EE619

A Cost-Utility Analysis of Low-Dose vs Standard-Dose Intravenous Alteplase in the Management of Acute Non-Lacunar Ischaemic Strokes: A Perspective From the NHS

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INTRODUCTION

Strokes cost the NHS ~£3 billion per annum, with additional economic losses of ~£4 billion due to lost productivity and informal care[1]. 85% of all strokes are ischaemic[2]. This evaluation will focus on acute non-lacunar ischaemic strokes (aNLIS) caused by >50% ipsilateral arterial stenosis, including infarcts of the penetrating arteries including basal ganglia, thalamus, internal capsule, corona radiata and pons[3]. This evaluation defined non-lacunar as an 'acute infarct lesion with maximum diameter >20mm or large vessel occlusion on angiography'[4]. These generally have a worse short-term prognosis compared to lacunar infarcts[5].

Acute Stroke Presentation Pathway

Figure 1. NICE Acute Stroke Pathway in the UK [6]

Thrombolysis is achieved via IV Alteplase, a tissue plasminogen activator[7]. According to NICE guidelines, 0.9mg/kg is given over 60 minutes with the initial 10% of the dose given as an IV injection and the rest as an IV infusion[8].

OBJECTIVES

The study objective was to perform a cost-utility analysis (CUA) of low-dose (0.6mg/kg) and standard-dose IV (0.9mg/kg) alteplase in treating aNLIS based on current literature. This is the first CUA to directly compare the two doses from the perspective of the NHS, which will help to determine the most efficient allocation of finite resources while upholding principles of comprehensive healthcare to provide the best value to the taxpayer. This will demonstrate if it is more cost-effective to change the current standard treatment for aNLIS.

METHODS

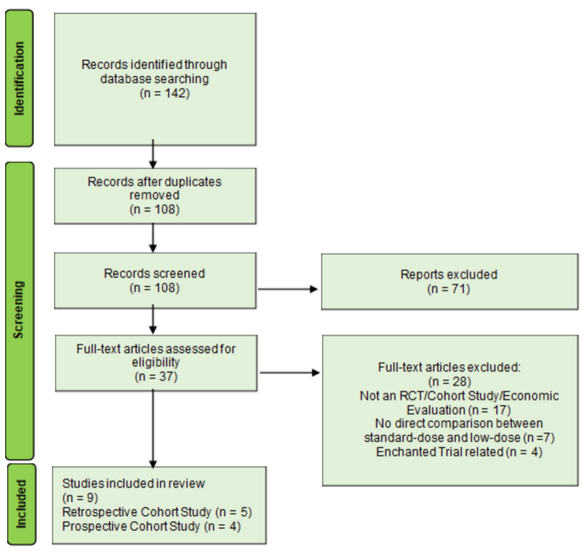

Figure 2. PRISMA Flow diagram of Literature Search and Selection

A systematic literature review (SLR) was conducted with the search string consisting of the following keywords (with relevant MeSH terms): "alteplase", "stroke", "low-dose*" and "standard-dose*". Studies from the SLR showed conflicting treatment success rates, ranging from 22.2% to 68.5% in low-dose groups, influenced by confounding variables like patient demographics and time windows. Notably, the 2006 Japanese Alteplase Clinical Trial influenced the adoption of low-dose alteplase in East Asian countries such as Korea, Japan and Taiwan[9]. Intriguingly, Both safety outcomes – ICH and 90-day mortality rates – had better prognoses, with 7/9 and 8/9 studies in the low-dose group.

Informed by the Zhou et al. analysis of the ENCHANTED randomised trial, the decision tree maps the mRS scores of patients with definite or probable aNLIS to low-dose and standard-dose alteplase treatment arms[4]. Within the trial, 18/490 patients suffered from ICH, however as there was 'no difference' between ICH and functional outcomes, the same mRS distribution was used for those with and without ICH[4]. ICH was determined through the SITS-MOST criteria, which aligned best with the UK population receiving this specific treatment[10].

The SLR categorised acute ischaemic stroke severity into functional outcomes: 'dependent' = mRS 0-2, independent = mRS 3-5, death = mRS 6[11,12,13]. These outcomes informed utility-weighted mRS (UW-mRS) scores for calculating QALYs[14]. Outcome probabilities were also taken from the Zhou et al. trial, which determined aNLIS patients had no disadvantage in being treated with low-dose alteplase rather than standard-dose alteplase[4]. Other studies, however, have shown using low-dose alteplase can lower ICH risk[15].

Costs, obtained from the British National Formulary and NHS reference costs, were analysed from the perspective of the NHS and are therefore non-inclusive of societal or patient costs. The alteplase of choice in the NHS is Actilyse 50mg, with the lower dose requiring half the number of current vials which each cost £432[16]. Healthcare professional administration costs totalled £1540.51[17]. Patient care costs were measured using the mRS scores dependent on the level of disability. Complications such as ICH result in an additional cost of £5968[18]. All costs taken from a 2022 database were discounted by 3.5% per NICE guidelines[19].

Study Value	Value Used	Reasoning
Treatment comparator	0.9mg/kg alteplase	Current gold standard pharmacological treatment for initial aNLIS management[8]
Analytic Horizon	90-day post-stroke	• Follow up period used in ENCHANTED trial[4] • Main complication post-alteplase treatment, sICH, is acute in nature (18.28hr mean time to sICH) thus justifying the use of a 3-month time-horizon providing ample time to account for complications[20]
Cost	Pound sterling (GBP)	British currency
Utility	Quality-Adjusted Life Years (QALYs)	Metric used by NICE as part of the decision-making process for resource allocation
Patient weight	76kg	Weight of the average stroke patient in UK clinical practice according to prior literature[21,22].

Table 1. Figures used in ICER calculations (non-exhaustive)

Univariate sensitivity analyses were conducted on utility values and costs, with the values assigned to the different levels of dependence deemed 'reasonable' as they were 'elicited from a UK population'[22]. Varying mRS scores in sensitivity analyses can be used to test the assumptions built into the original utility-weighted model[23]. The model was tested using the upper and lower bounds of each interval for utilities[22]. A third univariate analysis added the cost of alteplase powder for injection to each node. The patient weight was used to add a dose of 6.84 mg via injection, requiring the purchase of a 10 mg powder and solvent solution for £172.80[16]. For low-dose alteplase, the initial dose of 6.84 mg from IV injection remains the same, accounting for 15% of the total dose, so £172.80 was added to this treatment arm[4,22].

RESULTS

The calculated incremental cost-effectiveness ratio concluded low-dose alteplase would save the healthcare service provider £62,875.38 for every QALY gained compared to standard-dose alteplase. A ceiling ratio of £30,000 was used, representing the maximum willingness-to-pay in the UK; however, both monetary and health benefits remained positive (£429.27 and 0.014309), even when using the lower willingness-to-pay threshold of £20,000[13].

$$ICER = \frac{Cost\ (low\ dose) - Cost\ (standard\ dose)}{Effectiveness\ (low\ dose) - Effectivenss\ (standard\ dose)} = \frac{-290.61}{0.004622} = -£62,875.38$$

$$Net\ Monetary\ Benefit = (R_c * \Delta E) - \Delta C = (£30,000 * 0.004622) - (-£290.61) = £429.27$$

$$Net\ Health\ Benefit = \Delta E - \frac{\Delta C}{R_c} = (0.004622) - \frac{-£290.61}{£30,000} = 0.014309$$

Figure 3. Calculated ICER, net monetary benefit and net health benefit

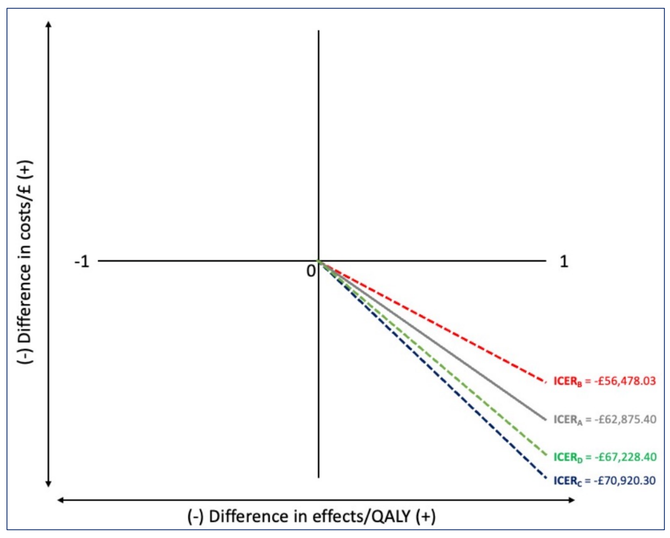

Figure 4. Cost-effectiveness plane displaying the different ICERs calculated in the univariate sensitivity analyses.

$ICER_A$	$ICER_B$	$ICER_C$	$ICER_D$
-£62,875.4	-£56,478.03	-£70,920.3	-£67,228.4

Table 2. Calculate ICERs from univariate sensitivity analyses. $ICER_A$ calculated using base case values; $ICER_B$ calculated using independence utility of 0.79 and dependence utility of 0.47; $ICER_C$ calculated using independence utility of 0.69 and dependence utility of 0.29; $ICER_D$ calculated using additional cost of IV alteplase injection

Utility	Base case value	Univariate sensitivity analysis
Independence mRS 0-2	0.74	0.69-0.79
Dependence mRS 3-5	0.38	0.29-0.47
Death mRS 6	0	0

Table 3. Univariate sensitivity analysis of UW-mRS scores within a 95% confidence interval

For each sensitivity analysis, the ICERs remain negative, due to a negative difference in costs and a positive difference in QALY effects; using low-dose alteplase is more cost-effective despite the uncertainty of the UW-mRS and costs over 90 days.

DISCUSSION

There is minimal difference between low-dose and standard-dose alteplase in terms of functional outcomes in aNLIS treatment, supported by data from the ENCHATED trial[24,15]. The odds ratio of a severe stroke (resulting in mRS >3) for patients with aNLIS was 0.95 (OR 0.79 - 1.15, p = 0.07)[4]. Further trials need to be conducted to determine whether the noninferiority of low-dose alteplase is statistically significant when compared to standard dosing. Low-dose alteplase results in lower procurement costs and potentially lower risk of ICH, making it a cost-effective alternative to standard practice.

The ENCHANTED trial had significant UK and international participation, offering insights into stroke management for diverse patient demographics[25,4]. Limiting the analysis to only UK participants could increase relevance to the NHS, however, a selection bias towards more elderly and frail patients reduces generalisability to the UK[25]. Variation in performance between Hyperacute Stroke Research Centres (HSRCs) and non-HSRCs, influenced by disparities in infrastructure, further reduces generalisability. In terms of patient demographics, recruited patients had milder AIS compared to other studies, which further impacts the generalisability of these results[25].

The primary limitation of the study was the short time horizon, assuming functional outcomes and mRS scores remain constant post-aNLIS. A long-term analytic Markov model would offer a more comprehensive view of lifetime outcomes, and further reduce the assumption that costs remain the same for acute and chronic stroke care[13].

Additional limitations include the use of utility-weighted mRS scores, assumptions about independence, and the impact of ICH on outcomes[23]. Finally, it was assumed that the retrieved costs cover all aspects of care within the 90-day time horizon. For greater accuracy, a probabilistic sensitivity analysis should be undertaken to more closely examine the likelihood of treatment cost-effectiveness[26].

REFERENCES

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