Has thrombolysis lost its mojo?

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No man can be a pure specialist without being
in the strict sense an idiot
George Bernard Shaw

In this issue, Asseburg and colleagues report a systematic review of 22 randomised trials to assess the effectiveness of primary angioplasty compared with thrombolysis and its relationship to time delays (*see article on page 1244*).¹ They conclude that angioplasty is superior provided that the additional time delay is less than 90 minutes. Although both a systematic review² examining essentially the same studies and a meta-regression³ showing the importance of the additional time delays have been previously published, Asseburg's work makes several unique contributions. First, it provides an updated review using full publications rather than abstracts, includes an additional study and makes several data corrections. Second, the authors have extended the analysis from 1 to 6 months' follow-up. Finally, the authors have performed a more rigorous and comprehensive analysis using Bayesian statistics. They conclude that while the additional benefits of angioplasty are affected by the associated time delays, this option is generally better than thrombolysis for delays of less than 90 minutes. Given the overall high quality of this systematic review, a reasonable question is whether there is still a place for thrombolysis.

Although Asseburg's conclusion is qualitatively similar to the much quoted previous meta-analysis² (mortality odds ratio (OR) = 0.70, 95% CI 0.58 to 0.85), their probability of a qualitative benefit is less certain and does not quite reach conventional statistical significance (OR = 0.68, 95% credible interval 0.46 to 1.01). The increased uncertainty results from their appropriate use of a random effects statistical model that accounts not only for within-study but also between-study variability, as well as their inclusion of a measure for additional time delays. Although each model undoubtedly has its proponents, the lack of statistical consistency attests to the underappreciated fragility of the present evidence for the therapeutic superiority of angioplasty.

Asseburg claims that a Bayesian analysis can more fully quantify the uncertainty associated with estimated relationships, but the advantages extend well beyond this aspect. In addition to permitting direct probability calculations for hypotheses given the observed experimental data (which is the inverse of what is provided by the standard statistical paradigm) and consequently

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more flexible inferences, another advantage of Bayesian analysis is that prior information, when available, can be incorporated into any analysis. This is reflected in Bayes' theorem, best known to clinicians in the context of diagnostic testing whereby a baseline (prior) disease probability is updated following exact probability equations with diagnostic test results to give a more refined (posterior) probability of disease. This reflects the natural diagnostic thinking process and analogously the cumulative nature of the scientific research enterprise. Although the choice of prior information may be subjective, its explicit nature and peer review allows investigators to gauge the reasonableness of any choice, and the analysis may be repeated across a range of reasonable prior choices, to assess robustness.

Returning to the clinical question at hand, there is an abundance of additional prior information about the importance of the delay to reperfusion therapy and patient outcomes that might be incorporated. The Fibrinolytic Therapy Trialists' (FTT)⁴ analysis of over 45 000 thrombolytic patients showed that each hour of treatment delay decreases survival by 1.6 lives/100 treated. Moreover, this relationship is initially non-linear and an hour delay in the first hour from symptom onset may lead to up to six additional deaths per 100 treated per hour,⁵ the so-called golden first hour of intervention that is only practically amenable to thrombolysis. A more informative Bayesian analysis of the relative merits of primary angioplasty in comparison with thrombolysis would have incorporated at least some of these prior data. As a safeguard, these prior data could have been partially discounted and the robustness of the conclusions assessed by employing both enthusiastic and sceptical prior distributions. This would have strengthened the present analysis, which though based on 22 studies, is actually driven by only 476 deaths, less than 10% of the deaths used to develop the FTT relationship.

Other pertinent prior information that might have been included explicitly in this Bayesian analysis is the proven 1% survival advantage of tissue plasminogen activator (t-PA) over streptokinase demonstrated in a randomised study of 41 000 patients.⁶ Because streptokinase was the comparator arm to angioplasty in eight of the older trials, the survival difference between angioplasty and more modern thrombolytic regimens may be overestimated. Bayesian meta-analyses do allow for this type of bias correction.⁷ The authors do consider the angioplasty/t-PA studies alone in a sensitivity analysis that provides no convincing evidence to support the statistical inferiority of t-PA thrombolysis in comparison with angioplasty.

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Moreover, even studies using t-PA have occasionally employed less than optimal adjunctive treatment accompanied by restricted use of rescue angioplasty.⁸

The authors also demonstrate the lack of evidence for the durability of any angioplasty survival advantage at 6 months, with widening credibility intervals showing a 95% probability that mortality with primary angioplasty may be decreased by up to 58% or even increased by 18% compared with thrombolysis. Although not included in the authors' analysis, the results from the GUSTO IIB trial,⁹ the largest of the trials, also failed to show a statistically significant reduction in the composite end point of death, non-fatal myocardial infarction, or stroke with primary angioplasty at 6 months. This lack of proof for a long-term survival benefit should be disconcerting to any clinicians or policy makers contemplating the radical restructuring of healthcare services that is necessary to provide increased accessibility to angioplasty.

Thus, the mortality benefit of primary angioplasty seems somewhat ephemeral. What about the other health benefits? A decreased risk of non-fatal stroke is certainly a welcome benefit for angioplasty, but fortunately this complication occurs infrequently with thrombolysis. Might the reported fewer non-fatal myocardial infarctions with angioplasty be the result of bias? Many of the trials do not report the use of blinded central adjudication committees, and a review of the three most recent studies^{8 10 11} (which included more than one-third of the fewer myocardial infarctions) disclosed different standards for its diagnosis depending on treatment allocation. In general, the biochemical criteria for myocardial infarctions were twice as stringent in the angioplasty groups, possibly decreasing the number of myocardial infarctions detected in this treatment arm. Also, in the more recent studies, angioplasty patients typically received dual antiplatelet therapy, with their known additional benefits, while the thrombolysis patients received only aspirin. These issues raise the possibility that potential ascertainment and performance biases contributed to the reported difference.

Importantly, Asseburg has indirectly provided strong evidence for the clinical equivalence of thrombolysis with t-PA or primary angioplasty. The authors' Bayesian analysis can calculate not only the probability that outcomes of the two interventions differ but also that they differ by clinically meaningful amounts. The totality of the 22 trials suggests that there are 82% and 47% probabilities that angioplasty saves an additional one or two lives per 100 treated, respectively. However, if only the fibrin-specific drugs are considered and remembering their 1% superiority over older agents, the probability that angioplasty saves a clinically meaningful one extra life per 100 treated becomes no more than an even chance.

Notwithstanding the above, in the idealised world of randomised clinical trials angioplasty promptly administered, does appear to be slightly better than thrombolysis, other things being equal. However, all things are not necessarily equal in the real world and it makes more sense to consider these two modalities as complementary rather than in competition. Although randomised trials are the most appropriate research design to minimise bias, thereby enhancing internal validity and determination of efficacy, the problem of external generalisability and effectiveness remains. For example, the 850 randomised patients in Widimsky's study¹⁰ were selected from 4853 screened patients with myocardial infarction, and the 11 centres from the Aversano study¹¹ enrolled only an average of 15 patients with myocardial infarction per centre per year. A recent American study¹² of 4278 patients transferred for primary percutaneous coronary intervention (PCI) at 419 hospitals found a median total door-to-balloon time of

180 minutes, with only 4.2% of patients treated within the median 90 minute institutional benchmark recommended by national quality guidelines. In passing, this benchmark seems overly generous as, by definition, it permits 50% of patients to exceed this standard, and the current analysis suggests that delays of even 90 minutes may lead to increased mortality with angioplasty. It is interesting to note that guidelines¹³ now call for door-to-balloon to be less than 90 minutes, while earlier guidelines¹⁴ were more demanding with a 60-minute limit. One may wonder why in the absence of compelling new data this was modified. The cynic might conclude that given the impossibility of systematically meeting the old performance standard, the best solution was simply to change it. Even maintaining differential delays of less than 60 minutes is likely to be increasingly difficult now as thrombolysis moves away from complicated infusion protocols to rapidly prepared and administered bolus treatments thereby reducing door-to-needle time.

Another question of generalisability is the ability of all PCI centres to duplicate the results from the centres of excellence participating in the trials.¹⁵ In the light of these questions about the validity and strength of the trial evidence, a rhetorical question needs asking: would the pressures for healthcare system modifications to accommodate more primary angioplasty and the accompanying scientific evidence be interpreted differently if first-line medical doctors and specialists were paid angioplasty rates (\$5000–10 000) for the rapid administration of thrombolysis to deserving patients?

Although in some situations angioplasty is the clearly preferred reperfusion option,¹⁶ an objective review of the evidence suggests that thrombolysis remains an attractive therapeutic alternative that does not require complete restructuring of the healthcare system. The mortality difference between reperfused and non-reperfused patients is much greater than any differences between the two techniques.¹⁷ The real task then is to promote reperfusion therapy by whatever means available as rapidly as possible to as large a segment of the population as possible. In this sense, primary angioplasty and thrombolysis should be seen as being complementary and not in competition. However, professional and industry self-interest in the promotion of angioplasty, with invidious comparisons overstating its benefits, may well lead to the demise of thrombolysis.

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IMAGES IN CARDIOLOGY

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“My heart is popping out of my chest”: left ventricular pseudoaneurysm with systemic arterial embolism

A 63-year-old man with prior coronary artery bypass surgery presented to hospital complaining of acute left leg numbness, and the sensation that, “my heart is popping out of my chest”. Examination showed a cold, blanched left leg, and a pulsating mass in his left chest wall. Echocardiography disclosed moderate–severe left ventricular (LV) dysfunction with an apical pulsatile mass. After urgent femoral arterial embolectomy, he underwent cardiac magnetic resonance imaging, confirming the diagnosis of LV apical pseudoaneurysm (panel, arrow), with thrombus visible in the pseudoaneurysm wall (panel, arrowhead; video footage available at <http://heart.bmj.com/supplemental>). He underwent surgical patch repair of the pseudoaneurysm, with an unremarkable recovery.

LV pseudoaneurysms (“false aneurysms”) form when cardiac rupture is contained by adherent pericardium. Although most cardiac ruptures result in cardiac tamponade and death, the rupture may be contained by the visceral pericardium; hence the term, “contained myocardial rupture”. Clinical presentations include congestive heart failure and chest pain; systemic embolism, as occurred in this case, is uncommon. Fifty-five per cent of pseudoaneurysms are caused by myocardial infarction, 33% by cardiac surgery, 7% by trauma, and 5% by infection. Diagnostic modalities include echocardiography, angiography, magnetic resonance imaging and computed tomography. Because the risk of rupture is 30–45%, anticoagulation is contraindicated and surgery is recommended.

To view video footage visit the *Heart* website—<http://heart.bmj.com/supplemental>

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