RECOMMENDATIONS

Recommendations on percutaneous coronary intervention for the reperfusion of acute ST elevation myocardial infarction

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Little information is currently available from the various societies of cardiology on primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI). Since primary PCI is the main method of reperfusion in AMI in many centres, and since of all cardiac emergencies AMI represents the most urgent situation for PCI, recommendations based on scientific evidence and expert experience would be useful for centres practising primary PCI, or those looking to establish a primary PCI programme. To this aim, a task force for primary PCI in AMI was formed to develop a set of recommendations to complement and assist clinical judgment. This paper represents the product of their recommendations.

Percutaneous coronary intervention (PCI) refers to a group of invasive procedures that aim to improve blood flow to the myocardium through the recanalisation of diseased coronary arteries. Interventions currently used in clinical practice include plain old balloon angioplasty (POBA), intracoronary stenting, coronary atherectomy, and thrombectomy.

PCI techniques, in conjunction with appropriate adjunct pharmacological medications, have been developed and studied in specific clinical situations, including acute myocardial infarction (AMI). Several studies have shown that primary PCI is preferable to intravenous thrombolysis for the treatment of AMI.[1–5] However, little information is available on primary PCI for AMI from the various cardiology societies. For example, the European Society of Cardiology (ESC) guidelines on AMI, which have been updated very recently, deal only briefly with PCI, and do not take into account recent developments in technology and medical treatment.[6 7] The new ESC guidelines discuss indications and contraindications for PCI in AMI, and state that PCI is superior to fibrinolysis; however, they do not detail the specificities and technical aspects of primary PCI. Our opinions extend the scope of the official guidelines and provide some additional updated information dedicated to mechanical reperfusion. Recent guidelines on PCI have been published by the American Heart Association/American College of Cardiology (AHA/ACC), but they deal only briefly with AMI.[8] No European recommendations are currently available concerning PCI.

Since primary PCI is the mainstay of reperfusion in AMI in many centres, and since of all cardiac emergencies AMI represents the most urgent situation for PCI, recommendations based on scientific evidence and expert experience would be useful for centres practising primary PCI or those looking to set up a primary PCI programme. Therefore, a group of European interventional cardiologists formed a task force to provide recommendations on this subject. This paper presents the product of their recommendations for all types of PCI in patients with acute ST elevation myocardial infarction (MI). The present recommendations do not deal with pain relief, antiarrhythmic drugs, discharge medications, secondary prevention, rehabilitation, or any other topic that would overlap with the official recommendations of the ESC. They focus mainly on the practical and technical aspects of management within the catheterisation laboratory.

These recommendations are intended for specialists who possess the necessary knowledge, experience, and skills to perform PCI, and who work in environments where the necessary resources and facilities are available; they are intended to complement and assist clinical judgment.

METHODS

The task force comprised eight interventional cardiologists, all based at high volume interventional centres, from eight European countries. A high volume centre is classified as a centre where more than 33 primary angioplasty procedures are performed per year. The task force met in 2002 to produce a set of recommendations on the use of PCI for the treatment of AMI. Where significant

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Abbreviations: ACT, activated clotting time; ACC, American College of Cardiology; AHA, American Heart Association; ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; ERV, emergency revascularisation; Gp, glycoprotein; IMS, initial medical stabilisation; IABP, intra-aortic balloon pump; LV, left ventricular; LVEF, left ventricular ejection fraction; LMWH, low molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; POBA, plain old balloon angioplasty; SVG, saphenous vein graft; TVR, target vessel revascularisation; t-PA, tissue plasminogen activator; UFH, unfractionated heparin.

data have been published after the meeting of the task force, the relevant papers have been referenced in this document. Hence, these recommendations are current as of December 2002.

These recommendations are a product of evidence and experience. Although some of the recommended techniques may be relatively new and largely unsupported by published data, on the basis of experience and current research, they are considered by the panel to represent important new developments.

Where available, evidence from randomised clinical trials was used to formulate these recommendations. However, the fast pace of advances in both technology and adjunctive pharmacotherapy in this area means that complete and reliable supportive data were not always available.

When lack of evidence or experience made it impossible to reach a consensus, discussions identify key points to help the physician through the decision making process.

PCI IN AMI

Indications for PCI in AMI

Background

PCI is an effective procedure for re-establishing coronary artery perfusion in AMI that gives very good short term (six month) and long term (five year) outcomes.[9 10] Where facilities are available, most AMI patients are candidates for PCI.[8] Where facilities are not rapidly available, PCI remains a valid option when thrombolysis is contraindicated or has failed, as well as in patients with cardiogenic shock. A recent review of 23 randomised trials comparing PCI and thrombolytic treatment concluded that PCI is a more effective reperfusion therapy than thrombolysis for treatment of ST segment AMI.[6]

Recommendations

When performed by experienced operators, we strongly recommend PCI as the reperfusion strategy of choice for patients with AMI. An experienced operator is one who performs at least 75 angioplasty procedures, of any type, per year.[8]

When thrombolysis is contraindicated or has failed, or when patients are in cardiogenic shock, rapid transfer to a secondary unit should be ensured. A secondary unit is a unit with primary angioplasty facilities.

Timing

Background

The value of PCI for AMI, as with thrombolysis, is time dependent, although the benefits extend beyond the therapeutic window for thrombolysis. The benefit of reperfusion with primary PCI appears to be present over the first six hours after the onset of chest pain, and a time window of 12 hours between onset of chest pain and PCI is usually accepted.

In the PAMI 2 trial, mortality was lowest among patients treated within two hours of symptom onset, but was relatively independent of time to therapy after 2 hours.[11] Brodie *et al* evaluated the importance of time to reperfusion for outcomes after primary angioplasty in 1352 patients.[12] They found that very early reperfusion (< 2 hours) was associated with lower 30 day and late mortality rates compared with later (≥ 2 hours) reperfusion (4.3% at < 2 hours *v* 9.2% at ≥ 2 hours; $p = 0.04$); 30 day mortality and late mortality were relatively independent of time to reperfusion in patients with reperfusion times ≥ 2 hours (9.0% at 2–4 hours, 9.3% at 4–6 hours, and 9.5% at > 6 hours). A time to reperfusion of < 2 hours was also important for the recovery of left ventricular (LV) function.[12] These data correspond to post hoc analyses, since randomisation was not carried out as a function of time.[9 10] Antoniucci *et al* also found a relationship between time to treatment and mortality in a real world population.[13]

Zijlstra *et al* found that the combined rate of death, non-fatal reinfarction, and stroke remained relatively stable with increasing time to reperfusion in 1302 patients treated by primary angioplasty (5.8% at < 2 hours, 8.6% at 2–4 hours, and 7.7% at > 4 hours).[14] Follow up in the STENT PAMI trial showed a higher incidence of re-occlusion and reinfarction in the late perfusion group (≥ 6 hours), although time to reperfusion had no effect on mortality in this study.[15] Likewise, in the 29 080 patients in NRMI 2, mortality was independent of the delay between symptom onset and hospital admission over a wide range from < 2 hours to > 12 hours.[16] However, mortality was linked to door to balloon time, with a significant increase in mortality when door to balloon times exceeded 2 hours.

Recommendations

We strongly recommend that PCI for AMI is performed swiftly, with a door to balloon time of < 2 hours.

When AMI is diagnosed at a primary unit (a unit without primary angioplasty facilities), we recommend that the time taken to transport the patient to a centre with interventional capabilities should be used to prepare the cardiac catheterisation laboratory and to alert all personnel involved. The patient should be directed to the cardiac catheterisation laboratory without any delay in the Accident and Emergency department. Crucial time can be saved by ensuring the presence of a guide to direct the ambulance crew on arrival.

Transfer

Background

When patients present to a primary unit without interventional capabilities, a decision needs to be made regarding appropriate treatment. The principal therapeutic options in such a situation are either thrombolysis, or transfer to a facility with a cardiac catheterisation laboratory (with or without adjunctive therapy). Any such transfer needs to be effected rapidly to take advantage of the early benefits of revascularisation.

Vermeer *et al* investigated the safety and feasibility of acute transport followed by rescue PCI or primary PCI in patients with AMI initially admitted to a hospital without PCI facilities.[17] Patients were randomised to three groups: thrombolysis (alteplase); thrombolysis followed by transfer and rescue PCI; or transfer and primary PCI. The differences in death or recurrent infarction within 42 days in the three groups were not significant but it was concluded that acute transfer for rescue PCI or primary PCI in patients with extensive AMI is feasible.

The PRAGUE study assessed patients with AMI presenting within six hours of symptom onset to primary units without a cardiac catheterisation laboratory. Immediate transportation for primary angioplasty was demonstrated to be more effective than thrombolysis (streptokinase) during transportation for angioplasty or thrombolysis (streptokinase) alone in reducing the frequency of the combined end point of death, reinfarction, or stroke at 30 days (8% *v* 15% *v* 23%; $p < 0.02$).[18] The incidence of re infarction was also notably reduced by transport for primary angioplasty (1% *v* 7% *v* 10%; $p < 0.03$). This was recently confirmed in the PRAGUE 2 study, which compared immediate thrombolysis (streptokinase) with transport to a PCI centre.[19] Mortality rates at 30 days were 10.4% in the immediate thrombolysis group, and 6.0% in the PCI group ($p < 0.05$).[19]

In the DANAMI 2 trial, a large multi-centre, randomised study, transfer of AMI patients for PCI was compared with on-site thrombolytic therapy using a 100 mg dose of tissue

plasminogen activator (t-PA).[20] Among the inclusion criteria, transfer time from referral hospitals to arrival in the catheterisation laboratory at the interventional treatment centre had to be < 3 hours. Ninety six per cent of patients were transferred within two hours. The median transfer distance was 50 km (range 3–150 km). The cumulative event rate (death, MI, or stroke) was 8.0% for patients receiving PCI, and 13.7% for patients receiving fibrinolysis (p = 0.0003).[21] These results are supported by data from the recently published AIR PAMI study, in which on-site thrombolysis was compared with transfer for PCI.[22] At 30 days, a 38% relative reduction in major adverse cardiac events was observed for the transfer group (8.4% *v* 13.6%, p = NS).

In the recently published CAPTIM trial, transfer of patients for primary angioplasty was compared with pre-hospital thrombolysis.[23] Patients randomised to the thrombolytic arm received thrombolytic therapy in the ambulance (and rescue PCI when required). Patients randomised to primary angioplasty received aspirin and heparin during transport. There were no differences between the two groups in 30 day mortality, reinfarction, or bleeding complications.

Recommendations

We strongly recommend the transfer of AMI patients to cardiac catheterisation laboratories if the expected time to arrival is likely to be ⩽ 2 hours. Transport to an invasive centre should ideally use the same ambulance stretcher and crew. On arrival at the secondary unit, the patient should be taken directly to the cardiac catheterisation laboratory, bypassing the accident and emergency department.

If a patient undergoing thrombolytic therapy does not have signs of reperfusion 90 minutes after starting thrombolytics (persistent chest pain and ST elevation), transfer for rescue PCI as quickly as possible should be considered.

Centres and operators

Background

Data from NRMI indicate that mortality rates in patients undergoing primary PCI for AMI are lowest in centres performing large numbers of procedures.[24] There is a 28% lower mortality rate in centres carrying out the most PCI procedures (> 33 per year) compared with those performing the least (< 12 per year), representing two fewer deaths per 100 patients treated. In NRMI 2, higher volume centres were also associated with improved outcomes.[24]

The ACC/AHA guidelines recommend that PCI for AMI should be performed in high volume centres (> 400 cases per year) with fully equipped interventional laboratories, experienced support staff, and on-site cardiac surgery teams (all available around the clock).[8]

However, these requirements effectively preclude a large eligible population from receiving PCI for AMI, which under appropriate circumstances (see above) is associated with improved outcomes compared with thrombolysis. Given that the rate of complications requiring immediate cardiac surgery intervention (abrupt closure, dissection, or perforation) is low (0.1% for perforation[25]), the C-PORT study (n = 451) was set up to investigate whether primary PCI is superior to thrombolytic therapy for the treatment of AMI in primary units.[26] All sites were required to complete a formal primary PCI development programme before randomising patients into the study. This programme consisted of setting standards, training staff, developing logistics, and creating a quality and error management programme.[26] The programme lasted approximately three months and was tailored for each institution.[26]

The combined incidence of death, repeat MI, or strokes was reduced in the PCI group at six weeks (10.7% *v* 17.7%; p = 0.03) and six months (12.4% *v* 19.9%; p = 0.03).[26] In addition, the mean duration of hospital stay was shorter in the PCI group than the thrombolytic group (4.5 *v* 6 days; p = 0.02).[26] These data show that primary PCI for AMI is superior to thrombolytic therapy, and indicate that primary PCI capabilities can be developed successfully in hospitals lacking cardiac surgery back up. However, patients at high risk or with complex coronary anatomy were excluded from the trial.

Wharton *et al* found that primary angioplasty in high risk AMI patients in hospitals without cardiac surgery facilities was safe and effective, with excellent acute and six month outcomes that compared favourably to those reported from high volume surgical centres.[27] The combined primary end point of death, reinfarction, and cerebrovascular accident occurred in 4.3% of patients at 30 days, and in 7.2% of patients at six months.[27]

Recommendations

PCI should ideally be performed in high volume centres (> 33 primary PCI procedures per year) with fully equipped interventional laboratories and experienced support staff (both available around the clock). In addition, all operators should be properly trained, possess appropriate technical skills, and have acceptable levels of experience to achieve short door to balloon times.[8]

Considering the high risks associated with many of these urgent procedures, we recommend that a complete and well trained team of nurses and, wherever possible, two physicians should be present in the catheterisation laboratory throughout the procedure: one senior interventional cardiologist for the PCI procedure, and one physician to monitor the patient's haemodynamic, respiratory, and, if necessary, anaesthetic state.[8] The lack of available data on this topic led to this recommendation from the group based on their expert opinion. The authors acknowledge that many centres use only one physician in the room. However, a single physician cannot manage the most difficult cases with complete safety (cardiac arrest, cardiogenic shock, need for intubation or ventilation during the procedure), this issue being mainly related to night time.

As demonstrated in the C-PORT study, good outcomes can be achieved in hospitals without cardiac surgery support, given successful completion of a PCI training programme and appropriate selection of cases.[26]

A broad range of catheters, guidewires, stents, and supportive devices, such as intra-aortic balloon pumps (IABP), should be available.

TECHNICAL ASPECTS

Balloons versus stents

Background

The STENTIM 1 study demonstrated that coronary stenting in AMI is feasible and safe.[28] The STENT PAMI pilot trial showed that routine stent implantation during mechanical reperfusion of AMI is associated with favourable event-free survival and low rates of restenosis.[29]

Several studies have shown the advantages of stenting over balloon angioplasty for AMI. The FRESCO,[30] GRAMI,[31] Zwolle,[10] PASTA,[32] and STENTIM 2[33] trials directly compared stenting with balloon angioplasty and demonstrated the benefits of stenting over PCI in reducing major events after the procedure. This was mainly because of a reduced need for repeat revascularisation procedures rather than a reduction in death and reinfarction rates. PASTA showed that primary stent implantation in selected patients with AMI resulted in a lower incidence of major cardiac events during the first 12 months post-procedure and a lower six month restenosis rate than primary balloon angioplasty.[34] The Zwolle trial showed better long term clinical outcomes with stenting at 24 months

versus balloon angioplasty.[34] The CADILLAC trial showed that routine stent implantation in AMI patients resulted in higher rates of event-free survival and better angiographic outcomes than PCI.[35]

Care should always be taken to avoid the undersizing of balloons and stents, since this is associated with worse outcomes. Undersizing may be more frequent in AMI patients than in those without AMI because of low flow, reduced output, and vasoconstriction. Repeated intracoronary glyceryl trinitrate (nitroglycerin) injections may be helpful to enable accurate judgment of vessel size.

Recent developments

The technique of direct stenting (implanting a stent without balloon pre-dilatation) has recently emerged as a potential interventional option. When compared with conventional stenting, direct stenting in AMI patients reduced the incidence of angiographic no reflow, thereby increasing ultimate effective myocardial reperfusion.[36] Loubeyre *et al* randomised selected patients with AMI to direct stenting or conventional stent implantation. They found direct stenting to be safe and effective, with less slow flow or no reflow at the end of the procedure and better ST segment resolution.[37] Direct stenting can be safely applied in patients where the full extent of the lesion is clearly visible.

Drug eluting stents have emerged to challenge conventional interventional approaches, and have demonstrated low rates of restenosis at follow up in patients with stable coronary disease.[38] In the RAVEL trial, the overall rate of major cardiac events was reduced at one year follow up by the use of a sirolimus coated stent compared with a standard stent (5.8% *v* 28.8%; $p < 0.001$). This difference was because of a higher rate of target vessel revascularisation in the standard stent group. However, as yet, the new sirolimus and paclitaxel eluting stents have not been tested in AMI.

Recommendations

We strongly recommend the use of stents for AMI and the use of direct stenting whenever possible.

Balloon counterpulsation

Background

The use of IABPs is a useful supportive therapy in patients with cardiogenic shock (reviewed in Bates *et al*[39]). Their use in AMI has been evaluated in a randomised study, which showed that careful use of prophylactic aortic counterpulsation can prevent re-occlusion of the infarct related artery, and can improve overall clinical outcomes in patients undergoing acute cardiac catheterisation during MI.[40]

The effectiveness of IABPs depends on heart rate and sinus rhythm (atrial fibrillation, ventricular tachycardia, other tachydysrhythmias, and the presence of aortic regurgitation can impair their function), as well as ''driving'' mean aortic pressure. The size of these devices can present some difficulties with tortuous anatomy, but newer versions continue to improve the utility of this therapy.

Recommendations

IABPs should be available in the cardiac catheterisation laboratory at the time of the intervention; bringing an IABP from the surgical theatre once the procedure has started is not a reliable option. The use of IABPs is strongly recommended in patients with AMI complicated by cardiogenic shock.

Arterial access

Background

Three arterial access approaches are used in PCI: femoral, brachial, and radial. The femoral approach is more commonly used, but the brachial and radial approaches have the advantage of allowing immediate post-procedural ambulation.

A randomised comparison of transradial, transbrachial, and transfemoral PCI with 6 French guiding catheters (the Access Study) showed that the three techniques have comparable results in experienced hands; procedural and clinical outcomes of PCI were similar for the three subgroups.[41] However, major access site complications were more frequently encountered after transbrachial and transfemoral PCI.

Transradial PCI in AMI is associated with fewer severe access site related bleeding complications than the transfemoral approach, which is particularly relevant in patients who may be receiving thrombolytics or glycoprotein (Gp) IIb/IIIa inhibitors.[42] Nevertheless, it should be noted that access failure is slightly more frequent during transradial PCI,[43] and that sheath sizes are usually limited to 6 or 7 French. Difficult AMI cases, such as shock or coronary artery bypass grafting (CABG) patients, are not optimal candidates for radial access.

Recommendations

The radial approach combines the advantages of decreased bleeding complications and early ambulation, and hence is likely to offer significant clinical safety benefits and cost savings. However, radial access is a good option only in centres already routinely using this approach for elective cases.

Closure devices

Background

Closure devices currently in use include collagen plug devices (AngioSeal, VasoSeal), percutaneous suture closure devices (Perclose), and external aids to manual compression (Femostop). In elective angioplasty, these devices enable early patient discharge; however, this is less of a concern in AMI patients.

A large study comparing AngioSeal, Perclose, and manual compression in PCI showed a similar overall risk with both devices compared with manual compression.[42] A trial comparing VasoSeal and Perclose with Femostop showed that VasoSeal and Perclose were at least as safe as Femostop, with similar late complications.[44]

Some of these devices are associated with specific risks; furthermore, the small percentage of patients in whom these devices fail are likely to develop more severe bleeding complications.

Recommendations

We do not recommend the systematic use of closure devices in AMI patients. When the physician is experienced in the use of closure devices, the use of such devices should be left to their discretion.

New developments: thrombectomy and distal protection devices

Background

A variety of devices have been developed in an attempt to reduce microvascular embolisation during balloon dilatation and/or stenting in AMI patients. However, to date, there are few published randomised studies regarding the use of these devices, and none specifically in ST segment elevation MI patients.

The X-Sizer is an atherectomy and thrombectomy device designed to aspirate excised atheroma, thrombus, and debris. Angiographic analysis of the first cohort of human subjects suggests that X-Sizer helical atherectomy is a feasible method for removing thrombus and is associated with a low rate of angiographic complications.[45] A randomised study found no significant increase in time to balloon dilatation in patients treated with X-Sizer and, although no significant difference

in TIMI grade 3 flow was seen between the groups, examination of the microcirculation using corrected TIMI frame counts showed lower counts (higher flow rates) in X-Sizer treated patients.[46] Use of the X-Sizer also resulted in significantly lower ST segment scores (a predictor of LV function recovery) at six hours post-procedure compared with PCI alone. Recently presented data from the randomised X-tract (thrombotic lesions and saphenous vein grafts) and X-amine (AMI) trials suggest that the use of the X-Sizer in thrombotic lesions improves flow and possibly also outcomes.[47 48] Encouraging preliminary results have also been reported with the Rescue percutaneous thrombectomy (PT) catheter in AMI, which aspirates thrombus in conjunction with a suction pump.[49]

The Acolysis system is an ultrasonic, catheter based device that uses high frequency sound waves to dissolve blood clots. Results from the Acolysis Registry indicated that Acolysis led to successful recanalisation (TIMI grade 2–3) in 75% of patients.[50]

The Angiojet Rheolytic Thrombectomy system is a catheter based device that uses a high speed saline jet to create a vacuum to break up and then suck out the blood clot. It is currently being evaluated in the AIMI trial, which aims to compare final infarct size and clinical and angiographic outcomes in AMI patients treated with rheolytic thrombectomy followed by immediate PCI versus primary PCI alone (without thrombectomy).

Distal protection devices

Distal protection devices have been developed to prevent distal embolisation of microparticles. It has been postulated that microembolisation is the primary cause of adverse events, such as MI and the no reflow phenomenon, during interventional procedures in saphenous vein grafts (SVGs).[51]

New catheter systems, such as the PercuSurge, Angioguard, and Filterwire devices, have been developed to contain and retrieve microparticles, thus protecting against distal embolisation. The randomised SAFER study showed that the PercuSurge device was associated with a significant 50% reduction in major adverse events, compared with stenting alone during elective PCI on diseased SVGs.[52] The ongoing, multicentre, prospective, randomised EMERALD study aims to assess PercuSurge specifically in AMI patients. Five hundred patients will be enrolled in the study, with half randomised to PCI with PercuSurge and half randomised to PCI without embolic protection.

Recommendations

A possible complication with thrombectomy and distal protection devices is the danger that they may dislodge thrombus during delivery. Furthermore, current devices are large and difficult to deploy.

Specific, randomised, adequately sized trials in AMI patients are required before the use of these devices in patients with AMI can be recommended on a routine basis.

ADJUNCT PHARMACOLOGICAL TREATMENT

Antiplatelet agents

Background

Platelet activation is a major determinant of the risk of subacute stent thrombosis following stent placement, and antiplatelet therapy is an important adjunctive treatment to reduce ischaemic complications in patients undergoing PCI.

Aspirin

Aspirin reduces the frequency of ischaemic complications after coronary angioplasty and is widely accepted and used.[8] The minimum effective dosage in PCI for AMI has never been established.

Thienopyridines

The thienopyridines, ticlopidine and clopidogrel, inhibit ADP induced platelet activation and are also widely used during PCI. The standard loading dose of clopidogrel tested in randomised studies of unstable angina and coronary stenting is 300 mg, followed by 75 mg daily.[53–55] The only concern that exists with regard to the early administration of clopidogrel is in patients who have to undergo urgent surgery (a very rare situation) who may require platelet transfusions and/or the use of drugs such as aprotinin. High loading doses of clopidogrel (600 mg) cause very pronounced platelet inhibition, reaching peak concentrations two hours after administration and lasting for two days.[56] A high loading dose of clopidogrel (450 mg) followed by 75 mg per day plus aspirin has been shown to be superior to aspirin plus standard clopidogrel (75 mg) or ticlopidine (250 mg twice daily) in inhibiting platelet aggregation.[57] However, these studies were small, were not powered to detect clinical differences, and did not involve AMI patients. The benefit of thienopyridine pretreatment with ticlopidine or clopidogrel has been shown in elective stenting with or without GpIIb/IIIa antagonists.[58 59] This kind of pre-treatment is limited in primary PCI for AMI by the short period of time preceding PCI (transfer time); however, the accelerated antiplatelet effect of clopidogrel may be beneficial in AMI patients undergoing PCI, possibly by improving the patency rate. This hypothesis is being investigated in the CLARITY study, which is enrolling AMI patients treated with a thrombolytic agent. Finally, considering the high rate of stenting in patients undergoing primary PCI for AMI (approximately 95%), clopidogrel treatment is necessary, and administration as early as possible seems appropriate.

Although the thienopyridines, in combination with aspirin, achieve a significant antiplatelet effect, this combination is not sufficient to reduce platelet dependent restenotic processes.

GpIIb/IIIa inhibitors

The binding of fibrinogen and other adhesive proteins to adjacent platelets via the GpIIb/IIIa integrin serves as the final common pathway of platelet thrombus formation. A large number of trials have demonstrated that GpIIb/IIIa inhibitors reduce the frequency of ischaemic complications during and after PCI.

In the RAPPORT trial, platelet inhibition with abciximab during primary PCI for AMI led to a reduction in death, reinfarction, and urgent target vessel revascularisation (TVR) at 30 days and six months.[60] However, this benefit was associated with an increased risk of bleeding in the abciximab treated group and no effect on the composite end point of death, reinfarction, and any revascularisation at six months.[60]

In the ISAR 2 trial, in addition to its effects on vessel patency, abciximab improved the recovery of microvascular perfusion, and enhanced the recovery of contractile function in the area at risk after PCI in AMI patients.[61] The rate of major adverse cardiac events was substantially reduced at 30 days.[62] However, angiographic restenosis at one year follow up was not reduced.

In the double blind ADMIRAL trial, early administration of abciximab in AMI (before sheath insertion in all patients and before reaching the catheterisation laboratory in 26% of patients) was associated with improvements in: coronary patency before stenting; the success rate of the stenting procedure; coronary patency at six months; LV function; and clinical outcomes at 30 days and six months compared with placebo, without an excess of major bleeding.[63] A substudy of this trial showed that abciximab dramatically reduced

platelet aggregate size and increased fibrin accessibility in ex vivo platelet rich clots in AMI patients.[64]

In the CADILLAC trial of patients undergoing POBA or stenting for AMI, abciximab reduced the rates of subacute thrombosis and recurrent ischaemia leading to repeat target lesion revascularisation, as well as the composite clinical end point of death/MI/urgent revascularisation at one month, but failed to reduce late cardiac events including restenosis at one year.[35]

The ACE trial compared infarct related artery stenting (using a Carbofilm coated stent) and abciximab with infarct related artery stenting (using a Carbofilm coated stent) alone in AMI patients. There were no enrolment restrictions based on age, clinical status on presentation (cardiogenic shock patients were enrolled), or high risk coronary anatomy. The primary end point of major adverse cardiac events at 30 days was significantly reduced in the abciximab arm (a multivariate analysis showed that abciximab had an independent protective effect). Furthermore, abciximab significantly reduced ST segment elevation; there was no difference between the two treatment arms in terms of bleeding complications.[65]

Finally, all five clinical trials testing abciximab in primary angioplasty showed significant reductions in ischaemic events at 30 days. The lack of late benefit observed in the subgroup of stented patients in the CADILLAC study is in contrast with the other studies, and may be because of the following: play of chance in subgroup analysis of a study with a factorial design; clinical and angiographic selection of patients; use of a low risk patient population; late administration of the drug; no adjudication of events; or drug cross over in an open study.

A meta-analysis of these five AMI trials showed a significant reduction in death or MI at 30 days and a favourable trend towards a reduction in mortality. Together with earlier trials of abciximab in the absence of AMI (including EPILOG,[66] EPIC,[67] EPISTENT,[68] and ERASER[69]), a significant mortality reduction is achieved with this agent.[70]

Eptifibatide, a small molecule GpIIb/IIIa inhibitor, has also been investigated in AMI patients. In a non-randomised study, eptifibatide was administered to AMI patients in the emergency room before primary angioplasty, and resulted in a higher incidence of partial or complete reperfusion compared with patients administered eptifibatide at the time of the procedure.[71] A randomised controlled trial of eptifibatide versus combination therapy with eptifibatide and lytics is in progress (ADVANCE MI).

The efficacy of tirofiban, another small molecule GpIIb/IIIa inhibitor, in patients undergoing PCI for AMI has been investigated in the randomised, open label TIGER PA pilot study.[72] Tirofiban was given as a bolus (10 μg/kg over three minutes) and infusion (0.15 μg/kg/min for 24 hours) in the emergency room before each patient was brought to the cardiac catheterisation laboratory; a control group received tirofiban in the cardiac catheterisation laboratory. A better patency rate was reported in the group that received the drug early.[72]

Recommendations

Aspirin should be given as early as possible, with a recommended starting dose $>$ 160 mg; a high dose administered intravenously is preferable.

A loading dose of 300–600 mg of clopidogrel is recommended before intervention (given the prevalence of stenting in interventional procedures, $>$ 90%). The patient should be continued on at least 75 mg of clopidogrel once daily for at least one month after stent PCI.

To date, abciximab is the only GpIIb/IIIa inhibitor proven to be clinically effective in PCI for AMI.[35 60 62 63 65] Immediate administration of abciximab on first presentation is recommended for AMI patients scheduled for primary PCI.

Anticoagulants

Background

Various anticoagulant drugs are available.

Unfractionated heparin (UFH)

When planning appropriate anticoagulation for a PCI procedure, consideration should be given to the anticipated transfer time and duration of the procedure, and the anticoagulation regimen should be adjusted accordingly. Furthermore, each patient's response to anticoagulation is different. UFH prevents clot formation at the site of arterial injury and on coronary guidewires and catheters used during PCI.[8] It is routinely given during PCI for AMI. Measurement of the activated clotting time (ACT) is useful for monitoring heparin therapy during coronary angioplasty.[73] Few prospective clinical data are available to define the optimal level of anticoagulation during PCI.

The ACC recommends that, in those patients who do not receive GpIIb/IIIa inhibitors, sufficient UFH should be given during coronary angioplasty to achieve an ACT of 250–300 seconds with the HemoTec device and 300–350 seconds with the Hemochron device. Weight adjusted bolus heparin (70–100 IU/kg) can be used to avoid excess anticoagulation. If target ACT values are not achieved after a bolus of heparin has been administered, additional heparin boluses (2000–5000 IU) can be given. Early sheath removal should be performed when the ACT falls to $<$ 150–180 seconds. The UFH bolus should be reduced to 50–70 IU/kg when GpIIb/IIIa inhibitors are given, in order to achieve a target ACT of 200 seconds using either the HemoTec or the Hemochron device. The currently recommended target ACT for eptifibatide and tirofiban is $<$ 300 seconds during coronary angioplasty. Post-procedural heparin infusions are not recommended during GpIIb/IIIa treatment.[8]

A recent meta-analysis of six randomised trials of novel adjunctive anti-thrombotic regimens for PCI identified an optimal ACT of 350–375 seconds for patients undergoing PCI without GpIIb/IIIa inhibitors.[74] In subgroups at a greater risk of thrombotic events, a steeper gradient of benefit between lower and higher levels of ACT is evident.[70] When using a GpIIb/IIIa inhibitor, a low dose of UFH (70 U/kg) is effective and safe.[74]

Low molecular weight heparins (LMWH)

LMWHs, such as enoxaparin, have significant advantages over UFH; they yield a more predictable and stable anticoagulant response than UFH and require no monitoring. The NICE 1 and NICE 4 trials investigated enoxaparin with and without abciximab in PCI, and demonstrated a low/minor incidence of bleeding and infrequent major cardiac events at 30 days.[75] Similar positive experiences have been reported with lower doses of LMWH.[76 77] The randomised, double blind REDUCE trial failed to show a benefit in restenosis with the LMWH reviparin, but showed a significant reduction in early ischaemic events with reviparin compared with UFH.[78]

Optimal dosing regimens for the administration of LMWH at the time of primary PCI have yet to be determined. However, the use of LMWH in AMI has been shown to be associated with reduced ischaemic complications compared with UFH in large randomised thrombolytic trials,[79 80] and is currently being investigated in two primary PCI trials (ADVANCE MI and FINESSE).

Patients who have received enoxaparin before the onset of ST segment elevation MI (1 mg/kg, twice daily, subcutaneous dose) do not require further administration of the drug if PCI is performed within 8 hours. Similarly, patients who would have received an ASSENT 3 regimen of enoxaparin after the

Trial acronyms

- **ACCESS:** A Comparison of Percutaneous Entry Sites for Coronary Angioplasty
- **ADMIRAL:** Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long term Follow up
- **ADVANCE MI:** Addressing the Value of Facilitated Angioplasty after Combination Therapy or Eptifibatide Monotherapy in Acute Myocardial Infarction
- **AIMI:** AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction
- **AIR PAMI:** Air Primary Angioplasty in Myocardial Infarction
- **AMISTAD:** Acute Myocardial Infarction Study of Adenosine
- **ASSENT:** Assessment of the Safety and Efficacy of a New Thrombolytic
- **ATLAS**: Acolysis during Treatment of Lesions Affecting Saphenous Vein Bypass Grafts
- **CACHET:** Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial
- **CADILLAC:** Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
- **CAPTIM:** Comparaison de l'Angioplastie Primaire et de la Thrombolyse Prehospitaliere a la Phase Aigue de l'Infarctus du Myocarde
- **CARESS:** Carotid Revascularization With Endarterectomy or Stenting Systems
- **CLARITY:** Clopidogrel as Adjunctive Reperfusion Therapy
- **C-PORT:** Atlantic Cardiovascular Patient Outcomes Research Trial
- **DANAMI:** Danish Acute Myocardial Infarction Study
- **EMERALD:** Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberalized Debris
- **EPIC:** Evaluation of c7E3 for Prevention of Ischemic Complications
- **EPILOG:** Evaluation of PTCA to Improve Long term Outcome with Abciximab GpIIb/IIIa Blockade
- **EPISTENT:** Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial
- **ERASER:** Evaluation of ReoPro and Stenting to Eliminate Restenosis
- **ESCG:** European Cooperative Study Group for rt-PA in Acute Myocardial Infarction
- **FINESSE:** Facilitated Intervention With Enhanced Reperfusion Speed To Stop Events
- **FRESCO:** Florence Randomized Elective Stenting in Acute Coronary Occlusions
- **GRACIA:** Grupo de Analisis de la Cardiopatia Isquemica Aguda
- **GRAMI:** Gianturco–Roubin in Acute Myocardial Infarction
- **GUSTO:** Global Utilization of Streptokinase and t-PA for Occluded Arteries
- **HEAP:** Heparin in Early Patency Randomized Trial
- **INTEGRITI:** Integrilin and Tenecteplase in Acute Myocardial Infarction
- **ISAR 2:** Intracoronary Stenting and Antithrombotic Regimen
- **NICE:** National Investigators Collaborating on Enoxaparin
- **NRMI 2:** National Registry of Myocardial Infarction 2
- **PACT:** Plasminogen-activator Angioplasty Compatibility Trial
- **PAMI:** Primary Angioplasty in Acute Myocardial Infarction
- **PAMI 2:** Second Primary Angioplasty in Acute Myocardial Infarction
- **PASTA:** Primary Angioplasty versus Stent Implantation in Acute Myocardial Infarction
- **PRAGUE:** Long Distance Transport for Primary Angioplasty versus Immediate Thrombolysis in Acute Myocardial Infarction
- **RAPPORT:** ReoPro and Primary PTCA Organization and Randomized Trial
- **REDUCE:** Reduction of Restenosis After PTCA, Early Administration of Reviparin in a Double-Blind Unfractionated Heparin and Placebo-Controlled Evaluation
- **REPLACE:** Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events
- **RESCUE:** Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints
- **SAFER:** Saphenous Vein Graft Angioplasty Free of Emboli Randomized Trial
- **SHOCK:** Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock
- **SPEED:** Strategies for Patency Enhancement in the Emergency Department
- **STENT PAMI:** Stent Primary Angioplasty in Myocardial Infarction
- **STENTIM:** Stenting in Acute Myocardial Infarction
- **SWIFT:** Should We Intervene Following Thrombolysis
- **TAMI:** Thrombolysis and Angioplasty in Myocardial Infarction
- **TIGER PA**, Tirofiban Given in the Emergency Room Before Primary Angioplasty Pilot Study
- **TIMI:** Thrombolysis in Myocardial Infarction

onset of symptoms do not require any additional anticoagulation in the catheterisation laboratory.[81 82]

Direct thrombin inhibitors

Direct thrombin inhibitors such as bivalirudin, are a new class of anticoagulant. Bivalirudin has been investigated in the CACHET,[83] REPLACE 1,[84] and REPLACE 2[85] studies in the setting of elective PCI. Direct thrombin inhibitors have yet to be investigated in patients with AMI.

Recommendations

We recommend the administration of heparin at a dosage adjusted to weight and/or ACT. We recommend 70 U of UFH per kg in patients undergoing PCI with adjuvant GpIIb/IIIa inhibitors. If higher doses of UFH are considered, the use of GpIIb/IIIa inhibitors is associated with a risk of over-anticoagulation.

Substitution of LMWH for UFH appears promising, but firm recommendations cannot be given at this time. Patients receiving enoxaparin (ASSENT 3 regimen) do not require any additional anticoagulation when they reach the catheterisation laboratory.

SPECIFIC CASES

Facilitated PCI

Background

Facilitated PCI refers to the use of pharmacological treatment to establish early reperfusion before catheterisation. This strategy combines the benefits of early revascularisation with easier intervention, since the artery will already be open in many patients. Facilitation may be obtained with full dose GpIIb/IIIa inhibitors, full dose thrombolytics, or a combination of half dose thrombolytics and full dose GpIIb/IIIa inhibitors.

Limited data have been published concerning the potential benefit of high doses of UFH before PCI, with conflicting results. The randomised HEAP study found no benefit from high dose heparin as a pre-treatment for primary angioplasty in AMI compared with low dose or no heparin.[86] In a non-randomised comparison, Zijlstra *et al* found that pre-hospital administration of aspirin and heparin in AMI patients resulted in a higher initial patency of the infarct related artery than later administration of these two drugs.[87]

Facilitated PCI with thrombolytic therapy

Conflicting results have been obtained so far with the combined approach of thrombolytics and PCI versus PCI alone or thrombolytics alone. Early trials using full dose thrombolytics produced equivocal results regarding the utility of post-thrombolytic intervention and, in general, reported an increased rate of bleeding complications. For example, the SWIFT,[88] TIMI IIA,[89] TAMI,[90] and ESCG[91] trials demonstrated no mortality benefit (and sometimes unfavourable trends) from thrombolysis followed by intervention compared with thrombolysis alone. Similar detrimental data were seen in a study by Vermeer *et al*[17] and in the PRAGUE 1 trial.[18]

More recent studies, however, have indicated that thrombolysis followed by early intervention may be beneficial. An observational study investigating immediate angioplasty with stent implantation after pre-hospital thrombolysis in a non-selected AMI population found it to be safe, achieving high and early patency rates.[92] The randomised PACT trial compared primary angioplasty with half dose thrombolytic (recombinant t-PA) followed by immediate, planned, rescue angioplasty.[93] The primary end point of this study, LV function at discharge, did not show any improvement from facilitated PCI. However, early TIMI grade 3 flow was associated with the preservation of LV function. The recent GRACIA study reported a significant clinical advantage of early systematic PCI (within 24 hours) over later ischaemic driven PCI after thrombolysis.[94 95]

Facilitated PCI with thrombolytic therapy is being investigated in the randomised ASSENT 4 trial. The two arms of the study are: aspirin, UFH, and PCI with GpIIb/IIIa inhibitors at the physician's discretion and clopidogrel if stented; and aspirin, tenecteplase, UFH, and PCI with no GpIIb/IIIa inhibitor but clopidogrel if stented.

Facilitated PCI with a combination of thrombolytic therapy and GpIIb/IIIa inhibitors

In the SPEED (GUSTO V pilot) trial, patients were randomised to standard dose abciximab, standard dose abciximab with low dose reteplase, or standard dose reteplase alone.[96] All patients had early angiography, and PCI was encouraged. Early PCI patients showed a procedural success rate of 88% and a significant reduction in the 30 day composite incidence of death, reinfarction, or urgent TVR (5.6% *v* 16%) compared with patients who did not undergo early PCI. The early PCI patients had 66.3% TIMI grade 2–3 flow pre-procedure (median time 63 minutes from the start of thrombolysis) and 97.6% ($p < 0.001$) TIMI grade 2–3 flow post-PCI. These patients also had fewer bleeding complications and required fewer transfusions than patients who did not undergo early PCI (9% *v* 16%; $p = 0.02$). Patients receiving abciximab with half dose reteplase and PCI showed a trend towards improved 30 day outcomes. Early facilitated PCI was, therefore, shown to be both feasible and associated with positive outcomes, especially with the use of a combination of abciximab with half dose reteplase.[97 98]

In the TIMI 14 trial, 888 AMI patients were randomised to full dose alteplase, abciximab alone, or abciximab with reduced dose alteplase or streptokinase.[99] In a group of patients who underwent adjunctive PCI, a combination reperfusion regimen of abciximab and half dose thrombolytic therapy was associated with greater ST segment resolution than reteplase alone, even after the procedure (51% *v* 3%).[100] Among patients treated with combination therapy and presenting at angiography with TIMI grade 3 flow, adjunctive PCI significantly improved ST segment resolution (57% *v* 24%), reflecting increased tissue and microvascular perfusion.[100] Two large trials tested the concept of combined therapy in AMI (reduced dose thrombolytics and full dose GpIIb/IIIa inhibitors versus full dose thrombolytics) but without early intervention.[101 102] No firm conclusions can be drawn from these trials about the benefits of facilitated angioplasty.

The efficacy of facilitated PCI as a reperfusion strategy is under investigation in a number of large randomised trials, including FINESSE, ADVANCE MI, TIGER,[72] and CARESS. FINESSE is a three armed, randomised, multi-centre, double blind, double dummy trial currently investigating 3000 patients with AMI undergoing primary/facilitated PCI after receiving either early abciximab alone, early abciximab plus half dose reteplase, or late abciximab at the time of PCI. PCIs are performed 60–240 minutes from the time of randomisation.

ADVANCE MI is a two armed, randomised, multi-centre, double blind trial currently investigating 6000 patients with AMI undergoing primary/facilitated PCI after receiving early eptifibatide alone or early eptifibatide plus half dose tenecteplase before PCI. There is also a second randomisation opposing anticoagulation with low dose enoxaparin or low dose UFH.

CARESS is a randomised, open label, multi-centre trial investigating 2000 patients with AMI in hospitals without cardiac catheterisation laboratories. Patients are randomised to abciximab plus half dose reteplase and transferred to a referral hospital with a cardiac catheterisation laboratory for immediate PCI, or are given the same combination therapy with transfer only as needed for rescue PCI. TIGER has a similar design using tirofiban and tenecteplase, with anticoagulation provided by enoxaparin in both arms.[72]

Recommendations

Data on full dose thrombolytics or combination therapy to facilitate PCI are awaited. Until data from randomised studies are available, firm recommendations on such strategies cannot be made.

Facilitation with abciximab is so far the only recommendation based on published positive studies.

PCI

PCI in CABGs

Background

In patients with previous CABG, it is estimated that the rate of MI is approximately 2–3% over the first five years, with recurrent infarction in as many as 36% of patients at 10 years.[103 104] In a study investigating primary PCI in patients with AMI and prior CABG,[104] previous CABG was associated with reduced success compared with patients without prior CABG; the success rate was lower still if the treated vessel

was an SVG. The increased incidence of adverse cardiac events appears to be largely caused by adverse baseline clinical characteristics and inherent problems associated with the treatment of degenerated vein grafts. SVGs have more no reflow phenomena and reinfarct more frequently than native vessels after PCI.

Recommendations

Considering the limited options available, PCI is a valid therapeutic strategy in these patients. When dilating an SVG, the use of distal protection devices or thrombectomy devices may help prevent post-procedural events, such as no reflow and cardiogenic shock.

Culprit vessel versus all vessel intervention

Background

While the patient is undergoing PCI for AMI, there is an opportunity to treat all or several major coronary vessels, not just the occluded vessel. Where there are waiting lists for interventional procedures, speed of therapy and cost reduction issues may warrant this approach. In addition, the anticoagulant effects of adjuvant pharmacological therapy that the patient has received will be maintained during other vessel intervention.

It should be noted that intervention in a non-culprit, non-ischaemic patent vessel runs the risk of undue complications in what is already a high risk situation. The ACC/AHA guidelines on PCI give elective PCI of a non-infarct related artery at the time of AMI a class III recommendation with a C level of evidence (for definition see Smith *et al*[8]).

Before taking the decision to intervene in other vessels, the haemodynamic status of the patient and the effect of angioplasty on the suspected culprit vessel, resolution, or not, of chest pain and ST segment elevation after a successful angiographic procedure should be taken into account. In contrast, in cases of cardiogenic shock, systematic intervention in multiple vessels may be required to optimise reperfusion of the heart.

Recommendations

Given the lack of conclusive supporting evidence, the consensus among experts is that culprit only intervention should be the recommended strategy. However, the panel also believes that all accessible vessels should be treated in patients with shock. Finally, if an experienced interventionist feels that it is in the patient's best interest (for example during persistent chest pain, lack of ST segment resolution, undetermined culprit vessel), multi-vessel PCI is not contraindicated on evidential grounds.

Cardiogenic shock

Background

Cardiogenic shock complicates 7–10% of AMI cases and is associated with a 70–80% mortality rate.[105] Early recognition and aggressive treatment are both very important in these patients. In addition, since the vast majority of patients develop cardiogenic shock after hospital admission, the assessment of predictors of shock appears to be of paramount importance.

A study characterising the clinical factors predictive of cardiogenic shock developing after thrombolytic therapy for AMI found the major factors to be age, systolic blood pressure, heart rate, and Killip class.[106] Other important risk factors have been identified including: sex, prior history of MI, heart failure, or CABG, diabetes, and multi-vessel disease.[107] The absence of aspirin, angiotensin converting enzyme (ACE) inhibitors or β blockers in the prescription was also associated with worse outcomes.[107]

A trial evaluating the use of angioplasty, thrombolytic therapy, emergency CABG, and support devices (such as IABP counterpulsation, Hemopump insertion, and ventricular assist devices) in patients with AMI complicated by cardiogenic shock found that the 30 day survival rate was significantly better in patients who underwent successful angioplasty of the infarct related artery than in patients with failed angioplasty (61% *v* 7%; $p = 0.002$) or no attempt at angioplasty (61% *v* 14%; $p = 0.003$).[107] The GUSTO I trial also found that in AMI patients who developed cardiogenic shock, only angioplasty was associated with a significantly lower mortality rate.[108] This difference was maintained over the one year follow up period. The only clinical variable that predicted survival was age < 65 years. This was confirmed in the larger, randomised SHOCK trial, which compared the effect of early emergency revascularisation (ERV), within six hours of randomisation, and initial medical stabilisation (IMS) on 30 day, six month, and one year survival for patients with AMI complicated by cardiogenic shock.[109] At 30 days, there was no significant difference in the frequency of the primary end point of overall mortality between the two groups (46.7% in the ERV group *v* 56.0% in the IMS group). However, the one year survival rate was 46.7% for patients in the ERV group compared with 33.6% in the IMS group ($p < 0.03$).[110] The investigators recommended the rapid transfer of AMI patients with cardiogenic shock, particularly those aged < 75 years, to medical centres able to provide early angiography and revascularisation procedures. The benefit of coronary artery stenting combined with the administration of abciximab in patients with cardiogenic shock has recently been analysed in two non-randomised studies.[111 112] This association has resulted in higher procedural TIMI grade 3 flow rates and better long term outcomes.

Recommendations

We recommend careful assessment of the risk of developing cardiogenic shock in each patient (knowing the risk factors for shock) in order to ensure early diagnosis and to allow rapid transfer and adequate intervention. A more aggressive approach is usually necessary in these patients, including more frequent use of IABPs, inotropic drugs, and GpIIb/IIIa inhibitors, as well as reperfusion that is as complete as possible.

No reflow and myocardial blush below grade 3

Background

There is growing recognition that a patent infarct related artery may not be sufficient to guarantee recovery of myocardial perfusion, and that patency of the coronary microcirculation is crucial.[113] The persistence of abnormally slow myocardial blood flow in the absence of angiographically significant obstruction, thrombus formation, or dissection, is termed no reflow (although it encompasses states of no flow, as well as significantly impaired blood flow).[114] Patients with no reflow have an increased risk of subsequent MI and death.[113] The mechanisms thought to be responsible are: vasoconstriction and vasospasm; loss of capillary autoregulation; distal embolisation (of angiographically visible vessels); microvascular plugging (vaso-occlusion of microvessels linked to vasoconstrictive mediators, platelet/leucocyte agreggates, inflammatory cytokines, endothelial dysfunction); tissue oedema; or a combination of these factors. No reflow affects 10–20% of patients undergoing intervention following AMI.[115] A study evaluating clinical factors related to the development of no reflow after successful coronary reperfusion in patients with AMI found that, in those patients where no reflow developed, it was related to the severity of myocardial damage (number of Q waves), the size of the risk area, and the occlusion status of the infarct related artery.[115] Ischaemic preconditioning (pre-infarction angina) appeared to attenuate no reflow.[115]

Pharmacological treatment of no reflow and diminished myocardial blush

Verapamil has been shown to be effective as a treatment for both no reflow and slow flow in both retrospective,[116] and prospective[117] studies. Intracoronary injection of verapamil after PCI for AMI has been shown to attenuate microvascular dysfunction and augment myocardial blood flow in patients with AMI, leading to better functional outcomes than PCI alone.[118] However, the clinical benefit remains hypothetical. Potential problems with verapamil include generation of arrhythmias, LV depression, atrioventricular block, and the development of shock. However, these have not been observed in trials.[117]

A small trial assessing whether intracoronary papaverine, a potent coronary microvascular dilator, could attenuate the no reflow phenomenon after PCI found that it significantly improved TIMI flow grade (only 15% of patients included were AMI patients).[118] Another study (in AMI patients) investigated the effects of nitroprusside, a nitric oxide direct donor, on no reflow. Nitric oxide is a potent vasodilator and is important in controlling coronary blood flow through the microcirculation. Nitroprusside led to a highly significant and rapid improvement in angiographic flow and blood flow velocity in patients with no reflow PCI.[119]

The potential role of adenosine in reducing infarct size in patients with AMI was investigated in the AMISTAD study.[120] Adenosine significantly reduced infarct size versus placebo (33% relative reduction). However, there was no difference in clinical outcomes, and, in fact, a trend towards more events was observed in the adenosine arm. Of note, a small, randomised study (54 patients) showed adenosine to reduce the incidence of no reflow phenomena (4% *v* 26% in patients receiving placebo).[120]

In the recently reported AMISTAD II study, anterior infarction patients (n = 2118) were randomised to high dose adenosine, low dose adenosine, or placebo, followed by thrombolysis or PCI.[120] Some effect of adenosine, limited to the highest dose tested in this study, was seen on infarct size but no significant difference was observed in clinical events (death/heart failure at six months).[121]

Part of the efficacy of GpIIb/IIIa inhibitors is believed to relate to direct effects on no reflow preventing distal embolisation. It has been proposed that GpIIb/IIIa inhibitors act on distal embolisation, platelet activation, and even plugging inflammation. Results observed on flow in AMI suggest that these drugs have a preventative effect.[63]

Interventional approaches to reduce no reflow or diminished blush grade

Direct stenting data suggest that stenting without balloon pre-dilatation may reduce the occurrence of no reflow.[37] Limited data are available on the use of distal protection devices in AMI.[40–42] However, peripheral studies indicate that such devices do protect against the risk of downstream embolisation during percutaneous procedures.

Recommendations

Glyceryl trinitrate, verapamil, papaverine, nitroprusside, and adenosine are frequently used to treat no reflow, although there are few data to support the use of these drugs. They are not recommended at this time. The best treatment for no reflow is still undetermined. Prevention should be encouraged and, in this respect, data with GpIIb/IIIa inhibitors look encouraging, as does the use of distal protection devices and direct stenting.

The elderly patient

Background

Patients aged > 75 years constitute almost one third of all AMI patients and this proportion is growing rapidly as the global population ages.[122 123] Elderly patients tend to have non-compliant arteries, more extensive disease, and more severe stenoses caused by an increased plaque load. Advanced age is a risk factor for adverse outcomes in patients with AMI,[122 124] and elderly patients, especially those aged > 80 years, are often excluded from studies.

The one year survival rate in octogenarian and older patients is significantly less than in younger patients.[124 125] The greater mortality in octogenarians is likely to be caused by the increased incidence of cardiac risk factors, including diabetes and hypertension, together with a greater frequency of heart failure and three vessel disease. De Boer *et al* studied a series of 87 patients aged > 75 years and concluded that primary coronary angioplasty for AMI had a significant clinical benefit when compared with intravenous streptokinase treatment.[126] These results suggest that primary PCI is beneficial in the elderly, and that an early aggressive strategy should be adopted for this age group.

A substudy of the GUSTO IIB trial investigated the effect of age on outcome in patients randomised to receive primary angioplasty or t-PA.[124] Outcome was improved with angioplasty compared with t-PA in each 10 year patient group, although risk increased with age irrespective of treatment.

Recommendations

Elderly patients are generally good candidates for angioplasty (but not for thrombolysis) although the procedure is more likely to be difficult in these patients.

POST-PCI

Length of hospital stay

Background

A substudy of the GUSTO I trial found that the hospitalisation of patients with uncomplicated AMI for > 3 days after thrombolysis is uneconomical.[127 128]

The PAMI II trial investigated whether discharge from hospital after three days is safe and cost effective in low risk patients with AMI treated with PCI.[129] Low risk patients (age < 70 years, left ventricular ejection fraction (LVEF) > 45%, one or two vessel disease, successful PCI, no persistent arrhythmias) were randomised to receive accelerated care (admission to a non-intensive care unit and day three hospital discharge) or traditional care. Patients who received accelerated care had similar in-hospital outcomes but were discharged three days earlier and had lower hospital costs than those who received traditional care. At six months, accelerated and traditional care groups had similar mortality rates and similar rates of adverse events (for example, unstable ischaemia, reinfarction, stroke, and heart failure).[128]

Recommendations

Early discharge on the third day after optimal PCI for uncomplicated AMI in low risk patients is recommended. Early discharge is not recommended in higher risk patients or following any complication or unsatisfactory procedure.

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