

Editorial

Old Drugs and Late Intervention – Can We Improve as the Struggle for Universal Primary Percutaneous Coronary Intervention Continues?

Fármacos antiguos e intervención tardía. ¿Podemos mejorar mientras continúa la lucha por el uso universal de la intervención coronaria percutánea?

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In the article published in *Revista Española de Cardiología*, Ruiz-Nodar et al. describe a series of 50 patients who received rescue percutaneous coronary intervention (rPCI) for failure to respond to administration of fibrinolytic therapy.¹ Within 6 days of intervention, patients underwent cardiac magnetic resonance (CMR) imaging with the aim of determining the myocardial salvage index (MSI). This is a measurement to determine the ability of rPCI to minimise the amount of actual myocardial necrosis within the area of myocardium at risk following acute ST segment elevation myocardial infarction (STEMI).

The authors conclude that the amount of myocardial salvage achieved in this cohort of patients is very small. They further speculate that the reason for the “almost nonexistent” benefit is related to the long period of time between the onset of initial symptoms and the restoration of effective antegrade flow in the infarct-related vessel.

This paper makes an important contribution to the literature on rPCI and the authors are to be congratulated for an elegantly conducted study and subsequent analysis. One conclusion any reader might draw is that this study is too small to make a categorical statement on the lack of benefit of rPCI in terms of myocardial salvage. That said, the available literature does not show consistent benefit with rPCI in terms of hard clinical end points and the authors have reached a conclusion that will not be a surprise to many researchers in the field. It is possible that a larger randomised controlled trial (RCT) might demonstrate meaningful myocardial salvage or other unequivocal benefit, but this is conjecture. Critically, new RCTs designed to specifically investigate options for patients with failed fibrinolysis are unlikely to be performed.

Although primary percutaneous coronary intervention (PPCI) in an established Heart Attack Centre (HAC) is the gold standard treatment for STEMI, fibrinolytic therapy continues to be widely utilised and its role debated. There are two particular scenarios: a) patients without timely access to PPCI (generally accepted as the time from first medical contact to PPCI exceeding 2 h), and

b) patients presenting very early after symptom onset. Of course, some patients fall into both categories. Inevitably, any debate on the role of fibrinolytic therapy involves discussion of rPCI, since fibrinolytic therapy frequently fails.

In the first scenario, lack of timely access to PPCI may be due to geography, poor transport links, inadequate catheter laboratory capacity, or inadequate expertise. A number of investigators have attempted to offset the delay to PPCI by “facilitation” – a strategy in which fibrinolytic therapy, a glycoprotein IIb/IIIa inhibitor, or a combination is started at first medical contact, with subsequent percutaneous coronary intervention (PCI) performed as soon as possible in all cases irrespective of clinical or electrocardiographic signs of successful reperfusion. This strategy is not endorsed by either the European Society of Cardiology (ESC)² or the American College of Cardiology/American Heart Association (ACC/AHA) following a series of trials producing divergent, although largely disappointing, results. In particular, ASSENT-4 was stopped prematurely after interim analysis demonstrated more patients had died in the fibrinolytic therapy + PCI arm than in the standard PPCI arm.³ In FINESSE, neither PCI preceded by abciximab and reteplase nor PCI preceded by abciximab alone was superior to abciximab used at the time of PPCI among patients presenting within 6 h of symptoms onset and who were in the catheterisation laboratory 1–4 h after randomisation.⁴

A common view is that the potential benefits of “facilitation” were diminished because intervention was performed too early, thus exposing the patient to increased bleeding hazard at the time of intervention, and before benefit from the pharmacological component of the strategy could be accrued. Commentators have suggested that in ASSENT-4, inadequate antithrombotic therapy and thienopyridine loading in the fibrinolytic + PCI arm also reduced the potential benefit of this strategy. A recent re-analysis of ASSENT-4 demonstrated higher residual thrombus burden in the fibrinolytic + PCI group compared to the PPCI group.⁵

In the second scenario of patients presenting very early, there remains interest in the role of fibrinolytic therapy. There is some evidence from CAPTIM⁶ that very early fibrinolysis combined with rPCI could be equivalent to PPCI. In a retrospective analysis of the main trial,⁷ there was a trend towards reduced mortality in those patients receiving fibrinolysis within 2 h of symptom onset

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compared to PPCI. However, this result must be taken in the context of the main trial results. There was a 24% relative risk reduction in the incidence of the primary end point (composite of death, nonfatal reinfarction, and nonfatal disabling stroke within 30 days) favoring the PPCI arm in a trial which enrolled two thirds of the intended number of patients. This result was observed even though 26% in the fibrinolytic arm received rPCI, 33% received urgent PCI, and 70% received PCI by 30 days – indeed, 85% in the fibrinolytic arm underwent coronary angiography before 30 days, despite systematic angiography following fibrinolysis being forbidden in the protocol.

The ESC currently recommends fibrinolytic therapy as soon as possible for all patients who cannot receive PPCI within 2 h of first medical contact.² For those with large myocardial infarction and low bleeding risk who present within 2 h of symptom onset, fibrinolytic therapy should be administered if PPCI cannot be delivered within 90 min of first medical contact.

If initial treatment for STEMI is fibrinolytic therapy, a strategy for those who fail to respond is required. One option is rPCI. By interventional cardiology standards, the literature on rPCI is not large. The two largest contributions to the literature are United Kingdom trials: MERLIN⁸ (Middlesbrough Revascularisation to Limit Infarction) and REACT⁹ (Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolytic). MERLIN was a direct comparison of rPCI with medical treatment which enrolled 307 patients from 3 regional Coronary Care Units between February 1999 and June 2002. REACT compared these two strategies and a third strategy of repeat fibrinolysis. REACT enrolled 427 patients from 35 centres between December 1999 and March 2004, with the trial ceasing prematurely because of falling recruitment.

Initial outcomes were reported for MERLIN at 30 days and for REACT at 6 months. In comparing rPCI with conservative management, neither trial demonstrated mortality benefit, reduction in the incidence of heart failure, or improved left ventricular function. MERLIN demonstrated a reduction in the incidence of the secondary end point, a composite of death/reinfarction/stroke/subsequent revascularisation/heart failure. This was driven by a statistically significant reduction in the incidence of subsequent revascularisation, although numerically fewer episodes of death from all causes, reinfarction, and heart failure were also observed. REACT demonstrated a significant reduction in the incidence of the primary end point (composite of death, reinfarction, stroke, or severe heart failure within 6 months) when comparing rPCI to continued medical therapy. This was driven by a statistically significant reduction in the incidence of reinfarction in the rPCI arm, although there were numerically fewer episodes of death from all causes and severe heart failure. There was no advantage in REACT from repeat fibrinolysis and the trial effectively excluded this as a treatment option.

Both trials observed more strokes in the rPCI arm compared with the conservative arm, but this was particularly the case in MERLIN where the stroke rate in the rPCI arm was an alarming 4.6%. Surprisingly, 6 of the 7 events were thromboembolic rather than haemorrhagic. Both trials demonstrated increased bleeding and higher transfusion requirement in the rPCI arms.

The MERLIN investigators concluded that “the benefits of rescue angioplasty observed in this trial are small, the principle effect being a reduced requirement for subsequent revascularization. . . This benefit of rescue angioplasty is achieved at the expense of more strokes and more transfusions and with no early preservation of LV [left ventricular] systolic function.” The REACT investigators were more positive and concluded that “rescue PCI, with transfer to a tertiary site if required,

should be considered for patients in whom thrombolysis for myocardial infarction with ST-segment elevation fails to achieve reperfusion.”

The difference in early clinical outcomes between the two trials was not profound. Each trial reported a reduction in the incidence of a composite end point favouring rPCI compared with medical therapy. In both trials, a single end point within the composite end point reached statistical significance in its own right (a significant reduction in reinfarction in REACT, a significant reduction in subsequent revascularisation in MERLIN). The differences in clinical outcomes that were observed may have been influenced by differences in trial design and enrolled patients. Compared with MERLIN, REACT utilised less streptokinase (57% versus 96%), more stents in the rPCI arm (69% versus 50%), more glycoprotein IIb/IIIa inhibitors in the rPCI arm (43% versus 3%), enrolled a younger patient group (61 versus 63), and had fewer patients with anterior myocardial infarction (42% versus 48%). Unlike REACT, MERLIN initiated rPCI at 60 min, rather than 90 min, after the initiation of fibrinolytic therapy. MERLIN recruited more quickly and from fewer centres, suggesting less patient selection, although a degree of selection in REACT was inevitable given the requirement for patients to be eligible for repeat fibrinolysis.

A meta-analysis of rPCI trials,¹⁰ including both REACT and MERLIN, concluded that rPCI conferred no mortality benefit over conservative treatment, but was associated with significant reductions in heart failure and reinfarction. The authors advised these benefits should be interpreted in the context of the potential risks of rPCI. The risks of rPCI include bleeding, stroke, lack of demonstrable benefit in the elderly, and the likelihood that a failed rPCI procedure confers additional risk over medical treatment (a result reported by several investigators).

Longer-term follow-up of both trials has been published. In REACT there was mortality benefit at a median follow-up of 4.4 years in the rPCI arm compared to both the conservative and repeat fibrinolytic therapy arms.¹¹ Analysis of the MERLIN patients at 3 years revealed no mortality benefit with rPCI, with clinical events in both arms being rare after the first year.¹²

The ESC currently recommends rPCI for large infarctions and evidence of failed reperfusion if PCI can be performed within 12 h of major symptoms (recommendation IIa, level of evidence A).² However, in many parts of Europe and certainly the United Kingdom, PPCI has resulted in a dramatic reduction in the use of fibrinolytic therapy and therefore less focus on the management of failed fibrinolysis. Despite the publication of MERLIN in 2004 and REACT in 2005, rPCI increased by only 5.6% in 2005 compared to the previous year,¹³ suggesting that interventional cardiologists were not persuaded by the data and/or were focussed on the development of PPCI pathways. PPCI increased by 35% in the same period. PPCI became the dominant mode of treatment for STEMI in England in the year ending March 2010, with an increase of 54% in the number of patients receiving this treatment compared to the previous year. The use of rPCI has fallen year on year from a peak in 2007 to a current rate of approximately 32 per million.

The key limitation of rPCI, as Ruiz-Nodar et al. remark,¹ is the delay from symptom onset to definitive treatment. In this paper the mean time from symptom onset to rPCI was well over 6 h. Similar times were seen in REACT (median 414 min) and in MERLIN (mean time 327 min). There are multiple points at which delay occurs: from first symptoms to call for medical assistance; from presentation to initiation of fibrinolytic therapy; from initiation of fibrinolysis to recognition of its failure; from diagnosis of failed fibrinolysis to arrival in a centre with PCI capability; from arrival in a PCI-capable centre to normal antegrade flow in the infarct-related vessel.

Some delay could be prevented by simple measures. If one assumes that patients with STEMI presenting to PCI-capable centres receive timely PPCI, fibrinolytic therapy should principally be in use for those who have delayed access to PPCI (accepting that fibrinolytic therapy will on occasion be considered for those who refuse PPCI or have no arterial access, etc.). These patients could receive prehospital fibrinolysis prior to admission to the nearest HAC (*not* the nearest hospital), or receive fibrinolysis in the hospital setting immediately before being transferred to the nearest HAC. This would allow an experienced angioplasty team to consider the patient for rPCI *as soon as the diagnosis of failed fibrinolysis is suspected*. The transfer of patients to a HAC *after* the diagnosis of failed fibrinolysis is made reduces the benefit that a policy of rPCI may offer. Furthermore, patients who do respond to fibrinolytic therapy and do not need rPCI would be “in the right place at the right time” to undergo coronary angiography with a view to revascularisation 3 to 24 h after its administration, a strategy also endorsed by the ESC.

Several studies have shown that transfer of patients receiving fibrinolytic therapy is safe. A version of “drip and ship” was tested in TRANSFER-AMI.¹⁴ This study randomised 1059 STEMI patients receiving fibrinolytic therapy at non-PCI centres to either standard treatment (including rPCI or delayed angiography) or immediate transfer for PCI within 6 h of fibrinolytic therapy. All patients received aspirin, tenecteplase, and heparin or enoxaparin. Concomitant clopidogrel was recommended. There was a significant reduction in the primary composite end point (death/reinfarction/recurrent ischemia/new or worsening congestive heart failure/cardiogenic shock within 30 days) in the immediate transfer group. The study did not differentiate between patients in the immediate transfer arm who had evidence of successful reperfusion on arrival at the HAC (and who therefore did not need urgent rPCI) and those who underwent urgent PCI for an infarct vessel that was found to be occluded, and so did not examine the strategy of “transfer and wait.” Instead, the study tested the hypothesis that routine transfer for PCI within 6 h of fibrinolytic therapy (a different strategy from previous “facilitated” PCI) would be superior to a strategy of “watch and wait” at a non-PCI centre.

The role of very early fibrinolytic therapy as a bridge to PCI in patients with STEMI who do not have access to immediate PPCI is being further tested in STREAM (STrategic Reperfusion Early After Myocardial Infarction).¹⁵ This important trial is randomising 2000 STEMI patients presenting within 3 h of symptom onset and without access to PPCI in <60 min to either fibrinolytic therapy followed by timely catheterisation (rPCI for failed fibrinolysis; angiography within 6-24 h for successful fibrinolysis) or to standard PPCI. Composite efficacy end points at 30 days include death, shock, heart failure, and reinfarction. Composite safety end points at 30 days include total stroke. Follow-up is extended to 1 year and includes all-cause mortality. One concern is that patients in the fibrinolytic arm who are admitted to hospitals without onsite PCI and fail to reperfuse will be disadvantaged by the delay to rPCI in a PCI centre. However, these patients differ from historical patients in the rPCI literature in 2 ways: *a*) early presentation and fibrinolysis, and *b*) failed fibrinolysis actively managed with prompt referral for rPCI.

To conclude, this study by Ruiz-Nodar et al.¹ is a reminder that fibrinolysis followed by transfer for rPCI is a strategy which is commonly associated with delay. Delay is associated with worse outcomes. Fibrinolytic therapy is still utilised because a considerable proportion of patients cannot access timely PPCI. Attempts to bridge the gap to PPCI with multiple combinations of

pharmacological agents and interventional strategies have not yet produced clarity. Some strategies (as outlined above) could be used to reduce delay and it is hoped that ongoing trials will define preferred pathways for particular patient subgroups. A critical point is that any strategy combining initiation of pharmacology in one location and transfer of patients to another is dependent on communication and collaboration between several key stakeholders. These include primary care physicians, emergency department physicians, general medical physicians, and cardiologists in centres without onsite cardiac catheterisation facilities, ambulance crews and other providers of emergency transport, and interventional cardiologists. This collaboration within a “network” of healthcare providers is of course vital for developing and expanding a successful PPCI program and thus fulfilling the objectives of the unique European Stent for Life initiative.

CONFLICTS OF INTEREST

None declared.

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