The EXTEND trial: towards a more inclusive but complex thrombolysis

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For most patients with acute ischaemic stroke, the odds of benefit from intravenous alteplase decline steeply over the first 4.5 hours.[1] This decay curve is derived from trials in which all participants were selected on the basis of non-contrast computed tomography (NCCT), which is widely available and valuable to exclude haemorrhage or other structural contraindications to treatment. However, NCCT has inherently low sensitivity to early ischemic changes and limited ability to discriminate irreversibly damaged from viable tissue.

Arrival at hospital outside the 4.5h time window or uncertainty about time of onset, most commonly due to waking with stroke, have restricted eligibility for intravenous thrombolysis.[2] More advanced physiological imaging has suggested that this short time window may be too conservative for some, including those "slow progressors"[3] with favourable leptomeningeal collateral circulation who are able to sustain a small core / large penumbra perfusion pattern (the "target mismatch" profile) over longer periods of time.

Wide variation among sites in imaging protocols, inconsistent post-processing, and small sample sizes, likely contributed to unsuccessful initial efforts to utilise physiological imaging biomarkers for thrombolysis eligibility beyond the 3 or 4.5 hour window based on CT perfusion (CTP) or Magnetic Resonance Imaging (MRI) diffusion-perfusion mismatch patterns (Table).

The imaging criteria used to identify the optimal responder population were initially variable[16] but have been refined with successive trials, and have been exploited successfully in several recent reperfusion trials. Among those with CTP-defined "target mismatch," tenecteplase has been shown to be potentially superior to alteplase,[17, 18] while in trials of mechanical thrombectomy (MT) (all EXTEND-IA,[19] and many SWIFT-Prime[20] patients) effect sizes were larger with perfusion imaging selection compared to trials that used NCCT brain imaging alone.

This narrative review did not involve additional data analysis, so no data are available for sharing.

The EXTEND trial tested the hypothesis that intravenous alteplase improves three-month functional outcomes when given in the 4.5-9 h window to patients with salvageable penumbra as defined by a commercially available automated software package. The trial used rigorous methodology with a relevant primary end-point (mRS 0-1), adjusted for baseline stroke severity. The trial permitted inclusion of a broad range of patients (baseline NIHSS score 4-26), with a definition of viable tissue (ratio 1.2 or < 10ml difference, <70ml core) more libera than other recent trials. The trial was stopped after recruitment of 225 of the 310 planned patients due to loss of equipoise after publication of the WAKE-UP trial,[11] which demonstrated significant benefit from alteplase based on FLAIR-DWI mismatch criteria. Exclusion of patients in whom mechanical thrombectomy was planned presumably led to loss of some recruitment among those fulfilling DAWN or DEFUSE-3 criteria in the latter stages.

Data on how many patients were screened and judged ineligible are unavailable but would be relevant for planning systems of care. Prior trials suggest exclusion of around 80% of clinically-eligible patients by CTP physiological imaging selection.[17] MRI FLAIR-diffusion mismatch excluded two thirds in the WAKE-UP trial.[11] Despite inclusive clinical and radiological criteria, the study enrolled moderately severe strokes (median NIHSS 12, approximately 70% having large vessel occlusion), with a very favourable ratio between core (2.4-4.6 ml) and hypoperfusion (74-78 ml). Intervention and control groups were generally well balanced, but alteplase-treated patients were

slightly older, and with more severe strokes as measured by both core volume and NIHSS score. Around 65% woke with symptoms present, therefore median onset-to-treatment time of around 7.5 hours reflects predominantly estimated onset time. The null hypothesis was rejected after pre-planned adjustment for age and baseline severity (35.4% vs 29.5% achieved mRS 0-1, OR 1.44 (1.01-2.06). No differences were observed in the mRS distribution analysis, but a higher proportion of alteplase-treated patients had major early neurological improvement, attained independent recovery (mRS 0-2 at day 90), and had imaging evidence of recanalization and reperfusion at 24h. As expected, alteplase-treated patients had an excess of symptomatic intracranial hemorrhage (6.2% vs. 0.9%)

EXTEND,[10] and an individual patient data pooled analysis of EXTEND, ECASS-4 and EPITHET,[21] provide further evidence supporting the concept that tissue viability on physiological imaging should be used for reperfusion therapy selection beyond the 4.5 h window or when onset time is uncertain, adding to [1021]evidence from WAKE-UP,[11] DAWN[14] and DEFUSE-3.[15] . EXTEND offers a longer time window for intervention in some by calculating estimated onset time as mid-way between last being well and imaging, whereas WAKE-UP required treatment within 4.5h of symptom recognition. The use of the same CTP technology often employed to screen for mechanical thrombectomy eligibility is a logistical strength. It remains unanswered whether thrombolytic drugs should be administered to late-window LVO patients eligible for MT when MT is immediately available, since that scenario was not tested in EXTEND.

EXTEND consolidates the concept of determining treatment eligibility based on physiological imaging rather than NCCT and the clock. Perfusion-based selection, as deployed in EXTEND, or MRI-based selection as per WAKE-UP, offer alternative imaging selection strategies that should be widely deployed for patient benefit. These findings significantly advance stroke treatment, but at the expense of additional complexity that will likely require review of systems of care. Triage decisions are likely to be dictated by locally available human expertise, imaging and interventional resources. Perfusion analysis equipment, software and technicians are expensive resources that might not be immediately available in smaller hospitals. For institutions delivering intravenous thrombolysis for stroke, acquiring automated imaging capabilities will allow treatment of late time window patients, as well as rapid LVO detection with bridging intravenous thrombolysis while in transit to thrombectomy-capable institutions. . The trial findings should further stimulate policymakers to consider resource distribution across regional networks to ensure optimal delivery of stroke care. While these advances clearly expand the options for intravenous thrombolysis for late arrivals and for strokes of uncertain onset time, we must avoid any misperception that stroke is less of an emergency. Time is still brain, and the emphasis should remain on expediting treatment in the face of growing imaging complexities that inform critical triage and transfer decisions.

Table: Previous randomised clinical trials of intravenous thrombolysis and thrombectomy based on imaging biomarkers in extended time windows (>4.5h since onset).

Trial	Year	Time Window	Imaging Methods
Intravenous Thrombolysis			
DIAS[4]	2005	3-6h	MRI diffusion-perfusion mismatch
DEDAS[5]	2006	3-9h	MRI diffusion-perfusion mismatch
EPITHET[6]	2008	3-9h	MRI diffusion-perfusion mismatch
DIAS-2[7]	2009	3-9h	MRI diffusion-perfusion mismatch or CTP
DIAS-3[8]	2015	3-9h	Intracranial large vessel occlusion
DIAS-4[9]	2016	3-9h	Intracranial large vessel occlusion
EXTEND[10]	2018	4.5-9h	CTP
WAKE-UP[11]	2018	4.5h after waking	MRI diffusion-FLAIR mismatch
ECASS-4[12]	2019	4.5-9h	MRI diffusion-perfusion mismatch
Mechanical Thrombectomy			
MR RESCUE[13]	2013	8h	MRI diffusion-perfusion mismatch
DAWN[14]	2018	6-24h	CTP defined core, or MRI DWI core
DEFUSE-3[15]	2018	6-16h	Defined core and mismatch ratio on either CTP or MRI

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