*Editorial comment*

# Rescue percutaneous coronary intervention for failed thrombolysis - is the evidence base coming of age?

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The "open artery hypothesis" has become a well-accepted concept. It dictates that following coronary artery occlusion restoration of flow leads to better short, medium and longer-term clinical outcome compared to ongoing no flow, providing it is within the time frame of myocardial cell viability. Further there is evidence that the quality of the patency achieved is important also. Data from the GUSTO-I Angiographic Sub-study Investigators[1], along with other published series such as that from the TIMI 10b Group[2], demonstrated that early (30-day) mortality was significantly improved (by up to 50%) if TIMI grade 3 patency (flow equivalent to a non-affected artery) could be achieved, when compared to those patients in whom only TIMI grade 0/1 was obtained. Even patients with TIMI grade 2 patency fared worse clinically than those with TIMI grade 3 flow. Ross et al.[3] later showed that there was evident benefit in the longer term also. It has also been well established that thrombolysis as a treatment strategy results in the desirable TIMI grade 3 patency in less than 60% of patients[4], and that the therapeutic plateau is likely to have been reached, with adjunctive (antiplatelet) medication providing little extra benefit, and additionally with excess adverse effects due to the narrow therapeutic window of clot lysis vs bleeding risk. It is for this reason that primary treatment of acute myocardial infarction with percutaneous coronary intervention (PCI) is increasingly considered the most appropriate therapy; TIMI 3 patency rates are generally > 90%, with treatment of the underlying stenotic lesion possible without the excess risk of bleeding associated with the use of increasingly potent lytic concoctions. The benefits were clearly demonstrated in a recent review of the trials by Keeley et al.[5]. Many countries particularly in Europe and the Far East have, as a result of the perceived and proven benefits, moved to primary PCI as the dominant therapy for acute myocardial infarction (AMI). This is not the case for all comers as was shown in the GRACE registry of 95 hospitals in 14 countries. The overall rate of reperfusion therapy in this study was only 65% made up of 47% thrombolytic and a mere 18% primary PCI[6].

This would suggest that for the time being at least and maybe for the next 3-5 years thrombolytic therapy will, for logistic reasons, remain a treatment option and therefore it will fail (in terms of achieving TIMI grade 3) in a significant minority (up to 45%) of patients. The question is, how should such patients be treated at that point. There are many situations where we think we know the correct treatment but are unable to select the patient who might benefit. That is not the case with lytic failure – much has been written on the relationship between resolution of ECG changes and TIMI grade perhaps the best data coming from Zeymer et al.[7] who suggested that the greater the ST-segment resolution the more likely TIMI grade 3 had been achieved. To some degree choice of cut-off will determine the degree to which all failures are captured or too many patent coronary arteries included (i.e. false positive and negative rates). Most would suggest a cut-off of 50% ST-segment resolution as being a good

compromise. Once "failed lysis" has been recognised the next decision concerns what to do with the patient. From the data on primary PCI the initial "obvious" answer is to undertake "rescue" PCI. However it is clear that there is currently no evidence to suggest that this is definitively the right option. Rescue PCI is *not* primary PCI: the patients are often sicker, they may have needed transporting for PCI and therefore present later, there will be a reason that they have failed lysis whereas others have not (plaque or thrombus burden), patency rates may be influenced by higher rates of no-reflow, pre-PCI lytic may influence the stability of peri-AMI thrombus which may make PCI outcome worse. Certainly rescue PCI patients in whom the PCI is unsuccessful do worse, with mortality rates of 30% or so. Finally there are no randomised studies comparing outcome of rescue PCI with alternative options including repeating the lytic which is standard therapy in some European centres or even doing nothing. While such considerations may seem counter-intuitive, until we have data that shows not only efficacy but in the modern cost conscious environment demonstrate cost-effectiveness also, then such questions need to be asked.

What data is there to help us and how does the study published by Steffenino et al.[8] in this edition contribute to our understanding of the role of rescue PCI? Previous data is scant. Ellis et al.[9] have published on rescue PCI. In the RESCUE I study they showed a fall in mortality from 10 to 5% and a reduction in severe heart failure from 7 to 1%, which combined reach the border of significance (p = 0.05). RESCUE II was a small study conducted between 1995 and 1998. It showed that the 14 rescue PCI patients appeared to have a *worse* 30-day outcome compared to those (n = 15) treated conservatively (death 7.1 and 0% respectively). One-year outcome was no different (death rescue PCI 7.1%, conservative 6.7%) although re-intervention was less in the rescue PCI group (21.4% vs conservative group 46.7%). The MERLIN study by de Belder's group has shown similar findings[10]. This is the first group to publish outcome data following randomisation of patients with failed lysis to either rescue PCI or conservative treatment. In a study of 307 patients with failed reperfusion but excluding cardiogenic shock, the primary endpoint of 30-day mortality was similar in the two groups (9.8% rescue PCI vs 11% conservative, p = 0.7). The composite secondary endpoint of death/stroke/subsequent revascularisation/heart failure was significantly less in the rescue PCI group (37.3 vs 50%, p = 0.02 – almost totally due to difference in vascularisation rates) but at the cost of more strokes (4.6 vs 0.6%, p = 0.03) and more blood transfusions (11.1 vs 1.3%, p < 0.001). Thus while long-term outcome is unclear since we need to await the longer-term results of such studies, early benefits of rescue PCI appear in this study at least to be driven by need for vascularisation, something cardiac physicians should be good at determining in the real world. Any early benefit in need for vascularisation is offset by the excess stroke risk. Thus any data that help us determine the role and value of a potentially costly intervention post failed lysis is welcomed and this is why the article by Steffenino et al. is important.

In their article they report a series of consecutive patients (n = 117) who underwent rescue PCI and compare outcome in them with a contemporary group who received primary PCI (n = 153). While this is an observational study it allows us to compare the benefit of the treatment under question (rescue PCI) with the "gold standard" (primary PCI) in the same centre with the same operators, although the entry criteria by ECG resolution appear variable. They confirm that even with an efficient triage system, patients not unsurprisingly take longer to get to the cath lab from onset of pain if they have received thrombolysis first. Why they have found more anterior AMIs in the rescue PCI group is less clear, since anterior AMIs in such a setting would be expected to receive if at all possible primary PCI; it may be that anterior AMIs "fail" lysis more often and therefore make up a greater proportion of patients receiving rescue PCI. Not surprisingly shock is more common reminding us of the potential shortcomings of lytic therapy. Is it justifiable to give lytic and then carefully monitor the patient and select out those who fail, rather than push for the establishment of a primary PCI service? Data from other sources suggest not, and indeed in the current paper supports this – final TIMI grade 3 flow (the predictor of short- and longer-term outcome) was present in only 62% of rescue PCI (a interestingly low rate) compared to 76% in the primary PCI group (also a bit lower than has been reported in other studies). Hospital mortality was 12% in the rescue PCI group (a rather high figure) and 6.5% in the primary PCI. It appears, as might be expected, that opening the vessel earlier and by a more efficient method (primary PCI) leads to better outcome than lysis with rescue for those that fail. This study along with currently available and upcoming data should make cardiologists push for such primary interventional options to be available to the population they cover despite the initial costs and logistic problems. What this study does not tell us is whether rescue PCI is worth the effort if lysis is still being used. de Belder's group[10] and earlier smaller studies suggest not. The REACT trial group of 427 patients randomised to either rescue PCI, repeat lytic, or conservative therapy has reported 30-day follow-up data[11] and by the time of publication will have 6-month primary endpoints. The 30-day data demonstrate improved outcome with rescue PCI (composite endpoint of death, re-AMI, severe heart failure or cerebrovascular accident). Time to first primary endpoint shows improved event-free survival with rescue PCI; survival rates: rescue PCI 88.9% vs repeat lysis 77.4%; vs conservative 75.2% (p = 0.009). Rescue PCI vs conservative: hazard ratio 0.42 (95% confidence interval 0.23-

0.76) (p = 0.004), and vs repeat lysis: hazard ratio 0.46 (95% confidence interval 0.25-0.84) (p = 0.012). Benefit was seen in all components of the endpoint. Should these results be confirmed at 6 months then this study together with the other available data including that in the current journal will help us make sensible decisions around the time of initial AMI treatment that should influence longer-term outcome. The evidence base surrounding rescue PCI appears, at last, to be coming of age.

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