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PERSPECTIVES IN REHABILITATION

Identifying implications of thrombolysis for stroke rehabilitation: Knowledge gaps in current research

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***Purpose*: Thrombolysis with tissue plasminogen activator (rtPA) is currently used throughout the world in acute ischaemic stroke management. In this review, we will explore the status of our current knowledge about the effects of rtPA on specific rehabilitation domains and highlight some key knowledge gaps. *Methods*: Narrative review of the larger clinical and postmarketing surveillance studies. *Results*: To date, most of the previous research into rtPA for acute ischaemic stroke has focused on safety and efficacy using general outcome measures and has ceased following patients 90 days after rtPA administration. This research has provided valuable information about the safety and efficacy of rtPA and has facilitated the introduction of rtPA into clinical practice for stroke management. However there is a paucity of knowledge about the long-term recovery patterns of patients post-rtPA, including the effect of rtPA on specific rehabilitation domains and its impact on post-acute service delivery. Furthermore, limited information is available about the effect of rtPA on post-stroke quality of life and participation in society. *Conclusion*: These knowledge gaps have substantial implications for the long-term management of patients by rehabilitation teams. Increasing our knowledge in these areas may assist us to predict which individuals are most likely to benefit from thrombolysis with rtPA, and enable us to provide optimal rehabilitation programs to maximise functional outcomes and quality of life post-stroke.**

Keywords: Thrombolysis, rtPA, stroke, allied health, outcomes, rehabilitation, review

Implications for Rehabilitation

- Thrombolysis with tissue plasminogen activator (rtPA) is currently used throughout the world in acute ischaemic stroke management.
- Previous research into rtPA has focused on largely on safety and efficacy using general outcome measures.
- There is a lack of knowledge about the long-term recovery patterns and service requirements of patients post-rtPA, which has important implications for the management of these patients by rehabilitation teams.

Introduction

Stroke is currently a major cause of death and disability throughout the world [1,2]. Worldwide, it has been estimated that approximately 15 million individuals will experience a stroke each year, leaving approximately 5 million individuals with permanent stroke-induced impairments [3]. Strokes can be classified into two main groups: ischaemic and haemorrhagic. Ischaemic strokes encapsulate approximately 80–85% of all strokes and are caused primarily by a blockage in a blood vessel within the brain [1,4]. Thrombolysis shortly after an ischaemic stroke may potentially reduce the neurological damage by facilitating tissue reperfusion via endogenous recanalisation mechanisms [4–6]. Some studies have revealed that thrombolysed stroke patients with extensive reperfusion have a greater chance of being functionally independent, or achieving a "good outcome" as defined by performance on one or more measures including the National Institutes of Health Stroke Scale (NIHSS) [7], modified Rankin Scale (mRS) [8], and/or Barthel Index (BI) [9,10]. As a result, thrombolysis has changed attitudes towards stroke management worldwide, with many countries now adopting thrombolysis as part of their management program for acute stroke patients [11]. However, despite

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the increasing use of thrombolysis in the management of acute ischaemic stroke throughout the world, very little is known about the effects of this acute drug administration on longer-term rehabilitation outcomes. Consequently, in this review we will summarise the main rehabilitation outcomes of pivotal research studies with rtPA and identify key gaps in current knowledge. Specifically, we will look at one of the most common thrombolytic agents (tissue plasminogen activator), discuss large-scale clinical trials and postmarketing surveillance studies into its safety and efficacy, and then examine the outcome measures employed in these studies. We will conclude by identifying some unanswered questions stemming from these studies and present some possible directions for future research.

Methods

A narrative review of rtPA literature was undertaken. A review of electronic databases of Web of Science and Pubmed was conducted up to January 2012. Keywords searched were 'thrombolysis', 'rtPA', 'tPA', 'alteplase' and 'stroke'. Articles that were included were large clinical or postmarketing surveillance studies that investigated the use of rtPA only. Only articles published in English were included. The reference lists of relevant papers were also searched to ensure all relevant studies were identified. We are aware of five large-scale clinical trials and four post-marketing surveillance studies that have investigated the safety and efficacy of rtPA in acute stroke management (see Tables I and II). These studies will be discussed throughout this narrative review.

Tissue plasminogen activator

There are a number of thrombolytic agents that have been trialled in the research literature. However, currently the only thrombolytic agent approved by drug monitoring agencies internationally for acute ischaemic stroke is tissue plasminogen activator (rtPA), or alteplase [12]. A secondary analysis of data from an early rtPA clinical trial (National Institute of Neurological Disorders and Stroke, NINDS) [13] found that compared with untreated control patients, rtPA administered within 3 h of stroke had the potential to add an average of 4 years and 4 months of healthy life to patients who experienced beneficial drug effects [14]. The positive outcomes of the NINDS trial led to the introduction of rtPA into clinical use for acute ischaemic stroke in the USA, and prompted the initiation of trials throughout other countries to investigate the efficacy and safety of rtPA. The relatively short (3 h) window for drug administration, however, was identified as a significant limitation to the clinical uptake of thrombolysis, as many patients were unable to arrive at hospital within the timeframe [12]. A growing body of research has suggested that thrombolysis may still be beneficial when administered shortly outside of the 3 h window [5,15–17]. However, a more recent meta-analysis has revealed that while clinical benefits may be derived from rtPA up to 4.5 h post-stroke, after this time window, the risks of adverse events may overshadow potential clinical benefits [18]. The researchers proposed that the benefits of rtPA may be greatest when administered within 90 min post-stroke, and that after 6 h there is an increased risk of mortality attributable to rtPA administration [18].

General outcomes of rtPA clinical trials

A recent Cochrane review concluded that thrombolysis appears to have a net beneficial effect defined by reduced stroke-related death and dependency (mRS score between 3 and 6), despite the increased risk of haemorrhagic events and death from all causes (although this was often early death stemming from intracranial haemorrhage) [6]. The review also noted that given the non-uniform response of patients to rtPA in previous clinical trials, the precise factors that predict which patients will be most likely to benefit from rtPA remain elusive [6]. As the primary objective of the Cochrane review was to examine the safety and efficacy of a variety of thrombolytic agents in acute ischaemic stroke management, the authors focused on the overall benefits and risks of the thrombolytic agents, and compared studies based on methodological aspects (such as blinding and randomisation, time to treatment) and general outcomes (such as death, dependency, frequency of haemorrhagic events) [6]. The review did not delve into the specific effects of rtPA on rehabilitation outcomes.

Investigations into the safety and efficacy of rtPA in acute stroke management have created a mixed picture. Some rtPA trials have reported significantly positive outcomes [13,19], some have reported nil significant differences [19–21], and other studies have reported significantly negative clinical outcomes [22]. The time-window of drug administration appears to influence the findings of clinical trials. Those clinical trials that have reported positive effects with rtPA have tended to administer the drug within 0–3 h post-stroke onset (e.g. [13]). In contrast, trials that have reported non-significant or non-beneficial effects with rtPA have tended to administer the drug after the 3-h time point (e.g. [19–22]). Confounding factors were also more prominent in non-significant trials. One trial that reported non-significant effects with rtPA (ECASS I) had 17.4% of patients experiencing major protocol violations with regards to both the inclusion criteria (e.g. required imaging data not available) and drug administration process (e.g. prohibited simultaneous therapy, randomisation but not treatment of patients, and deviation from the pre-specified study assessment time points) [21]. When these patients were removed from the analysis, the remaining patients treated with rtPA performed significantly better on the study outcome measures and were discharged earlier from hospital compared with the placebo group [21].

Drug dosage does not appear to explain the varying outcomes of the clinical trials. The majority of trials, across both positive and negative/non-significant outcomes, have used 0.9 mg/kg of rtPA to a maximum of 90 mg [13,16,17,19,20,22]. Differences in stroke severity also seem not to account for the differences in outcomes between the trials. The ATLANTIS B trial (which found non-significant effects for rtPA) [20] did indeed have patients with more severe strokes in the rtPA group, while the NINDS trial (which found positive effects with rtPA) [13] tended to have fewer patients with more severe strokes in the rtPA group. However, subsequent analysis of the

Table I. Summary of previous large-scale research into the effects of rtPA for acute ischaemic stroke.

Trial	n	Clinical outcome measures	Assessment times	Notes	RCT outcomes
ATLANTIS A Clark et al. [22]	142	NIHSS BI mRS GOS	NIHSS 24 h, 30 days Barthel Index, mRS 30 and 90 days	0–6 h post-stroke Phase II RCT 0.9mg/kg rtPA or placebo	-
ATLANTIS B Clark et al. [20]	547	NIHSS BI mRS GOS	NIHSS 90 days Barthel Index, mRS, Glascow outcome scale 30 and 90 days	3–5 h post-stroke Phase III RCT 0.9mg/kg rtPA or placebo	nil
ECASS I Hacke et al. [21]	620	BI mRS SSS NIHSS Mortality at day 30, length of hospital stay, overall mortality, haemorrhagic events	BI, mRS90 days NIHSS 24 h, 90 days SSS 2 h, 8 h, 24 h, 7 days, 30 days	0–6 h post-stroke RCT 1.1mg/kg rtPA or placebo 0–6 Plagued by protocol violations	nil
ECASS II Hacke et al. [19]	800	BI mRS SSS Change in NIHSS baseline-day 30SF-39 Mortality at day 30, length of hospital stay, overall mortality, haemorrhagic events	BI, mRS, SSS, SF-39 90 days NIHSS 24 h, 90 days	0–3 or 3–6 h post-stroke RCT 0.9mg/kg rtPA or placebo	nil
ECASS III Hacke et al. [17]	821	BI mRS GOS Mortality, symptomatic oedema, haemorrhagic events	mRS 30, 90 days Barthel Index 30, 90 NIHSS 1, 7, 30, 90 days Glascow outcome scale 90 days	3–4.5 h post-stroke RCT 0.9mg/kg rtPA or placebo	+
EPITHET Davis et al. [16]	101	NIHSS mRS Haemorrhagic events recorded	NIHSS pre-rtPA, 3–5 days, 90 days mRS pre-rtPA, 90 days	3–6 h post-stroke Phase II RCT 0.9mg/kg rtPA or placebo	nil
NINDS NINDS rtPA stroke study group [13]	Part 1 = 291 Part 2 = 333	Part 1 NIHSS Part 2 mRS BI GOS NIHSS Haemorrhagic events, systemic bleeding, death, new CVA	 NIHSS within 24 h All at 3 months	0–3 h post-stroke Randomised double blind	+
SITS-MOST Wahlgren et al. [25]	6483	mRS NIHSS MortalityHaemorrhagic events	NIHSS 2, 24 h, 7 days Mortality and sICH within 3 monthsmRS 3 months	0–3 h Prospective open label observational study Postmarketing surveillance study Reported pre-stroke mRS	N/A
CASES Shobha et al. [26]	1112	mRS mortality sICH	mRS 90 days	Postmarketing surveillance study	N/A
J-MARS Nakagawara et al. [24]	7492	mRS NIHSS Haemorrhagic events	sICH within 36 h, 3 months mRS 3 months NIHSS 24 h	0.6 mg/kg 0–3 h post-strokeopen-label, nonrandomized observational study Postmarketing surveillance study Reported pre-stroke mRS	N/A
STARS Albers et al. [23]	389	NIHSS mRS haemorrhagic eventsmajor systemic bleeding	NIHSS at baseline mRS 30 days	Postmarketing surveillance study	N/A

Note. n = number of participants; RCT = randomize controlled trial; mRS = modified Rankin Scale, BI = Barthel Index; SSS = Scandinavian Stroke Scale; ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; ECASS = European Cooperative Acute Stroke Study; EPITHET = EchoplanarImaging Thrombolytic Evaluation Trial; NINDS = National Institute of Neurological Disorders and Stroke; NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; GOS = Glascow outcome scale; CASES = Canadian Alteplase for Stroke Effectiveness Study; SITS-MOST = Safe Implementation of Thrombolysis in Stroke Monitoring Study; J-MARS = Japan post-Marketing Alteplase Registration Study; STARS = Standard Treatment withAlteplase to Reverse Stroke; + = statistically significant positive effect for rtPA compared to placebo; - = statistically significant negative effect for rtPA compared to placebo; nil = no significant difference between rtPA and placebo; N/A = not applicable as there was no placebo group

Table II. Summary of commonly used outcome measures in rtPA studies.

Measure	Reference	Description
NIHSS	Brott et al. [7]	A scale that measures impairment across 15 areas (e.g. level of consciousness, gaze, facial palsy)
mRS	Van Swieten et al. [8]	Global measure that records independence on a single scale ranging from 0 (no symptoms at all) through to 5 (severe disability)
BI	Mahoney and Barthel [9]	Measures the amount of time and physical assistance required to complete 10 activities (e.g. stairs, dressing, feeding)
SSS	Scandinavian Stroke Study Group [52]	A scale that measures function across 9 areas (e.g. level of consciousness, eye movements, arm motor power, orientation)
GOS	Jennett and Bond [53]	5 item scale that classifies individuals after brain damage according to their level of social and personal functioning

NINDS data taking severity into consideration still revealed an overall significantly positive benefit with rtPA [6].

As clinical trials differ from everyday clinical situations, a number of studies have investigated the safety and efficacy of rtPA within a postmarketing surveillance framework. These open-label studies usually compared their results with the findings of the large-scale clinical trials and other postmarketing surveillance studies with rtPA. Findings from these studies have highlighted that rtPA can be administered safely in clinical facilities outside of a clinical trial situation and achieve beneficial outcomes (usually as measured by mRS scores) [23–25]. Although, the Canadian Alteplase for Stroke Effectiveness Study (CASES) [26] reported a non-significant trend towards increased incidence of haemorrhagic events and death in patients who received rtPA 3–4.5 h post-stroke compared to patients 0–3 h post-stroke [26].

Outcome measures used in rtPA trials

The vast majority of large-scale clinical trials with rtPA have used a general functional outcome measure such as the NIHSS [7], Barthel Index (BI) [9] or mRS [8]. However, these measures may not be specific enough to provide a true reflection of functional improvements achieved across the recovery spectrum (see Tables I and II). Research with non-thrombolysed patients suggests that these measures may not provide a complete measure of an individual's stroke-induced impairments and disability and consequently, also their recovery. One study by Roth, Heinemann [27] found that while impairment measures correlated with disability measures, between 2% and 36% of the variance in disability on the measure was predicted by impairment. The authors discovered that patients who experienced nil or marginal changes on the NIHSS (a measure of impairment) still achieved substantial changes in Functional Independence Measure (FIM)® scores (a measure of disability) [27]. Evidence also suggests that there may be a dissociation between different human functions, with weaker relationships between cognitive impairment and disability measures compared to physical impairment and disability measures [27,28]. It has also been proposed that the NIHSS may not be as good a predictor for cortical strokes (as opposed to subcortical strokes) [28]. Given the high frequency of impairment and disability across the spectrum of human function after stroke, these results suggest that there is a need for more comprehensive measures to establish a complete picture of the nature of the impairment and disability outcomes post-rtPA.

The BI [9] has also frequently been employed to evaluate the effects of rtPA within the disability context in acute ischaemic stroke management. The BI measures the amount of time and physical assistance required by an individual to complete 10 daily activities [29]. The traditional version of the BI is limited as it does not specifically address cognition, communication, mood, social interaction or vision. Furthermore, the BI has floor and ceiling effects, making it less than ideal for mild or severe strokes [30]. This has implications for rtPA clinical trials, as many of the studies have used the resolution or improvement of stroke symptoms to very mild levels as a key endpoint. For example, ECASS III [17] used a BI of >95 as a study endpoint. However, this does not account for the premorbid status of the patient. A patient who had a BI score lower than this premorbidly and returned to the same lower BI score following rtPA would have been classified as having a poor outcome, despite returning to his/her premorbid functioning. Thus, the use of a minimally clinically important difference (MCID), which has been identified as a change of approximately 2 points on the BI [31] may have revealed more favourable results for rtPA in the trial. Research also suggests that the BI may be less accurate when administered with elderly or cognitively impaired individuals as interviewees [30]. This also has implications for rtPA clinical trials, as many patients who experience a stroke are elderly and often have cognitive impairments post-stroke [32].

The mRS [8] is another commonly used measure in rtPA studies. This measure is a global measure of independence on a single scale, in comparison to the BI, which focuses on performance of specific activities [29,33] (see Table II). The scale ranges from 0 (no symptoms at all) through to 5 (severe disability) [8]. Unfortunately, research suggests that the mRS has less than ideal reliability [34–36]. Quinn et al. [35] found substantial inter- and intra-observer variability on the mRS, with the highest variability noted between scores 1 and 4. This has implications for rtPA trials which have used the mRS as an endpoint and have dichotomised mRS scores to determine favourable or unfavourable outcomes with rtPA. Balu et al. [29] suggested that by dichotomising the mRS, there will be a significant reduction in the sensitivity of the measure, resulting in the potential omission of treatment effects. It has been proposed that outcome measures used in stroke trials should use shifts in disability using nonparametric statistics rather than dichotomization between favourable and unfavourable outcomes [54]. As the mRS was designed to evaluate the

residual effects of stroke after a recovery period by comparing the patient's functioning at that point with their functioning just before the stroke, administrators need a pre-stroke comparison in order to be able to score a mRS of 0,1 or 2 [34]. This has implications for rtPA clinical trials which have often used a mRS score of 0–1 or 0–2 to denote a favourable outcome. It is also therefore difficult to calculate a pre-stroke mRS score as a comparison measure is required. Despite this, the J-MARS, EPITHET and SITS-MOST studies reported pre-stroke mRS scores. Indeed, these observations led Balu et al. [29] to conclude that neither the BI nor the mRS are able to provide a complete description of the functional ability of an individual treated with neuroprotectants following stroke. Thus, given that stroke can result in impairment and disability across a multitude of human functions and that the management of these impairments and disabilities is the primary focus of rehabilitation programs, there is a need to investigate the effects of rtPA on these outcomes to help guide health professionals in the management of these patients.

rtPA, cognition, communication and physical recovery

Stroke has the potential to detrimentally change multiple key facets of human behaviour including language, cognition, mood, motor and visual function [37], and these areas are often the focus of long-term rehabilitation programs. While previous research has provided valuable information about the efficacy and safety of rtPA, only general outcome measures have typically been employed. As a result, there is currently a gap in our knowledge about the effects of rtPA on these specific areas of rehabilitation interest. It is unknown if the recovery profiles of patients who have received rtPA differ in specific areas of functional outcome compared with non-thrombolysed patients. Thus, we do not know whether patients who have received rtPA will require similar rehabilitation programs to non-thrombolysed patients. A recent study by Meyer et al. [38] has provided important preliminary evidence about rehabilitation outcomes following thrombolysis. The researchers measured rehabilitation outcomes based on Functional Independence Measure® scores (a measure that records the assistance required to complete activities of daily living and is heavily weighted on physical aspects), length of stay, and discharge destination [38]. The study revealed that patients who received thrombolysis were typically discharged earlier [38]. Clinically, in rehabilitation settings, patients who are discharged home return to hospital for ongoing outpatient services by multidisciplinary rehabilitation teams, rather than ceasing their involvement with the healthcare system entirely. As the study by Meyer et al. [38] did not continue to follow patients for use of services post discharge, further research is required to investigate the economic aspects of service delivery to patients who have received thrombolysis, given that they may rely more heavily on outpatient rather than inpatient allied health services. Additionally the study by Meyer et al. [38] focused on progress through rehabilitation rather than the level of involvement of individual allied health disciplines. As we do not know whether rtPA exerts differential effects and magnitudes of effects on the different areas of human function, understanding the varied involvement of the different allied health professionals in both inpatient and outpatient rehabilitation may assist with planning of service provision. This is particularly important given that evidence in non-thrombolysed stroke patients suggests that motor recovery tends to occur earlier and to a greater extent than cognitive recovery [27], and that early cognitive function predicts functional outcome at 13 months [39]. This lack of knowledge about the effects of rtPA on specific human functions has the potential to hinder the provision of optimal rehabilitation programs to thrombolysed patients. Thus, in order to enable health practitioners to provide effective management programs for patients who have received rtPA post-stroke, there is a need for further research into the effects of rtPA on specific facets of human function that are often compromised by stroke, such as communication, cognition and motor skills. Finally, as most of the previous research into rtPA has ceased following patients 3 months post-stroke, there is a paucity of knowledge about the long-term impact of rtPA on recovery post-stroke. Longer follow up is required as we know that recovery after stroke can extend for several years [40].

rtPA, quality of life and participation in society

Previous research has largely focused on overall death and general dependency. Minimal research has been directed towards the health-related quality of life of patients who have received rtPA for acute ischaemic stroke. Indeed, the recent Cochrane review into thrombolysis for acute ischaemic stroke commented that further research is required to provide randomised data about the impact of thrombolysis on quality of life (QOL) [6]. Studies with stroke patients in general suggest that a large number of individuals who have suffered a stroke experience poorer QOL than the rest of the population [41–43]. Lower life satisfaction has been linked with less participation in society [44], which has in turn been linked with higher rates of depression [45]. The ECASS II trial [19] measured QOL using the SF-36 (short form 36). The researchers found no significant difference between the rtPA or placebo groups on the SF-36. However, as this is a generic QOL scale it may not be sufficiently sensitive to detect stroke specific QOL impairments. Therefore, use of a stroke specific QOL measure might have detected a difference post rtPA. An alternative possibility is that the majority of the participants in ECASS II were 3–6 h post-stroke. As previous research has highlighted, rtPA may be more effective when administered earlier post-stroke [18], it is possible that differences in QOL post-rtPA may emerge in patients who are thrombolysed shortly after stroke.

rtPA and elderly patients

The effects of rtPA on the recovery of patients over the age of 80 years is largely unknown, as many of the large-scale studies into the effects of rtPA for acute ischaemic stroke have excluded or had very limited numbers of patients over the age of 80 [46]. This is despite the fact that 30% of individuals who experience an ischaemic stroke are over the age of 80 [46]. A review by Derex & Nighoghossian [46] was conducted of the limited data available from open studies. This review suggested that patients over the age of 80 may still achieve beneficial outcomes with rtPA, however, the authors acknowledged that

the results may be an artefact of patient selection. As a result, larger RCTs into the effects of rtPA with elderly patients are warranted. This observation is important given that research suggests that having survived a stroke, older and younger patients exhibit similar potential for functional recovery [47]. Furthermore, given the ageing population there will be more older stroke survivors. Thus, the lack of knowledge about the effects of rtPA on elderly patients has important implications for multidisciplinary rehabilitation teams, as this group constitutes a significant proportion of the rehabilitation caseload. Thus, multidisciplinary health professionals working in these settings lack information about the optimal rehabilitation plans for elderly patients who have received rtPA.

Conclusion

The introduction of rtPA has undoubtedly been a major breakthrough in acute stroke management. Research to date has largely yielded promising results with regards to safety and efficacy, which have led to substantial changes to the acute management of stroke patients. However, the effects of rtPA on post acute management of stroke survivors remain unknown, particularly with regards to response to rehabilitation and quality of life.

Thus, there are a number of questions based around the rehabilitation of patients post-rtPA that warrant consideration. Given the broad nature of the outcome measures employed by previous studies, which also often ceased following patients 3 months post-stroke [48–51], little is known about the impact of thrombolysis on specific functions (e.g. cognition) and long-term recovery profiles. It is unknown whether patients who receive rtPA will respond differently to conventional rehabilitation methods post-stroke when compared to patients who do not receive rtPA. This lack of knowledge has significant implications for facilities currently administering thrombolysis, as it is unknown whether we are optimising recovery in these patients and whether targeted rehabilitation programs are required. Additionally, given that communication/cognitive recovery does not always mirror physical recovery after stroke, it is possible that rtPA may not have the same effect on communication as it does on physical function/dependency. As a result, there is a need for research into the effects of rtPA on the recovery of human functions after stroke and the resulting use of rehabilitation services to achieve a good functional outcome. The optimal time to commence rehabilitation programs with thrombolysed patients and the most effective intensity of rehabilitation is also unknown. Specifically, it is unclear whether patients who have received rtPA will recover at different rates and during different phases post stroke when compared with non-thrombolysed patients. This has the potential to influence post acute rehabilitation planning and service delivery with regards to distribution of services between inpatient and outpatient settings. Another issue that warrants attention in future research is the paucity of information about the effects of rtPA on quality of life post-stroke and participation in society. Thus, there are several keys areas that we need to increase our knowledge about the effects of rtPA that may assist our ability to predict which individuals will be most likely to benefit from rtPA in acute ischaemic stroke management, and enable us to provide optimum rehabilitation programs for these patients.

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