoređuje rani i kasni farmakoinvazivni pristup.

NORDISTEMI

Ovaj RCT je uspoređivao strategiju neodložnog transfera radi PCI s pristupom u kojem je PCI indicirana u slučaju dokumentirane ishemije[22]. U studiju je uključeno 266 bolesnika iz ruralnih područja 100-400 kilometara udaljenosti od bolnice s mogućnošću PCI (medijan 158 km) u područjima s etabliranim sistemom prehospitalne fibrinolize, u kojih je očekivani transport do PCI bolnice trajao dulje od 90 minuta. Nakon primjene tenekteplaze, enoksaparina, acetilsalicilatne kiseline i klopidogrela (čak u 57% fibrinolitička terapija je primijenjena prehospitalno), bolesnici su randomizirani na skupinu koja je odmah transportirana u PCI centar i na skupinu koji su nastavili liječenje u matičnoj ustanovi i transportirani radi PCI u slučaju potrebe za rescue PCI ili u slučaju kliničkog pogoršanja. U farmakoinvazivnoj skupini medijan veremena od primjene fibrinolitičke terapije do dolaska u kateteterizacijski laboratorij je iznosio 130 minuta, a PCI je učinjena u 89% bolesnika. U standardno liječenoj skupini rescue PCI je učinjena u 27% bolesnika, a u čak 93% preostalih bolesnika je učinjena invazivna obrada s medijanom od 5,5 dana. U ovoj "konzervativno" liječenoj skupini je PCI učinjena u 71% bolesnika, a u 12% kardiokirurško premoštenje. Kao i u TRANSFER AMI ispitivanju, gotovo svi bolesnici su invazivno obrađeni relativno rano tijekom studije. Primarni zajednički ishod je bila kombinacija smrti, reinfarkta, inzulta i novonastale ishemije u 12 mjeseci i nije se značajno razlikovao među skupinama. Ovakav rezultat je objašnjiv obzirom na agresivan način liječenja bolesnika u konzervativnoj skupini, s vrlo liberalnim i ranim upućivanjem na invazivnu obradu. Autori naglašavaju da je nakon 12 mjeseci praćenja značajno niža učestalost smrti, inzulta i reinfarkta u skupini bolesnika liječenih ranim farmakoinvaziuvnim pristupom (6% naspram 16%; p=0,008).

STREAM

U ovoj je studiji bilo uključeno 1.892 bolesnika sa STEMI unutar 3 sata od početka simptoma, a pPCI se nije mogla

group (p = 0.005), as a consequence of reduction of refractory ischemia. The main disadvantage of the study is the fact that a half-dose of fibrinolytic drugs was administered in combination with GP IIb/IIIa inhibitors and heparin, which is not a classical fibrinolytic therapy.

TRANSFER AMI

In this study, 528 patients were randomized to early PCI within 4 hours after fibrinolytic therapy (early pharmacoinvasive strategy) and 511 patients to the standard treatment defined as rescue PCI in case of failed fibrinolysis and with the recommendation that coronary angiography should be done in all patients within 2 weeks[20]. Coronary angiography and PCI were performed in 99% (median 2.8 h) and 85% of patients (median 3.2 h) in the group with early pharmacoinvasive approach and in 89% (median 32.5 hours) and 67% of patients (median 21.9 h) in the standard group. The common primary endpoint (a combination of death, reinfarction, congestive heart failure, severe recurrent ischemia and shock) after 30 days follow-up occurred in 11.0 % of patients treated by the early invasive approach, and 17.2 % in "standard" treatment group (p = 0.004) due to reduction of recurrent ischemia and reinfarction. The design of the study was the reason why a very high rate of 89% of involved patients was invasively treated in the standard group, which is significantly higher number than the number that reflects the everyday routine practice[21] and basically this study compares the early and late pharmacoinvasive approach.

NORDISTEMI

This RCT compared the strategy of a transfer for PCI with no delay by using the approach where PCI is indicated in the case of documented ischemia[22]. The study included 266 patients from rural areas 100-400 kilometers away from the hospital that is capable of performing PCI (median 158 km) in areas with established system of prehospital fibrinolysis where the expected transport to a PCI hospital lasted over 90 minutes. After tenecteplase, enoxaparin, acetylsalicylic acid and clopidogrel were administered (57% fibrinolytic therapy was applied prehospitally), patients were randomized to a group that was transported to a PCI center with no delay and to a group that continued treatment in the principle institution and transported for PCI in the case of the need for rescue PCI or in the case of clinical impairment. In the pharmacoinvasive group, the time median from the administration of the fibrinolytic therapy to admission to the catheterization lab was 130 minutes, and PCI was performed in 89% of patients. In the group undergoing standard treatment, rescue PCI was performed in 27% of patients and even 93% of the remaining patients underwent invasive treatment with a median of 5.5 days. In this group undergoing conservative treatment, PCI was performed in 71% of patients and 12 % of them underwent coronary artery bypass. As in TRANSFER AMI trial, nearly all patients were treated invasively relatively early during the study. The common primary endpoint was a composite of death, reinfarction, insult and newly occurred ischemia in 12 months and did not differ significantly among the groups. Such a result can be explained considering the aggressive method of treatment of patients in the conservative group with a very liberal and early referral to invasive treatment. The authors emphasize that after 12 months follow-up the incidence of death, insult and reinfarction is significantly lower in the group of patients treated by early pharmacoinvasive approach (6% versus 16%; p = 0.008).

organizirati unutar 60 minuta[23]. Bolesnici su bili randomizirani na pPCI i na fibrinolitičku terapiju tenekteplazom, uz primjenu klopidogrela, enoksaparina i acetilsalicilatne kiseline prije transporta u bolnicu s mogućnosti PCI. Nakon uključivanja 21% planiranih bolesnika, protokol fibrinolitičke terapije je promijenjen tako da je doza tenekteplaze prepolovljena kod bolesnika starijih od 75 godina, jer je u ovoj grupi pregistriran porast intrakranijskih krvarenja. U slučaju neuspješne reperfuzije bolesnici su odmah transportirani radi rescue PCI, a kod ostalih bolesnika je koronarografija učinjena 6 do 24 sata nakon randomizacije. Zajednički primarni cilj (kombinacija smrti, kardijalnog šoka, kongestivnog srčanog popuštanja i reinfarkta) tijekom 30 dana praćenja se javio u 12,4% bolesnika u skupini s farmakoinvazivnim pristupom te u 14,3% u skupini s pPCI (p=0,21). Rescue PCI je učinjena u 36,3% bolesnika liječenih fibrinolizom, a u ostalih bolesnika iz ove skupine je učinjena sa medijanom od 17 h nakon randomizacije. Fibrinoliza je bila povezana s povećanim rizikom intrakranijskog krvarenja (1,0% naspram 0,2%, p=0,04; nakon promjene protokola 0,5% naspram 0,3%, p=0,45). Nije bilo značajne razlike u drugim krvarenjima među skupinama.

Komentar prikazanih rezultata istraživanja

Među prikazanim studijama postoje značajne heterogenosti. Navedena istraživanja se međusobno razlikuju u završnim ciljevima praćenja, postoji varijabilnost u terapijskim strategijama i protokolima, učestalosti učinjene invazivne obrade i PCI u konzervativno liječenim skupinama, učestalosti rescue PCI, vremenima od primjene fibrinolize do rane PCI, vrsti primijenjenih fibrinolitika, učestalosti primjene inhibitora GP IIb/IIIa te značajne razlike u primjeni klopidogrela između invazivno i konzervativno liječenih skupina bolesnika. Postoje velike razlike u načinu definiranja rekurentne ishemije i različite klasifikacije klinički značajnih krvarenja.

Borgia i sur[24] u metaanalizi u koju su uključena sva klinička istraživanja prikazana u ovom članku, osim STREAM studije koja je objavljena tek nedavno, zaključuje da rana rutinska PCI iza fibrinolitičke terapije u bolesnika sa STEMI značajno smanjuje reinfarkt i rekurentnu ishemiju, bez značajnog porasta krvarenja te da koristi ovog pristupa perzistiraju i nakon 6-12 mjeseci, pa stoga zagovaraju rani farmakoinvazivni pristup za sve bolesnike koji iz organizacijskih razloga ne mogu biti liječeni metodom pPCI. *Bogaty*[25] se radi navedenih razlika među istraživanjima odlučuje svoju analizu nazvati sistematskim prikazom RCT, a ne metaanalizom te vrlo oprezno zaključuje da ne postoje dovoljno čvrsti dokazi za donošenje definitivnih zaključaka o optimalnoj učestalosti koronarografije i revaskularizacije nakon fibrinolize niti je li farmakoinvazivna strategija superiornija od pravilnog selektivnog pristupa vođenog dokumentiranom ishemijom. Ranija metaanaliza *Wijeysundera i sur*[26] uključivala je pet do tada objavljenih RCT, a autori su zaključili da rana rutinska invazivna strategija nakon fibrinolitičke terapije značajno smanjuje smrtnost i reinfarkt, ali također i da rezultati metaanalize mogu samo generirati hipotezu da je rutinska invazivna strategija iza fibrinolitičke terapije povezana s boljim kliničkim ishodima, ali nisu dovoljni za definitivne preporuke.

U sustavnom pregledu RCT u ovom članku nije navedena pojavnost klinički značajnih krvarenja jer su sve navedene studije uključene u metaanalizu *Borgia i sur*[24] koja pokazuje da nema povišenog rizika krvarenja u bolesnika s farmakoinvazivnim pristupom u odnosu na bolesnike liječene sa

STREAM

1,892 patients with STEMI were included in this study within 3 hours from the onset of symptoms, while pPCI could not be organized within 60 minutes[23]. Patients were randomized to pPCI and fibrinolytic therapy by administering tenecteplase clopidogrel, enoxaparin and acetylsalicylic acid prior to the transport to a hospital capable of performing PCI. After including 21% of the planned patients, fibrinolytic therapy protocol was changed so that the dose tenecteplase was halved in patients over 75 years of age, because an increase in intracranial hemorrhage was recorded in this group. In case of unsuccessful reperfusion, patients are immediately transported for rescue PCI, and other patients underwent coronary angiography 6 to 24 hours after randomization. Common primary endpoint (a composite of death, cardiac shock, congestive heart failure and reinfarction) at 30 days follow-up was found in 12.4% of patients in the group with pharmacoinvasive approach and in 14.3 % of patients in the group with pPCI (p =0.21). Rescue PCI was performed in 36.3% of patients treated by fibrinolysis, and other patients in this group underwent it with a median of 17 h after randomization. Fibrinolysis was associated with an increased risk of intracranial hemorrhage (1.0% vs. 0.2%, p = 0.04; after changing the protocol 0.5% vs. 0.3%, p=0.45). There were no significant differences in other bleeding among the groups.

Comment to the presented trial results

Significant heterogeneities exist among the presented studies. The above trials differ from each other in the final follow-up objectives, there is variability in therapeutic strategies and protocols, frequency of performed invasive management and PCI in the conservatively treated groups, frequency of rescue PCI, times from the early fibrinolysis to early PCI, type of administered fibrinolytic drugs, frequency of the use of GP IIb/IIIa inhibitors, and significant differences in the use of clopidogrel between invasively and conservatively treated groups of patients. There are major differences in the way of defining recurrent ischemia and different classification of clinical major bleeding.

Borgia et al[24] in a meta-analysis which included all clinical trials presented in this article, except for STREAM study, which has been published only recently conclude that early routine PCI following the fibrinolytic therapy in STEMI patients significantly reduces reinfarction and recurrent ischemia, with no major increase in bleeding and the benefits of this approach persist even after 6-12 months, and therefore they advocate early pharmacoinvasive approach for all patients who for organizational reasons cannot be treated by using the PCI method. For the differences among the trials specified above, *Bogaty*[25] decides to call its analysis a systematic review RCT, not a meta-analysis and very cautiously concludes that there is no evidence strong enough for reaching definitive conclusions about the optimum frequency of coronary angiography and revascularization after fibrinolysis or whether pharmacoinvasive strategy is superior to the proper selective documented ischemia-guided approach. An earlier meta-analysis of *Wijeysunder et al*[26] included up to five previously published RCTs, and the authors concluded that early routine invasive strategy after fibrinolytic therapy significantly reduces mortality and reinfarction, but also that the results of the meta-analysis can only generate a hypothesis that a routine invasive strategy after fibrinolytic thera-

standardnom terapijom, identično zaključku *Wijeysundera*[26].

Povišen rizik ishemijskih i hemoragijskih komplikacija koji je diskreditirao facilitiranu PCI ne postoji u studijama s farmakoinvazivnim pristupom. Pravovremeno i dobro odabrano vrijeme kada je PCI učinjena (u novijom istraživanjima između 3 i 6 h nakon primjene fibrinolize) izbjegava se rizik krvarenja, a uporabom suvremene antitrombocitne i antikoagulacijske terapije izbjegava se rizik reokluzije, rekurentne ishemije i tromboze stenta u protrombotskom periodu nakon primjene fibrinolitika. Jedino je u STREAM studiji registrirano povećanje rizika intrakranijskog krvarenja, ali ono je nakon korekcije doze tenekteplaze praktički neznatno.

Studija STREAM koja je nedavno objavljena i nije uključena u navedene metaanalize bila je dizajnirana po trenutno važećim europskim smjernicama o liječenju bolesnika sa STEMI. Ovo je istraživanje definitivno etabliralo farmakoinvazivnu strategiju i pokazalo da farmakoinvazivna strategija koju čine fibrinolitička terapija uz istovremenu primjenu suvremene antitrombocitne i antikoagulacijske terapije (primijenjena unutar 3 sata od nastanka simptoma, u bolesnika kod kojih nije moguće učiniti pPCI unutar jednog sata od prvog kontakta sa sustavom organizirane medicinske skrbi, nakon koje slijedi pravovremena invazivna obrada) jednako učinkovita kao pPCI.

Rezultati iz Zapadne Slavonije

Od srpnja 2010. do srpnja 2011. u OB "Dr. Josip Benčević" Slavonski Broj bilo je liječeno ukupno 128 bolesnika sa STEMI. U to vrijeme liječenje metodom pPCI bilo je dostupno samo tijekom radnog vremena u prvoj smjeni te je zbog ovih organizacijskih ograničenja u svakodnevni rad uveden farmakoinvazivni pristup. Intrahospitalni letalitet u kod bolesnika liječenih pPCI iznosio je 3%, a kod bolesnika liječenih farmakoinvazivnim pristupom 5%. Zaključili smo da je u područjima gdje se pPCI ne može organizirati u vremenski prihvatljivim okvirima, urgentna PCI unutar 24 sata od fibrinolitičke terapije gotovo jednako siguran i efikasan način reperfuzije[27]. U ovom broju časopisa prikazali smo i protokol zbrinjavanja bolesnika sa STEMI u Zapadnoj Slavoniji u koju smo u naš svakodnevni rad implementirali farmakoinvazivni pristup[28].

Što kažu smjernice?

U najnovnijim europskim[29] i američkim[30] smjernicama o liječenju bolesnika sa STEMI opcija liječenja pPCI ostaje preferirana metoda reperfuzije ukoliko se može obaviti pravovremeno od strane iskusnih operatera. Preporučeni način trijaže bolesnika predstavlja uključivanje sustava hitne medicinske pomoći s izravnim transportom bolesnika u bolnicu koja ima mogućnost liječenja metodom pPCI.

Obje smjernice u algoritmu imaju odvojene preporuke ovisno tome da li bolnica u kojoj se bolesnik prezentira ima ili nema mogućnost pPCI. Za bolesnike koji se prezentiraju u bolnicu s mogućnošću izvođenja PCI ciljno vrijeme od prvog kontakta sa sustavom organizirane medicinske skrbi (FMC, first medical contact) do reperfuzije iznosi do 60 minuta u europskim, dok američke smjernice dopuštaju 90 minuta.

Nešto su značajnije razlike u slučaju da bolesnik sa STEMI dolazi u bolnicu bez mogućnosti pPCI. U europskim smjernicama se uvode kategorije poželjnog i prihvatljivog vremena do reperfuzije te se bolesnici kategoriziraju ovisno i o vre-

py is associated with better clinical outcomes, but are not sufficient for definitive recommendations.

The systematic review of RCT in this article does not mention the incidence of major bleeding because all the mentioned studies included in the meta-analysis *Borgia et al*[24] show that there is no increased risk of bleeding in patients with pharmacoinvasive approach compared to the patients treated with standard therapy, identical to the conclusion reached by *Wijeysunder*[26].

Increased risk of ischemic and hemorrhagic complications, which discredited facilitated PCI does not exist in the studies with pharmacoinvasive approach. Timely and well-selected time when PCI was performed (in more recent studies between 3 and 6 h after administration of fibrinolysis) avoids the risk of bleeding, and the use of modern antiplatelet and anticoagulant therapy avoids the risk of reocclusion, recurrent ischemia and stent thrombosis in the prothrombotic period following the administration of fibrinolytic drugs. It is only the STREAM study where an increase in the risk of intracranial hemorrhage was recorded, but it is practically negligible after the correction of the tenecteplase dose.

The STREAM study that has been recently published and is not included in the above meta-analyses was designed according to the current European guidelines on the treatment of patients with STEMI. This trial has definitely established the pharmacoinvasive strategy and showed that pharmacoinvasive strategy consisting of fibrinolytic therapy with concomitant use of modern antiplatelet and anticoagulant therapy (administered within three hours from the onset of symptoms in patients who are unable to undergo pPCI within one hour from the first medical contact, to be followed by timely invasive treatment) is as effective as pPCI.

Results from Western Slavonia

From July 2010 to July 2011 a total of 128 patients with STEMI were treated in the General Hospital "Dr Josip Benčević" in Slavonski Brod. During that period, the treatment by applying the pPCI method was accessible only during the working hours in the first shift, so a pharmacoinvasive approach was introduced in the daily work due to such organizational limitations. Intra-hospital lethality in patients treated by pPCI was 3%, and in patients treated by pharmacoinvasive approach it was 5%. We concluded that in the areas where pPCI cannot be organized in acceptable timeframes, urgent PCI within 24 hours from the moment of fibrinolytic therapy is also equally safe and efficient method of reperfusion[27]. In this issue of the journal we have presented a protocol of management of patients with STEMI in Western Slavonia, whereas we have implemented a pharmacoinvasive approach in this protocol in our daily work[28].

What do the guidelines suggest?

According to the most recent European[29] and American[30] guidelines on the treatment of patients with STEMI, pPCI remains the preferred method of reperfusion if it can be performed timely by experienced operators. The recommended way of triage of patients represents the involvement of the emergency medical service with direct transportation of patients to a hospital capable of treating patients applying the pPCI method.

Both guidelines in the algorithm have separate recommendations depending on whether the hospital where the patient

menu koje je prošlo od FMC do reperfuzije. Tako europske smjernice preporučuju da je poželjno vrijeme od FMC do pPCI unutar 90 minuta, a prihvatljivo do 120 minuta, a za bolesnike s ranom prezentacijom (vrijeme od početka bolova do FMC manje od 120 minuta) je poželjno vrijeme <60 minuta, a prihvatljivo do 90 minuta. Za sve bolesnike za koje pPCI nije moguće izvesti unutar 120 minuta je indicirana tromboliza unutar 30 minuta od FMC, poželjno prehospitalno i unutar prvih 120 minuta od početka simptoma. Sve bolesnike liječene trombolizom treba transportirati u centar s mogućnošću pPCI bez odlaganja, neovisno o uspjehu fibrinolitičke terapije (klasa IA), gdje će se donijeti odluka da li će se odmah izvršiti rescue PCI ukoliko neme znakova reperfuzije ili rutinska angiografija u vremenskom roku od 3 do 24 sata ako je fibrinoliza bila uspješna.

U američkim smjernicama za bolesnike koji se prezentiraju u ustanovi koja nema mogućnost izvođenja pPCI uvodi se pojam DIDO (engl. door-in-door-out time) i napominje da je vrijeme ≤30 minuta povezano s nižim hospitalnim mortalitetom. Metoda pPCI se preferira kao način reperfuzije ako se može organizirati unutar 120 minuta. Za sve bolesnike za koje je vrijeme od FMC do pPCI zbog kašnjenja koja se ne mogu izbjeći duže od 120 minuta pristup je identičan kao u europskim smjernicama: indicirana je fibrinoliza unutar 30 minuta od FMC. I američke smjernice preporučuju rutinsku koronarografiju svih bolesnika koji su liječeni fibrinolizom, s time da se za bolesnike u kardijalnom šoku te s teškim akutnim popuštanjem preporuča urgentna invazivna obrada (klasa I preporuka), više ne koriste pojam rescue PCI i za sve ostale bolesnike liječene fibrinolitičkom terapijom rutinska koronarografija ima preporuku klase IIa, preporuča se učiniti ju što je prije moguće, idealno unutar 24 sata, ali ne unutar prva 2 do 3 sata od primjene fibrinolitičke terapije.

Smjernice s obje strane Atlanskog oceana jasno naglašavaju princip da je važnija pravilna i pravodobna primjena jednog od mogućih oblika reperfuzijskog liječenja, od samog izbora terapije.

Zaključak

Farmakoinvazivna strategija obuhvaća dobru trijažu bolesnika na terenu i selektivnu primjenu fibrinolitičke terapije pravilno odabranim bolesnicima nakon koje slijedi neodložan transport bolesnika u PCI centar i organiziranje invazivne obrade unutar 3-24 sata. Treba ju razmotriti kao mogući način reperfuzije u bolesnika sa STEMI kod kojih je fibrinolitičku terapiju moguće započeti unutar tri sata od početka bolova, a očekivano vrijeme do reperfuzije metodom pPCI (vrijeme prolaska žice kroz odgovornu leziju) prelazi dva sata. Ovakav način reperfuzije dovodi do značajnog smanjenja reinfarkta i rekurentne ishemije bez povišenog rizika od krvarenja te ju treba implementirati u regionalne protokole zbrinjavanja bolesnika sa STEMI, čime bi se povećao broj bolesnika kojima je pružena pravilna i pravodobna primjena reperfuzijske terapije.

Recived: 16th Nov 2013
*Address for correspondence: Opća bolnica "Dr. Josip Benčević", Štampareva 42
HR-35000 Slavonski Brod, Croatia
Phone: +385-35-201-685
E-mail: deiti.prvulovic@sb.t-com-hr

is presented is or is not capable of performing pPCI. For patients who are presented in the hospital capable of undertaking PCI, the target time from the first medical contact, FMC to reperfusion is 60 minutes in the European, while the American guidelines allow for 90 minutes.

The differences are somewhat more significant in the case when a patient with STEMI comes to the hospital not capable of undertaking pPCI. The European guidelines introduce the categories of desirable and acceptable time to reperfusion and patients are also categorized depending on the time that has elapsed from FMC to reperfusion. Thus, the European guidelines recommend that the desirable time from FMC to pPCI is 90 minutes and acceptable up to 120 minutes, while for the patients with early presentation (time from onset of pains to FMC less than 120 minutes) the desirable time is < 60 minutes and acceptable time up to 90 minutes. For all patients in whom pPCI cannot be performed within 120 minutes undergo thrombolysis within 30 minutes from the FMC, preferably prehospitally within the first 120 minutes from the onset of symptoms. All patients treated with thrombolysis should be transported to the center capable of undertaking pPCI without delay, regardless of the success of fibrinolytic therapy (class IA), where it will be decided whether rescue PCI will be immediately performed if there are no signs of reperfusion or whether the routine angiography will be performed within the period from 3 to 24 hours if fibrinolysis was successful.

For patients who present to an institution that is not capable of performing pPCI the American guidelines introduce the concept of DIDO (door-in-door-out time) and suggest that the ≤30 minutes time is associated with lower hospital mortality. The pPCI method is a preferred method of reperfusion if it can be organized within 120 minutes. For all patients for whom the time from FMC to pPCI due to delay not to be avoided is longer than 120 minutes, the approach is identical to the European guidelines: fibrinolysis is indicated within 30 minutes from FMC. The American guidelines also recommend routine coronary angiography for all patients treated with fibrinolysis, whereas the patients in cardiac shock and severe acute failure are recommended to undergo emergency invasive treatment (class I recommendation), the term rescue PCI is no longer used and the routine coronary angiography has a class IIa recommendation for all other patients treated with fibrinolytic therapy, whereas it is recommended to be undertaken it as soon as possible, ideally within 24 hours, but not within the first 2-3 hours after the fibrinolytic therapy was performed.

The guidelines on both sides of the Atlantic Ocean clearly emphasize the principle that the proper and timely application of one of the potential forms of reperfusion therapy is more important than a choice of therapy itself.

Conclusion

Pharmacoinvasive strategy encompasses a good triage of patients in the field and selective use of fibrinolytic therapy for properly selected patients to be followed by prompt transportation of patients to a PCI center and organizing invasive treatment within 3-24 hours. It should be considered as a potential method of reperfusion in STEMI patients in whom fibrinolytic therapy can be initiated within three hours from the onset of pains, and the expected time to reperfusion by the pPCI method (time of passage of the guide wire through the responsible lesion) exceeds two hours. This method of reperfusion leads to a significant reduction in rein-

farction and recurrent ischemia without an increased risk of bleeding and should be implemented in regional protocols for management of patients with STEMI, whereby a number of patients receiving proper and timely reprefusion therapy would increase.

Literature

1. Meier P, Lansky AJ, Baumbach A. Almanac 2013: acute coronary syndromes. Cardiol Croat. 2013;8(12):424-434.

2. Rollando D, Puggioni E, Robotti S, et al. Symptom onset-to-balloon time and mortality in the first seven years after STEMI treated with primary percutaneous coronary intervention. Heart. 2012;98:1738-42.

3. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361:13-20.

4. Huynh T, Perron S, O'Loughlin J, et al. Comparison of primary percutaneous coronary intervention and fibrinolytic therapy in ST-segment-elevation myocardial infarction: bayesian hierarchical meta-analyses of randomized controlled trials and observational studies.Circulation. 2009;119(24):3101-9.

5. Taher T, Fu Y, Wagner GS, Goodman SG, et al. Aborted myocardial infarction in patients with ST-segment elevation: insights from the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 Trial Electrocardiographic Substudy. J Am Coll Cardiol. 2004; 44:38-43.

6. Verheugt FW, Gersh BJ, Armstrong PW. Aborted myocardial infarction: a new target for reperfusion therapy. Eur Heart J. 2006;27:901-4.

7. Widimsky P, Budesinsky T, Vorac D.'PRAGUE' Study Group Investigators. Long distance transport for primary angioplasty vs. immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial-PRAGUE-2. Eur Heart J. 2003;24:94-104.

8. Kalla K, Christ G, Karnik R, et al. Vienna STEMI Registry Group. Implementation of guidelines improves standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (VIENNA-STEMI Registry). Circulation. 2006;113:2398-405.

9. Steg PG, Bonnefoy E, Chabaud S, et al. Comparison of Angioplasty, Prehospital Thrombolysis In acute Myocardial infarction (CAPTIM) Investigators. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. Circulation. 2003;108:2851-6.

10. Dauerman HL, Sobel BE. Synergistic treatment of ST-segment elevation myocardial infarction with pharmacoinvasive recanalization. J Am Coll Cardiol. 2003;42:646-51.

11. Collet JP, Montalescot G, Le May M, Borentain M, Gershlick A. Percutaneous coronary intervention after fibrinolysis: a multiple metaanalyses approach according to the type of strategy. J Am Coll Cardiol. 2006;48:1326-35.

12. Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, et al.Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. J Am Coll Cardiol. 2007;49(4):422-30.

13. 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.

14. Stone GW, Gersh BJ. Facilitated angioplasty: paradise lost. Lancet. 2006;367:543-6.

15. Scheller B, Hennen B, Hammer B, et al. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. J Am Coll Cardiol. 2003;42:634-41.

16. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A,et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. Lancet. 2004;364:1045-53.

17. Le May MR, Wells GA, Labinaz M, et al. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). J Am Coll Cardiol. 2005;46:417-24.

18. Armstrong PW. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early Stelevation myocardial infarction Therapy) study. Eur Heart J. 2006,27:1530-8.

19. Di Mario C, Dudek D, Piscione F, et al. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. Lancet 2008, 371:559-568.

20. Cantor WJ, Fitchett D, Borgundvaag B, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med. 2009;360:2705-18.

21. Kaul P, Chang WC, Lincoff AM, et al. Optimizing use of revascularization and clinical outcomes in ST-elevation myocardial infarction: insights from the GUSTO-V trial. Eur Heart J. 2006;27:1198-206.

22. Bohmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and Safety of Immediate Angioplasty Versus Ischemia-Guided Management After Thrombolysis in Acute Myocardial Infarction in Areas With Very Long Transfer Distances Results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction). J Am Coll Cardiol. 2010;55:102-10.

23. Armstrong PW, Gershlick AH, Goldstein P, et al. STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2013;368(15):1379-87.

24. Borgia F, Goodman SG, Halvorsen S, et al. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a metaanalysis. Eur Heart J. 2010;31:2156-69.

25. Bogaty P, Filion KB, Brophy JM. Routine invasive management after fibrinolysis in patients with ST-elevation myocardial infarction: a systematic review of randomized clinical trials. BMC Cardiovascular Disorders.2011;11:34.

26. Wijeysundera HC, You JJ, Nallamothu BK, Krumholz HM, Cantor WJ, Ko DT. An early invasive strategy versus ischemia-guided management after fibrinolytic therapy for ST-segment elevation myocardial infarction: a meta-analysis of contemporary randomized controlled trials. Am Heart J. 2008; 156:564-572, 572.e1-2.

27. Hadžibegović I, Prvulović Đ, Vujeva B, et al. Routine urgent PCI after fibrinolysis versus primary PCI in STEMI patients. 2nd Dubrovnik Cardilogy Highlights - An ESC Update Programme in Cardiology. Final Programme and selected abstracts. Dubrovnik, Croatia, 2011, p.35. http://www.kardio.hr/component/docman/doc_download/57-konacan-program-.html (29.9.2011).

28. Prvulović Đ. Application of pharmacoinvasive strategy in primary percutaneous coronary intervention network in Western Slavonia. Cardiol Croat. 2013;8(12):435-443.

29. Steg G, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569-619.

30. O'Gara PT, Kushner FG, Ascheim DD, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e362-e425.