Acute Ischemic Stroke
Time, Penumbra, and Reperfusion

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Current guidelines advocate intravenous thrombolysis for patients with ischemic stroke <4.5 hours from onset without additional imaging beyond noncontrast computed tomography (CT) of the brain. Rapid administration of intravenous tissue-type plasminogen activator (IV-tPA) will reduce disability. Treatment of patients within 3 hours has an odds ratio of 1.53 (95% confidence interval, 1.26–1.86) for a favorable outcome (modified Rankin scale [mRS], 0–2) at 3 months. However, this represents an absolute increase of 9% compared with placebo and is available to a minority of patients with ischemic stroke because of the rigid time constraints. Modern stroke imaging grants unprecedented access to the pathophysiology in individual patients with stroke. Time remains of key importance with respect to patient outcomes. However, it is now possible to not only routinely visualize the causative occlusion, but also estimate the ischemic core, the penumbral tissue at risk if reperfusion does not occur, and the state of the collateral blood supply. The current focus of Acute Ischemic Stroke (AIS) intervention should be to achieve reperfusion of the penumbra. Recent trials point to potential avenues to improve patient access by imaging-based patient selection and the importance of rapid and complete reperfusion of the penumbra.

Penumbral Imaging for Patient Selection
Three parenchymal vascular states exist in varying proportions in each AIS patient. These are the ischemic core, the penumbra, and a region of benign oligemia. Separating the penumbra from the ischemic core is of critical importance in guiding stroke therapy. So too is separating the penumbra from the region of benign oligemia. By definition, the penumbra is the region of tissue that is at risk of being recruited into the ischemic core. Thus, the penumbra is the principal target for reperfusion and, therefore, should dictate patient selection. Given the progressive nature of ischemic stroke, establishing the continued existence of the penumbra becomes particularly pertinent in extended time windows. Poor sensitivity or specificity in penumbral selection will lead to patients being inappropriately included for or excluded from therapy with obvious consequences.

A key question is to what extent current imaging approaches can accurately achieve this. An association between reperfusion and improved clinical outcome in patients with a penumbral imaging pattern has been demonstrated. Observational series have demonstrated feasibility of imaging selection for IV-tPA treatment beyond 4.5 hours and suggested reasonable safety. A small randomized trial successfully used penumbral imaging to demonstrate improved outcomes in patients treated with tenecteplase versus tPA. However, there has not yet been a large randomized trial to establish penumbral imaging definitively as an effective means to identify patients who will benefit from a treatment.

The noncontrast CT and clinical selection used in traditional IV-tPA trials allow considerable heterogeneity in pathophysiology, which may dilute the apparent effectiveness of treatment. Some patients eligible using these criteria have already reperfused or never had a major vessel occlusion in the first place. These individuals have a high likelihood of good outcome, regardless of treatment. Others have poor collaterals and a large ischemic core at baseline, with no potential benefit from thrombolysis and potentially increased risk of hemorrhagic transformation. In addition, tPA has limited success in rapidly recanalizing large-vessel occlusions, even within current time guidelines, further diluting the effect of treatment.

The DEFUSE (Diffusion and Perfusion Imaging Evaluation For Understanding Stroke Evolution) study delivered the first sophisticated analysis of the role of perfusion imaging in AIS management. Patients with a target mismatch profile showed a substantial effect of reperfusion on clinical outcome (odds ratio, 5.4; P=0.039). The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) of IV-tPA versus placebo also demonstrated a clear association of reperfusion with improved clinical and radiological outcomes in those patients with a target mismatch. Much was learned from these studies, and penumbral criteria were refined, leading to the DEFUSE-2 prospective cohort study in patients undergoing intra-arterial...
(IA) therapy. This trial used a fully automated postprocessing system (RAPID) to accelerate interpretation and improve reproducibility. Patients were treated 3 to 12 hours after symptom onset using IA-tPA and older generation endovascular devices. In this study, patients with a target mismatch who achieved reperfusion had an adjusted odds ratio of 4.0 (95% confidence interval, 1.3–12.2) for good functional outcome. The most exciting result of DEFUSE-2 was that imaging dispensed with time from symptom onset as the principal determinant of success. Mismatch patients treated early (≤6 hours) or late (>6 hours) showed no significant difference in favorable clinical response to reperfusion. This suggests that patients who are able to maintain a penumbra longer, presumably relating to good collateral vessels, represent a subpopulation who will benefit the most from reperfusion. A similar finding has also been demonstrated in functional outcomes using CT perfusion–based selection. The significance of this time-insensitive patient selection with respect to improving access to therapy for patients presenting beyond the current time limits or with unclear symptom onset cannot be overstated.

Recently, the first randomized controlled trial using penumbral imaging before IA therapy has been published, MR-RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy). Both MRI and CT perfusion were used to screen patients again with automated postprocessing software, RescueOnSite. Disappointingly, MR-RESCUE failed to demonstrate a favorable response to endovascular therapy based on penumbral patterns.

Significant differences in imaging protocols between DEFUSE-2 and MR-RESCUE may explain the contrasting outcomes. Patients in DEFUSE-2 had a median time from imaging to femoral puncture of 42 minutes. A median time from imaging to completion of intervention and therefore reperfusion of 90 minutes was reported. Reperfusion assessment was performed acutely, with median time from baseline MRI to follow-up MRI being 222 minutes. In contrast, MR-RESCUE reported a mean time from imaging to femoral puncture of 120 minutes. Unfortunately, no indication of procedure times has been given. The long time delay likely relates, in part, to randomization in MR-RESCUE. However, stroke is a dynamic condition, and penumbral status could have changed significantly during that time delay. Furthermore, reperfusion was not assessed until day 7, by which time spontaneous reperfusion is common but may have occurred too late to save brain.

The mismatch criteria used by the RAPID software in DEFUSE-2 were optimized based on DEFUSE and EPITHET data. In this work, determinants of the ischemic core and penumbra were based on longitudinal MRI studies in the presence or absence of reperfusion. Critically, reperfusion was assessed by perfusion imaging at a relatively early time point. Although the analysis was rigorous, the determinants were relatively simple. Ischemic core was defined using MR diffusion (apparent diffusion coefficient <600 × 10^-6 mm²/s). Penumbra was identified using a T_max >6-second threshold based on analysis of the best baseline perfusion lesion threshold to predict follow-up infarction in patients who did not reperfuse. These seemed to be robust on analysis of the DEFUSE-2 data set. MR-RESCUE used a remarkably complex multiparametric algorithm to estimate ischemic core that even included baseline National Institutes of Health Stroke Scale (NIHSS) in the case of CT perfusion. Maximum core volume for penumbral pattern was 90 mL in contrast to 70 mL in DEFUSE-2, and the penumbra in MR-RESCUE was estimated using T_max >4 seconds (which generates significantly larger volumes than T_max >6 seconds). These 2 factors would increase the likelihood of patients being classified as having mismatch in MR-RESCUE versus DEFUSE-2.

The primary analysis of DEFUSE-2 was reperfusion versus no reperfusion, whereas in MR-RESCUE it was embolectomy versus standard care. This meant that, although similar endovascular techniques were used in both trials, the low thrombolysis in cerebral infarction (TICI) 2b/3 successful recanalization rate of 27% in MR-RESCUE made it difficult to show benefit of treatment. MR-RESCUE did show trends toward improved functional outcomes in patients who achieved recanalization in both penumbral and nontumbral groups, but numbers were too small for detailed statistical comparison. Only 13.6% of patients achieved good functional outcomes (mRS, 0–2) in the absence of recanalization at day 7, all of which were from the penumbral group. In patients achieving recanalization, 28.4% also achieved good functional outcomes. The relatively small difference in good outcome between those with a penumbral pattern versus those without (34% versus 21%) suggests that the algorithm used in this trial had only modest success in identifying treatment responders.

In both DEFUSE-2 and MR-RESCUE, lack of investigator equipoise seems to be an issue. In DEFUSE-2, an average of 5.1 patients per site per year were enrolled versus 0.8 patients per site per year in MR-RESCUE. In contradistinction to DEFUSE-2, MR-RESCUE had larger initial ischemic core volumes despite a narrower time window (≤8 versus ≤12 hours). The low rate of enrollment and the larger ischemic cores imply that investigators, possibly because of personal convictions about the efficacy of IA therapy, did not randomize patients with smaller cores. Whereas the converse may be true for DEFUSE-2, investigators may have deemed reperfusion futile in patients with larger cores and not enrolled them. In fact, MR-RESCUE penumbral patients had similar cores to nontarget DEFUSE-2 patients (36 versus 45 mL). This likely explains the similarities in the functional outcomes in these 2 apparently contradictory groups (mRS, 0–2; ≈19% in both).

The significance of baseline ischemic core volume has only recently been refined. Current generation trials give this issue considerably greater emphasis (SWIFT-PRIME [ClinicalTrials.gov NCT01657461] <50 mL and EXTEND-IA [NCT01492725] <70 mL). The results of MR-RESCUE and DEFUSE-2, which at first seem to be contradictory, highlight the significance of ischemic core volume and its importance in patient selection. Furthermore, they highlight the importance of appropriate penumbral selection, particularly in patients treated later. Current trials are in a position to benefit from this experience, and this is reflected in their design.

**Endovascular Reperfusion Therapy**

Rapid and complete reperfusion is the goal of AIS intervention. Although the rates of reperfusion achieved with IV-tPA are modest in major vessel occlusion, particularly...
Compared with more aggressive modern techniques, it remains the only treatment with proven clinical benefit. The results of Prolyse in Acute Cerebral Thromboembolism Trial II (PROACT II) propelled intra-arterial thrombolysis forward and may be responsible for the developments in endovascular intervention today. PROACT II reported marked benefit compared with heparin control with a 15% treatment effect, surpassing even the National Institutes of Neurological Disorders and Stroke (NINDS) trial. At the time, it was felt that IA-tPA would lead to significantly improved reperfusion and thus better outcomes. Recently, 2 large multicenter randomized controlled trials have reported results comparing intravenous with IA thrombolysis. Both failed to demonstrate an advantage of an IA approach. These trials highlight the importance of patient selection, the need for speed, and the shortcomings of thrombolysis-based reperfusion.

The Italian SYNTHESIS trial compared endovascular therapy (the majority of patients receiving IA-tPA) with IV-tPA. It failed to show an advantage of IA compared with IV-tPA (odds ratio, 0.71; 95% confidence interval, 0.44–1.14). There was considerable delay in IA treatment (225 versus 165 minutes; P<0.001) and concerns about the intention-to-treat analysis and patient crossover. More significantly, the trial design underestimated the relevance of imaging-based patient selection. Patients were randomized based only on noncontrast CT brain to exclude hemorrhage. Noninvasive angiography was not performed to determine the presence of a vascular occlusion, and the absence of an occlusion on digital subtraction angiography was not a contraindication to IA-tPA. Furthermore, no attempt was made to exclude patients unlikely to have a target lesion clinically. Consequently, patients randomized to endovascular therapy had NIHSS of only 13 (median) with mild strokes (NIHSS as low as 2) included. In PROACT II, there was no significant difference between IA thrombolysis and heparin-treated controls in patients with NIHSS ≤11. The issue is well illustrated by the original SYNTHESIS pilot trial. In this study, patients more likely to have a target lesion were enrolled. The NIHSS of endovascular patients was 17 (median), with a range of 7 to 23 indicating exclusion of patients with mild strokes unlikely to have vascular occlusions. In this small study (n=54), 3-month good functional outcomes (mRS, 0–2) were achieved in 56% of patients treated with IA-tPA compared with 31% of those treated with IV-tPA.

The Interventional Management of Stroke III study (IMS III) tested a bridging approach of IV-tPA followed by IA therapy. The trial was stopped early because it crossed the prespecified boundary for futility. Two major criticisms of IMS III are the delay to endovascular treatment (mean 249 minutes after onset) and that patients were almost exclusively treated with either IA-tPA or older mechanical devices. As was shown for IV tPA, in the absence of penumbral imaging, time remains the most critical determinant of success in reperfusion therapy.

This would be expected to be of even greater significance in an AIS patient population selected based on severity (NIHSS ≥10 or >7 with a defined vessel occlusion). Obviously, the critical factor is time to reperfusion rather than time to starting intervention. No direct indication of procedural times is available for IMS III; however, relatively lengthy procedures can be inferred given the use of IA-tPA in 80% of patients. The IMS III protocol allowed for IA-tPA infusions ≤120 minutes, and in DEFUSE-2, the median IA-tPA procedure time was 90 minutes. In comparison, in the largest series published on the current-generation stentriever devices, procedure times are reported at 40 minutes (median). Furthermore, an endovascular bypass is often achieved, at least temporarily, at the time of first deployment, which was reported at only 26 minutes (median).

IMS III illustrates the absolute importance of quality reperfusion, building on reperfusion data from the previous IMS trials. Partial or complete reperfusion (TICI, 2–3) was achieved in 65% of internal carotid artery, 81% of M1, and 70% of M2 occlusions. On the surface, this would seem to compare with success rates using stentriever devices. However, these figures include patients who achieved reperfusion of less than half the affected vascular territory (TICI 2a). If TICI 2a patients are excluded, the IMS III rates of TICI 2b–3 reperfusion are 38% for internal carotid artery, 44% for M1, and 44% for M2 occlusions. This effectively halves the quoted reperfusion rate and is in stark contrast to previous studies.

Figure. Rates of good functional outcome (modified Rankin scale [mRS], 0–2) at day 90 stratified by thrombolysis in cerebral infarction (TICI) reperfusion grade. Data derived from IMS-III.
to stentrieversthat achieve TICI 2b-3 in >75% of patients in less than half the time.28,38

The prognostic relevance of quantifying the degree of reperfusion was investigated in DEFUSE-2. In patients with favorable penumbral imaging, the degree of reperfusion, assessed on early follow-up MRI, was divided into quartiles. A strong relationship between favorable clinical response and the degree of reperfusion was seen with rates increasing across each successive quartile: Q1 29%, Q2 44%, Q3 65%, and Q4 94%.39 Similar results were seen on analysis of IMS III reperfusion data.34 The degree of reperfusion (TICI) achieved directly correlated with good functional outcomes at 90 days (Figure). It seems that too few patients achieved quality reperfusion fast enough to save brain. In line with this interpretation, several recent studies have demonstrated that clinical outcomes after TICI 2a align closely with TICI 0 to 1 and that good outcomes usually require TICI 2b or preferably TICI 3.39,40 Subsequently, a recent position statement has recommended that procedures be performed with a view to a minimum reperfusion of TICI 2b.41 The hope for the future is that modern devices may more than double the rate of quality reperfusion in less than half the time.

Currently, stentrieversthe are the most appropriate first-line endovascular intervention supported by the literature, with technical results that seem superior to most other techniques and devices.42–45 Recently, stentrieversthave been demonstrated to improve functional outcomes compared with either IA-tPA or Merci Retriever.46 This suggests a direct translation from technical success to clinical success. The recent Solitaire Flow Restoration Thrombectomy for Acute Revascularization registry has demonstrated compelling technical success rates.29 Quality reperfusion was achieved, with 79.2% achieving TICI 2b-3 as adjudicated by the core laboratory. Significantly, the majority of these patients achieved TICI 3 reperfusion (54.7%). These results were achieved with a maximum of 3 Solitaire passes and a mean procedure time of 32 minutes from puncture to reperfusion. The importance of shaving off minutes once a patient reaches the site of care has already been well demonstrated for thrombolysis.47,48 Although there was no control group, the 58% rate of mRS 0 to 2, 7% mortality, and 1.5% symptomatic hemorrhage rate are impressive. It compares favorably with a recent study of IV-tPA in a similarly severe stroke population (median NIHSS=17) in which the rate of mRS 0 to 2 was 35%.11 Certainly, this is encouraging for current randomized trials involving stentrieversthat use more sophisticated imaging selection strategies.

Conclusions
Rapid reperfusion of the penumbra should be at the core of all AIS interventions. The highly individualized nature of the pathophysiology in AIS patients and the variability in achieving quality reperfusion among the various noninvasive and invasive interventions are becoming apparent. Technical advances in clot retrieval offer exciting prospects when combined with thoughtful patient selection and highly organized systems of care to expedite therapy. The current generation of randomized trials appear to acknowledge this complexity and will hopefully demonstrate clear advantages to aggressive strategies able to achieve timely, high-quality reperfusion to the ischemic penumbra.

Disclosures
Dr Campbell, Co-PI EXTEND-IA, received speakers’ honoraria from Boehringer Ingelheim and is a consultant for Lundbeck; Dr Chapot is a consultant for Coviden, Microvention, and Balt. The other authors report no conflicts.

References

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Topical Reviews

急性缺血性卒中
时间，半暗带和再灌注
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目前，对于发病 4.5 小时以内的缺血性卒中患者，推荐治疗方案是静脉溶栓，而且无需对患者大脑进行非增强计算机断层扫描(CT)以外的检查。迅速静脉注射组织纤溶酶原激活物(tPA)可以有效降低患者致残率。发病 3 小时内接受治疗的患者，3 个月内预后良好(改良Rankin量表[mRS], 0-2)的优势比为 1.53(95%CI, 0-2)。但是，与对照组相比，绝对增加仅为 9%，而且由于严格的时间限制，只有极少数的缺血性卒中患者能够采用该方案治疗。现代卒中影像技术使得获得每个卒中患者的病理生理机制非常方便。最关键的是患者的治疗效果。 目前，不仅可以通过常规观察栓塞病灶，还可以评估缺血核心区、未灌注区处于风险的半暗带组织，以及侧支供血状况。目前急性缺血性卒中(Acute Ischemic Stroke, AIS)介入治疗应当着重于半暗带区域的再灌注。最近研究已指出可通过影像筛选适合的患者，增加患者及时受治疗的机会，实现快速完全的半暗带再灌注很重要。

半暗带成像在患者筛选中的应用

每位 AIS 患者的三种实质性血管状态比例不同，这三种实质血管状态是缺血核心、半暗带、良性供血减少区。将半暗带同缺血核心区域分开，对于指导卒中的治疗非常关键。同样，将良性供血减少区同半暗带区分开也至关重要。根据定义，半暗带是处于会变成缺血核心区的风险组织。因此，半暗带是缺血再灌注的必要目标，也决定了病人的选择。鉴于缺血性卒中不断进展，在延迟的时间窗内保持半暗带持续存在就至关重要。在半暗带选择上，较高的敏感性或特异性都会导致患者不恰当地被纳入治疗范围内或排除到治疗范围外，造成明显不良后果。

关键的问题在于目前的成像方法能有多大程度精确完成半暗带的选择。目前已证明半暗带成像模式患者的再灌注和临床结果改善之间的联系。一系列观察研究说明，根据影像学成像技术选择发病超过 4.5 小时的患者行静脉 tPA 治疗是可行的，并且是安全的。一项小规模随机试验成功地应用半暗带成像技术表明了替奈普酶在改善临床结局方面的优势比为 4.0 (95%CI, 1.3-12.2)。DEFUSE-2 最令人兴奋的成果是影像检查免除了将症状开始的时间作为评估临床成功的主要决定因素。对于再灌注治疗后有良好临床结局，有半暗带的患者生存率(> 6 小时)或改善临床结局(n = 9)。然而，DEFUSE-2 研究未能证明血管内治疗对于半暗带模式的患者具有明确的临床治疗反应。DEFUSE-2 和 MR-RESCUE 研究成像方案的显著差异或许可以解释这种对立的结果。在 DEFUSE-2 研究中，患者从完成影像学检查到进行动脉内治疗的中位时间为 92 分钟，从完成影像学检查到完成介入治疗实现再灌注的中位时间为 90 分钟。然而行急性再灌注影像评

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估计,这样从基线 MRI 到随访 MRI 的中位时间为 222 分钟。相反,在
MR-RESCUE 研究中,从完成影像学检查到行股动脉穿刺的中位时间
为 120 分钟。不幸的是,未给予手术时间。在 MR-RESCUE 研究中,
长时间的延迟在一定程度上可能与随机化分组有关。然而,卒中是动
态变化的,半暗带状态可能在延迟时间内发生显著变化。此外,直至
第 7 天才进行再灌注评估,到那时自发性再灌注已很常见,但或许因
为出现太迟而无法挽救大脑。

在 DEFUSE-2 研究中使用的 RAPID 软件定义的不匹配标准,是
基于 DEFUSE 和 EPITHET 数据进行了优化。在该研究中,缺血核心
和半暗带的决定因素,是基于纵向 MRI 影像上的再灌注出现或缺乏。

血管内再灌注治疗

快速、完全的再灌注是 AIS 干预的目的。对大血管阻塞,虽然
IV–IA 治疗所实现的再通率有限,尤其相对于不断发展的现代技术,
但它仍然是证实具有临床获益的唯一疗法。PROACT II (Prolyse in
Acute Cerebral Thromboembolism Trial II) 研究结果向前推动了
动脉内溶栓,是今天血管内介入治疗发展的主要原因。PROACT II
研究结果显示了显著的获益,超过了肝素 15% 的疗效,甚至超过了
NINDS 研究成果。当时认为 IA–IA 治疗能显著改善再灌注,产生更
好的临床结局。最近,2 个大型的双中心随机对照试验比较了静脉溶栓
与动脉溶栓的疗效,结果均未证明 IA 治疗的优势。但这些试验强调了患
者筛选、治疗率的重要性,以及溶栓后再灌注损伤。

意大利 SYNTHESIS 试验比较了血管内治疗 ( 大部分患者接受
IA–IA 治疗 ) 与 IV–IA 治疗,也未能证明 IA 治疗相比 IV–IA 治
疗的疗效优势 ( OR 0.71; 95% CI 0.44–1.14)。在 IA 治疗以及考虑
性治疗分析和患者对照上都有相当大的延迟 (225 vs. 165 min, P<0.001)。

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为出现太迟而无法挽救大脑。
在 DEFUSE-2 中，研究了量化的再灌注程度与预后的相关性。在具有良好半影成像的患者，早期应用 MRI 随访评估，将再灌注程度分为四分位。随着每个连续四分位百分率的增加：Q1 29%，Q2 44%，Q3 65%，和 Q4 94%，可观察到良好临床反应与再灌注程度强烈相关。在 IMS III 再灌注数据中也能观察到类似结果。再灌注程度 (TICI) 与 90 天良好功能结局直接相关 (图)。但似乎只有很少的患者能快速达到良好的再灌注从而挽救大脑。与此结论一致的是，最近的研究也表明血流分级 TICI 2a 的临床结局与 TICI 0-1 相似，良好的临床结局通常需要 TICI 2b，最好是 TICI 3。因此，最近一种观点推荐进行手术至少应使再灌注血流达到 TICI 2b。期望未来能借助现代化的设备，使良好再灌注率加倍，并且实现再灌通时间不到当前时间的一半。

目前，根据已发表文献，Stentrievers 是最适合血管内介入治疗的首选装置，其技术疗效似乎比其他大多数技术和设备都优越。最近，有研究证明，相比 IA-tPA 或 Merci 取栓器，Stentrievers 能改善功能结局。这表明了从技术成功到临床成功的直接转化。最近 Solitaire 取栓用于急性血运重建登记研究已取得了令人瞩目的技术成功率，有 79.2% 的患者达到核心实验室判定的 TICI 2b-3。更值得注意的是，大部分患者都达到了 TICI 3 再灌注 (64.7%)。这些患者中最多使用了 3 次 Solitaire，而且从穿刺到再灌注的平均手术时间为 32 分钟。溶栓治疗时，非常重要的一点是缩短患者到达医疗机构的时间。虽然没有对照组，但有 58% 的患者 mRS 0-2，死亡率 7%，症状性脑出血率 1.5%，这些研究结果非常可观。而最近一项在类似严重卒中患者 (中位数 NIHSS =17) 应用 IV-tPA 治疗的研究，mRS 0-2 的百分率仅 35%。当然，对于当前应用 Stentrievers 装置的随机研究，配合使用更加高级的影像筛选策略更鼓舞人心。

结论
实现快速的半暗带再灌注应是所有 AIS 干预措施的核心。AIS 患者病理生理的高度个体化差异，以及应用侵入性和非侵入性干预措施后取得良好再灌注的可变性越来越明显。取栓技术的进步，加上合理化患者筛选以及加快治疗的高度组织化医疗系统，都提升了未来卒中治疗的完美前景。当前的随机试验似乎都承认了这些复杂性，希望未来能够阐明实现缺血半暗带及时、高质量再灌注积极策略的明显优势。

参考文献