

## Prehospital Thrombolytic Therapy JRCALC Position Statement: July 2004

1. The case for prehospital fibrinolytic (thrombolytic) therapy is strong [1]. Most would regard it as uncontroversial as an option in suitable circumstances – and in particular where ambulance transport times are relatively long and where no incompatibility exists with a local policy for Primary Coronary Intervention (PCI).

A working party of the European Society of Cardiology and the European Resuscitation Council had recommended in 1998 that appropriate means should be sought - even if no physicians are on the ambulances - for thrombolytic drugs to be administered in the prehospital phase if journey time and hospital delays are likely to exceed 60 minutes [2]. The National Institute for Clinical Excellence endorsed prehospital treatment within the United Kingdom, and favoured the newer bolus thrombolytic agents [3].
2. Current Department of Health policy (England) sets a standard of giving thrombolysis within 60 minutes of calling for professional help. From a baseline of 38% of patients being treated within 60 minutes, the Priorities and Planning Framework 2003-6 target is that there should be a 10 percentage point increase each year in the proportion of thrombolysis-eligible patients who receive thrombolysis within 60 minutes [4]. The national expectation for England is therefore that at least 48% of patients should have been receiving treatment in 60 minutes or less by the end March 2004. Prehospital thrombolysis is playing a small but increasing role in meeting this progressive target.
3. Advice on prehospital thrombolysis falls within the remit of JRCALC, but the committee recognized that many members had no special expertise in this area and also that the Ambulance Service nationally should participate in any decisions on policy. It therefore sought partners to create a *Joint Thrombolytic Subcommittee* which was set up to include three cardiologists from the main committee, together with four nominees from the British Cardiac Society, and participation from the Ambulance Service Association and the Department of Health.
4. JRCALC, which has relied on advice from the Joint Thrombolysis Committee, recommended the adoption by Ambulance Trusts of one or more of five strategies for speeding thrombolysis. The first and second related to alerting the receiving hospital so that preparations could be made for prompt administration of the drugs after arrival at hospital. The third related to cooperation with primary care physician willing to administer the agents outside hospital. The fourth and fifth strategies provided for prehospital administration by paramedics – either under direct hospital control or acting autonomously. *This statement relates primarily to prehospital administration of thrombolytic drugs in England and Wales.*

5. Thrombolytic drugs can be administered legally by paramedics in one of three ways: first, under Patient Group Directions set up by individual ambulance Trusts; secondly by a specific instruction on a named patient basis by a physician who is likely to have seen a transmitted electrocardiogram; thirdly under the Prescription Only Medicines (POMs) provisions which until recently covered only streptokinase. The JRCALC submission of 2000 to the then MCA could not include the newer bolus agents which at the time were not licensed for the treatment of myocardial infarction – but legislation extending approval to tenecteplase and reteplase is now in place (from April 2004) following a new application from JRCALC in 2002.
6. In its application for extension of the POMs order to include the bolus drugs, JRCALC also dealt with the issue of adjuvant therapy. Aspirin is recommended by JRCALC for all patients likely to have an acute coronary syndrome and administration is regarded as routine. Early intravenous heparin is not needed with streptokinase which has little clot specificity and creates an antithrombotic state by depleting circulating fibrinogen to a marked degree. Tenecteplase and reteplase have much greater clot specificity and like all thrombolytic agents they also increase platelet activation [5] and increase coagulation activation and inflammatory markers [6]. Heparin is therefore recommended to reduce the risk of re-occlusion. The Summary of Product Characteristics (SPCs) for both drugs include this recommendation.
7. The superiority of accelerated t-PA (alteplase) over streptokinase was demonstrated in the GUSTO 1 trial [7]. Some of this advantage was ascribed to the concurrent use of intravenous heparin that had *not* been part of the protocol for ISIS-3 which showed equivalence of the drug regimens that were tested in this earlier comparative study [8], ‘front-loading’ of t-PA being the other major difference between the two trials. This evidence reinforced the belief that heparin should be given at the same time as both t-PA and its analogues.
8. Adjunctive intravenous heparin was already the standard of care in the United States before ISIS-3 [9], although this was not based on clinical outcome data. It was seen as having two functions: first to enhance thrombolysis, and secondly to reduce the incidence of re-occlusion after clot dissolution. Experimental data offers discordant results with evidence that heparin enhances thrombolysis [10], tends to inhibit it [11], or has no effect at concentrations used during routine therapy [12]. In clinical practice, coronary patency studies have confirmed that t-PA achieves faster lysis in the presence of heparin: at 7 to 24 hours a patent vessel was found in 88% compared with 52% with aspirin only [13]. The evidence for an overall favourable clinical effect is, however, relatively

weak. The only meta-analysis of clinical endpoints is based on 1735 patients in six trials comparing thrombolytic treatment either with intravenous heparin or without heparin [14] that found little difference in mortality before discharge (5.1% v 5.6%, C.I 0.59 – 1.39) and similar rates of re-infarction. Three of the trials involved t-PA but no data relate to the modern bolus agents. Despite lack of firm clinical evidence even now [15], there is a strong consensus that heparin *is* useful at least to reduce the incidence of post-thrombolytic re-occlusion after treatment with both t-PA and the newer bolus analogues - and that this may be reflected in improved outcome. *JRCALC shares this view.* Re-occlusion cannot, however, be prevented by heparin – as discussed further in paragraph 13.

9. Adjunctive heparin was considered by the Joint Thrombolytic Committee, in the knowledge that intravenous heparin may not be administered *under the POMs regulation* except in the very small doses used to prevent clotting in in-dwelling venous cannulae. The option of seeking POMs approval for therapeutic unfractionated heparin was considered but rejected. It would have taken appreciably longer than the extension of legislation to cover tenecteplase and reteplase (it could not yet have been in place or imminent) – by which time it was believed that enoxaparin and not unfractionated heparin would be the recommended adjuvant. Twin strategies were therefore agreed:-
  - a. that unfractionated intravenous heparin could be used at the discretion of Trusts under PGDs, to which end a model PGD (by courtesy of Essex Ambulance Trust) was provided for the JRCALC website.
  - b. that Trusts not wishing to take this responsibility might still use prehospital bolus thrombolytics but without prehospital heparin provided this could be administered later in hospital well within the duration of continuing effect of the thrombolytics. Slightly different limits were set for the two agents based on what JRCALC was told at the time about effective half lives, and was set at 30 minutes for tenecteplase (which is also the timing currently recommended on the Department of Health Emergency/First Contact Care Services PGD Template for heparin injection – adjuvant treatment for thrombolysis: expiry date 25/01/2006), and 20 minutes for reteplase. Estimates of the half lives are inconsistent (depending in part on how they are measured) and the distinction in the permissible delay for heparin administration may be inappropriate.
10. Many ambulance journeys in rural areas are long, and delayed administration of heparin is then inappropriate. In such cases, a PGD for therapeutic heparin is clearly important. Moreover, some journeys take longer than one hour, and the lack of an infusion to maintain the heparin effect may then have adverse effects. JRCALC suggests that in such cases a further intravenous injection of heparin (half the original dose) might be considered provided this policy is agreed by regional cardiologists. This situation is not covered by the

SPCs for the agents which are written primarily for hospital use, but the total heparin dose over 2 hours is then likely to be similar to that which would have been given if the general recommendation had been followed.

11. JRCALC accepts that the administration of heparin may be delayed if time constraints can be met primarily because it believes that important benefits of prehospital administration can still be obtained, and that more Trusts may be prepared to adopt the strategy of prehospital thrombolysis than would be the case if immediate intravenous heparin were considered mandatory. This compromise was believed to be appropriate in the light of evidence of efficacy of thrombolytics even without heparin (see paragraph 8) and was supported by expert opinion. The policy of caution was of only secondary interest in this matter but did have some bearing initially.
12. Caution was given high priority in the *first phase* of prehospital thrombolysis. For this reason, JRCALC advised that for prehospital use the conventional indications for thrombolysis be tightened and the contraindications widened. This original policy of giving emphasis to safety – even if it reduced the number of patients treated - was generally accepted, though the right of Trusts to take a more liberal view was always fully recognized. The policy of ‘safety first’ was not intended to be permanent. A move towards alignment with hospital practice was taken in July 2003 after the first 200 cases had been treated. JRCALC has no doubt that in due course policies in relation to adjunctive therapy should also be as near as possible identical to those generally used in hospital because these policies are likely to represent best practice and uniformity has considerable advantages. It had been anticipated that the convergence on adjunctive therapy would be on the basis of enoxaparin rather than unfractionated heparin. This has not occurred because the safety of enoxaparin for this indication remains to be demonstrated. It may, however, become the drug of choice in due course when current studies have been completed with a view to reducing the excess of cerebral haemorrhage seen in one major trial in relation to older subjects [16]. It will be more convenient for use in the prehospital setting than unfractionated heparin.
13. Concern has been expressed because the *delayed* administration of heparin contravened the advice given in the SPCs of both drugs as mentioned in paragraph 6. There is, however, no legal imperative to follow the SPCs. If there were, then the drugs could not be administered in the prehospital phase (they are to be used “only under intensive care conditions”). They could not – until recently – have been used in diabetic patients who may have retinopathy which has only recently ceased to be an absolute contraindication according to the SPCs. Moreover, the fact that JRCALC wished to make provisions outside the SPCs was written into the submission, stressed orally to MRHA who approved the policy after consultation, and was accepted by the Medicines Commission and their

expert advisors. Both companies providing bolus drugs were also informed about the JRCALC intention in January 2002 before the submission was made, and neither raised any serious objections to JRCALC at the time.

14. This concern has been heightened because some have believed that “more re-occlusion than expected” has occurred in patients receiving delayed heparin. No data have been offered to support this. Heparin given in recommended doses does *not* prevent re-occlusion. Whilst there is no agreed definition of this complication – particularly with regard to when it should be measured - a meta-analysis suggests that re-occlusion occurs in 10 to 18% of cases within a few hours and in 30% of cases by 6 weeks [17]. The same meta-analysis mentions that re-occlusion was known to have occurred *during* intravenous heparin infusion in 7 of the cases considered. Indeed this paper reiterated the opinion that there is no definite evidence for the efficacy of adjunctive heparin, but which is incontrovertible for aspirin. JRCALC emphasises, however, its support for the notion that heparin *should* be given sufficiently soon to counter new clot formation and *ideally* should be given concurrently with the bolus thrombolytic agent.
15. In supporting the policy of some Ambulance Trusts to use immediate intravenous heparin under PGDs and delayed use in others that do not wish to take this responsibility, JRCALC recognizes that misunderstandings and concerns may have arisen - in part because some of the information made available has lacked clarity. For example, one template for applying for a PGD for intravenous heparin that can be accessed from the JRCALC website states: “Heparin should be injected within 30 minutes of Tenecteplase treatment” (see para 9b), which we believe to be true – but we had anticipated that the PGD mechanism would be used primarily by Trusts that intended to use heparin *concurrently* with the thrombolytic as would also be expected if journey times are long. JRCALC will seek to rectify this confusion.
16. JRCALC is aware of other concerns in relation to prehospital thrombolysis. Some have seen conflict between the general advice given by JRCALC and local cardiological opinion. JRCALC can endorse specifically only the advice that it offers for general use, but recognizes that Trusts are fully entitled to use their own guidelines that are at variance with this - and may well do so on the advice of local cardiologists. More responsibility then falls on the ambulance Trust (and possibly the hospital Trust), but JRCALC supports the reality of local autonomy. Special problems have arisen where ambulance Trusts take patients to more than one hospital, particularly if they have to cover two or more hospital Trusts that may all have different views on thrombolytic policy. These differences can relate to the type of reperfusion (thrombolysis or PCI), to the choice of drug, to

the use of heparin, or even to acceptance that paramedics should play a major role in treatment. JRCALC is not in a position to help resolve such problems but sees clearly the advantages of achieving agreements that cover all interested parties. Clearly it is of crucial importance to ensure that where such conflicts in practice do exist all parties are aware and that robust lines of communication are established and maintained to avoid any potential confusions in treatment that may arise.

- 17 Patient consent is required before the administration of an agent with potentially harmful side-effects. The suggested information for a patient to receive pre-hospital thrombolysis remains unchanged and is as follows:-

“It is likely that you have suffered a heart attack, and the best treatment is a clot dissolving drug called xxx. The quicker you receive this drug, the lower the risk from the heart attack - which is why doctors recommend the treatment is started as soon as possible. These drugs can cause serious side effects in a small minority of patients which I can explain to you in more detail if you so wish, but the risks attached to this treatment are very much less than the likely benefit. Would you like me to give you the injection or would you prefer to have more details?”

In the unlikely event that patients do want more information they should be given the following information:-

“Treatment at this stage saves the lives of about 4 patients for every 100 we treat. But it can sometimes cause serious bleeding. The biggest risk is stroke which affects about 1 patient in every 200. Some patients also have allergic and other effects that do not usually cause any major problem.”

18. The view of JRCALC and the Joint Thrombolytic Committee on prehospital thrombolysis can be summarized as follows:-

- JRCALC and the Joint Thrombolytic Committee strongly support the use of prehospital thrombolysis where this is agreed locally and especially where it can help achieve target intervals for call to needle time.
- JRCALC and the Joint Thrombolytic Committee recognize that thrombolytic therapy is the first treatment that can be given by paramedics that has an inescapable potential for harm to a minority of patients as well as considerable gain for the majority and wish to ensure that all concerned feel they are adequately supported.
- JRCALC and the Joint Thrombolytic Committee decided – as a matter of policy – to give high priority to safety whilst paramedic-administered thrombolysis was gaining acceptance by the medical community, but

more importantly by paramedics themselves. This initial phase is now passing.

- For this reason, JRCALC and the Joint Thrombolytic Committee originally advocated indications and contraindications that have been notably more cautious than those used generally in hospitals, but always with the intention of moving towards standardization in the light of experience - provided this is achieved without evidence of unacceptable hazard. The first revision for broader criteria was made in July 2003.
- JRCALC and the Joint Thrombolytic Committee recognize that each ambulance Trust has individual responsibility for clinical governance, and may choose to adopt more liberal criteria for prehospital thrombolysis - and thereby to accept a greater degree of responsibility. The new bolus thrombolytics can now be given using any of the policies set out in paragraph 3 above, including autonomous use under the POMs legislation. In principle, the POMs mechanism is preferred because this offers uniformity of practice.
- Similar considerations apply to adjunctive therapy with heparin. This has been considered relevant for two reasons: the first was the belief that it enhanced the thrombolytic properties of the agents, but the evidence is no longer judged to support this effect; the second is to reduce the chances of thrombotic re-occlusion which is believed to be both valid and important. Advocacy of immediate heparin was based primarily on the first concept, but there is a consensus that even for the second effect very early administration may confer clinical advantage.
- JRCALC had anticipated an eventual application for a POMs mechanism for low molecular weight heparin that seemed well suited to initiation in the prehospital phase. At present, however, the most suitable preparation of heparin for adjunctive use with thrombolytics remains unknown. Even if approval had been sought in the last POMs application for intravenous unfractionated heparin, it would not yet be in place.
- Currently adjunctive heparin can be used in one of two ways: either concurrently with a thrombolytic in the prehospital phase using Trust PGDs or delayed administration at the time of hospital admission for those without PGDs. The former mechanism is the only possibility for Ambulance Trusts with many long journey times. Moreover, if these exceed an hour, agreement should be sought with local cardiologists for a modified PGD that includes a second (ideally smaller) intravenous injection of heparin after an hour has elapsed since the first adjuvant dose. Delayed heparin is suitable only for shorter journeys of less than 20 or 30 minutes (depending on the agent used, and subject to consideration of revision).

- In accepting delayed heparin when time constraints permit, JRCALC and the Joint Thrombolytic Committee sought to promote the use of prehospital thrombolysis in Trusts that do not wish to use the PGD pathway. Delayed heparin also fitted well the original policy of caution, but this was a secondary consideration that now has less relevance. Moreover, the committees recognize that journey times expected to fall within the tight time limits for delayed heparin may sometimes exceed them. Concurrent intravenous heparin (under a PGD) is thus the treatment of choice, and particularly for areas where journey times are *or may be* prolonged.
- JRCALC and the Joint Thrombolytic Committee favours moves towards increasing uniformity in terms of strategies for speeding thrombolysis, criteria for use, and policies for adjunctive drugs. Complete uniformity will, however, never be attainable because local conditions must influence reperfusion policies, especially in relation to PCI. Disparate policies between neighbouring hospital Trusts that are not related to inevitable difference in relation to PCI are particularly unfortunate but should be open to negotiation. JRCALC wishes to emphasise that where such conflicts in practice do exist all parties be aware and that robust communication strategies must be established (and maintained) to avoid any potential confusions in treatment that may arise.
- JRCALC and the Joint Thrombolytic Committee recognize that some advice may need clarification and updating. The first revision to broaden criteria was made as planned after the first 200 cases of prehospital thrombolysis. The number treated by May 2004 already exceeded 600 so appreciably more experience has been gained. The justification for different time criteria for delayed heparin between the two bolus drugs may need to be re-examined but at the present time there seems neither need nor scope for any major revision of policies in relation to either thrombolytic agents or adjuvant therapy.

## References

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