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Review

The Aspirations of Direct Aspiration for Thrombectomy in Ischemic Stroke: A Critical Analysis

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The treatment of acute ischemic stroke by mechanical thrombectomy has been revolutionary, however most of the clinical trials were done with the use a stent retriever. At the same time, an alternative technique of thrombectomy through direct aspiration with a large bore distal access catheter at the face of the clot is rapidly gaining popularity. Nonetheless, the data supporting this new technique is not yet as mature as that available on stent retrievers. This review is a critical analysis of the evidence supporting the principle of direct aspiration thrombectomy and a discussion of its potential strengths and weaknesses in comparison to the available studies on stent retrievers. While this is by no means a conclusive review, it should serve as a yardstick of where the science is currently, and what are the next trials that are necessary.

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Introduction

The treatment of acute ischemic stroke (AIS) has been revolutionized by the advent of modern endovascular techniques. Currently, the two most widely used methods of mechanical thrombectomy are the use of a stent retriever and the direct aspiration approach. The majority of patients in the recent randomized trials of endovascular stroke therapy that established the role of mechanical thrombectomy in AIS were treated with stent retrievers. At the same time, an alternative technique of thrombectomy through direct aspiration has gained popularity,[1] where the clot is removed through suction applied with a large bore distal access catheter at the face of the clot. If this primary suction fails, a rescue treatment is commonly performed with a stent retriever coaxially introduced through the same distal aspiration catheter.[2,3] In spite of the recent increasing popularity of direct aspiration,[1] the data supporting this technique is not yet as mature as that available on stent retrievers. This review is a critical analysis of the evidence supporting the principle of direct aspiration thrombectomy and a discussion of its potential strengths and weaknesses and a suggestion of what future trials should focus on.

Statistical, clinical, and radiological endpoints in thrombectomy trials

While statistical significance data is often reported by the authors of a study in an effort to claim that they have a positive

and clinically impactful study, it is important to examine the study design to determine the validity of their data. The difficulty with comparing these various direct aspiration studies and stentretriver thrombectomy studies stems from the unequal endpoints and trial design.

It should be clear from the study design if it is a superiority, non-inferiority or equivalence trial as the sample size is usually markedly different, not to mention the clinical conclusions which can be drawn from it. The readers should note if the outcomes are reported in an "intention to treat" format or in a "per-protocol" format. The type of primary outcomes noted as "clinical outcomes" are considered a higher quality of evidence than "radiological outcomes" in stroke trials. An example would be that a modified Rankin Scale (mRS) improvement is considered to be higher quality evidence than the radiological modified treatment in cerebral ischemia (mTICI) 2b–3 recanalization. In turn there are some outcomes which are more widely accepted than others, for example: mRS 0–2 is more widely accepted than mRS 0–1 and similarly mTICI 2b–3 is more accepted than mTICI 2–3. Finally, statistical significance is not the same as clinical significance. With sufficient subjects a study would be powered to tease apart the difference between a 95% recanalization device from a 94% recanalization device, but it would not have much clinical difference. With this in mind, we looked at the available direct aspiration randomised controlled trials (RCTs).

THERAPY

While there is incontrovertible evidence that mechanical thrombectomy with stent retrievers is superior to intravenous tissue plasminogen activator (IV tPA) in the management of AIS with large vessel occlusion (LVO), there is no comparable robust randomised data favouring direct aspiration versus IV tPA. Since the principle of recanalization with a stent retriever is different from that with direct aspiration, blind extrapolation of the virtues of the former to the latter is not prudent. This may seem self-evident but the only randomised study comparing direct aspiration + IV tPA versus IV tPA alone was the The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (THERAPY) study.[4] It was terminated early because of concerns that treating patients with IV tPA alone would be unethical in light of the successful stentretriver thrombectomy trials. Based on the analysis of the 108 patients recruited into this study, before it was aborted, the investigators concluded that THERAPY did not achieve its primary endpoint of superiority over IV tPA, notwithstanding a trend to-

Table 1. Study design and outcomes in the aspiration trials

Title	Study design	Primary outcome	Power and target sample size	Treatment arm	Control arm	Results (primary outcome)	*P*	Comments
THERAPY	Superiority	mRS 0–2	692 Patients, 80% power, α value of 0.05 ,10.6% difference in mRS 0–2 at 90 days	Aspiration (n=55)	IV tPA (n=53)	ITT (19/50, 38% vs. 14/46, 30%)	0.44	Terminated prematurely
ASTER	Superiority	mTICI 2b/3	380 Patients, 90% power with a α=0.05, and 15% difference in recanalization	Aspiration (n=192)	Stentretriver (n=189)	ITT (164/192, 85.4% vs. 157/189, 83.1%)	0.53	Used radiological endpoints not clinical endpoints
Penumbra separator 3D	Non-inferiority	mTICI 2/3	206 Patients, 85% power with a α=0.05 and difference of 15%	Intermediate catheter aspiration+stentretriver (n=98)	Intermediate catheter aspiration (n=100)	ITT (82/94, 87.2% vs. 79/96, 82.3%)	0.34	Unusual mTICI 2/3 endpoint Possibly underpowered
COMPASS	Non-inferiority	mRS 0–2	244 Patients, 80% power, one sided, non-inferiority margin of 15% and α=0.05	Direct aspiration (n=134)	Stentretriver (n=136)	ITT (49% vs. 52%)	0.0014	Provisional information, awaiting final publication

THERAPY, The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke; mRS, modified Rankin Scale; IV tPA, intravenous tissue plasminogen activator; ITT, intention to treat; ASTER, Direct Aspiration First Pass Technique for Thrombectomy Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke; mTICI, modified treatment in cerebral infarction; 3D, 3-dimensional; COMPASS, comparison of direct aspiration versus stent retriever as a first approach.

wards a benefit. Because the study was underpowered due to the early termination, we cannot be certain that there is a benefit with the aspiration devices used in the trial as compared to medical therapy. The treatment effect based on the point estimates observed in THERAPY was lower than seen win stent retriever trials, but this may be due to the fact that they excluded patients with thrombus length <8 mm or patient selection factors in addition to differences in thrombectomy efficacy.[5]

In any case, now that stent retrievers have become the standard of care for LVO stroke, for ethical reasons, future thrombectomy devices should be compared against established stent retrievers and not IV tPA (Table 1).

ASTER

The Direct Aspiration First Pass Technique for Thrombectomy Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke (ASTER) study was a randomized controlled trial with the aim of comparing direct contact aspiration technique to stent retriever thrombectomy in acute stoke with a primary endpoint of mTICI 2b or better revascularization at the end of all endovascular procedures.[6] It enrolled 381 subjects with 192 in the aspiration arm and 189 in the stent retriever arm. There were several protocol violations in the study as seen by the 18 patients randomized to the aspiration group who did not receive aspiration, while in the stent retriever group, five patients were mistakenly treated with direct aspiration.

The study had a higher than expected mortality rate with 19.3% in the contact aspiration arm and 19.2% in the stent retriever arm. The adverse event rate was also high for symptomatic intracranial haemorrhage, subarachnoid haemorrhage and new strokes in different vascular territories in both arms of the study. This was despite excluding patients with more complicated occlusions such as tandem cervical plus middle cerebral artery (MCA) occlusions as well as basilar occlusions.

For the primary outcome measures, if we examine the figures provided in the paper, the mTICI score was actually better in the stent retriever group after the first-line strategy alone, with a higher proportion of mTICI 2b–3 (63% in the contact aspiration vs. 68% in the stent retriever group). Although not statistically significant, the absolute number of TICI 3 recanalization were also higher with frontline stent retriever use as compared to contact aspiration (35.4% vs. 28.6%). As stent retriever thrombectomy was a bail-out strategy for failed contact aspiration thrombectomy, recanalization results of the contact aspiration group must be interpreted with great caution: at the end of all endovascular procedures, the contact aspiration group had a larger proportion of mTICI 2b–3, but only after it was bailed-out with stent retrievers. Hence, there is an uncertainty on how much of the trend towards better mTICI scores in the contact aspiration arm is attributable to the additional use of stent retrievers. This is reflected in the higher use of bail-out procedures in the aspiration group (32.8%) compared to the stent retriever group (23.8%), although this did not reach statistical significance.

It is important to note that the ASTER trial's primary endpoints were mTICI 2b–3 recanalization which is a radiological marker. While mTICI 2b–3 is associated with better functional outcomes, this is nonetheless not a clinical marker and is therefore a lower level of evidence compared to actual functional markers such as the mRS.

In the supplementary section of the ASTER study, data was shown where the mRS 0–2 at 3 months was 45.3% (82/181) in the contact aspiration group and 50% in the stent retriever group (91/182). The mRS 0–1 was 32.6% (59/181) and 42.9% (78/182), the mRS 0 was 13.3% (24/181) and 22.0% (40/182) in the aspiration and stent retriever arms, respectively. There was a statistically significant better excellent outcomes (mRS 0–1) with stent retrievers compared to contact aspiration, but good outcomes (mRS 0–2) did not reach statistical significance.

Finally, the initial aim of the trial was to show 'superiority' of contact aspiration compared to stent retrievers;[7] however, the authors concluded that contact aspiration was 'non-inferior' to stent retrievers. At 80% power with a 2-sided significance level of 0.05 to detect a 5% clinical difference, the sample size of a non-inferiority trial would require four times as many patients (Supplementary material).[8,9] The study was underpowered to reach their conclusions based on their initial superiority design. So, in essence, the study proved neither superiority nor non-inferiority of direct aspiration to stent retrievers (Table 1).

M2 occlusions

The ASTER trial investigators later looked at a sub-study which compared direct aspiration against stent retriever use in M2 occlusions.[10] Forty-eight patients were randomized to the direct aspiration arm and 31 to the stent retriever arm. The authors found no significant difference between the two arms for mTICI 2b–3 reperfusion and 90 days mRS scores.

M2 lesions generally occlude branches that supply smaller areas than more proximal M1 or internal carotid artery (ICA) occlusions with a smaller clinical deficit and therefore, with a small sample size of 79 patients the authors were unable to find a significant difference. This may be largely due to the study being underpowered to show a difference. However, it is

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worthwhile noting that there was a higher but not significant rate of mTICI 3 reperfusion when stent retrievers were used as a first line compared to aspiration (38.7% vs. 29.2%, *P*=0.33). It is also noteworthy that the two reported instances of 'embolization to new territory' events occurred in the aspiration cohort with none in the stent retriever arm.

Another interesting observation in the ASTER sub-study was that the 24-hour change in National Institute of Health Stroke Scale (NIHSS) score had a trend towards better outcomes with stent retriever treatment and so was the change in ASPECT score at 24 hours. Similarly, there was considerably higher mortality at 90 days in the aspiration cohort (19.6% vs. 3.3%, *P*=0.078) together with a non-significantly higher rate of procedure related adverse events (14.6% vs. 9.7%, *P*=0.73). It is debatable if a slightly larger sample size would render these findings statistically significant.

Penumbra separator 3D trial

The 3-dimensional (3D) revascularisation device is a new stentretriver from Penumbra (Alameda, CA, USA), not to be confused with the aspiration catheter from the company. A multicentric randomized control trial from North America was performed to study whether this novel device in conjunction with an intermediate aspiration catheter, was non-inferior to direct aspiration with the intermediate catheter alone.[11] They recruited 198 patients with 98 in the combination arm and 100 in the direct aspiration alone arm.

The primary endpoint for the trial was mTICI 2–3 recanalization, which was achieved in 87.2% of the patients in the stent retriever group compared with 82.3% in the direct aspiration group (difference, 4.9%; 90% confidence interval [CI], −3.6% to 13.5%). This is an unusual endpoint as most current thrombectomy studies define successful recanalization as mTICI 2b–3 rather than mTICI 2–3. If we examine this endpoint, 81.9% of the patients treated with the combination therapy achieved mTICI 2b–3 recanalization compared to 69.8% of the direct aspiration patients, with a significant difference favouring the combination therapy group (difference, 12.1%; 90% CI, 2.0% to 22.2%). This is not surprising as many of the recent studies using a combination of stent retrievers and aspiration catheters, such as in the stent retriever assisted vacuum-locked extraction (SAVE) technique, show high rates of mTICI 2b–3 recanalization.[12]

The authors used a 15% non-inferiority margin to calculate their sample size; however, looking at the ASTER trial, there was only a 5% difference in the mTICI 2b–3 recanalization rate. This could mean that using such a large difference of 15% to calculate the sample size, the trial was likely underpowered to detect a real difference between the two treatment modalities. Similarly, for the secondary endpoints such as mRS 0–2 at 90 days or mortality, it will also be insufficiently powered.

In this trial, the direct aspiration group seems to be faster than the stent retriever group from groin puncture to mTICI 2b–3 recanalization by a median of 10 minutes although it was not analysed if it was statistically significant. This is not surprising as the combination therapy constitutes two techniques merged into one therapy. In most of the other direct aspiration versus stent retriever trials; however, a similar trend is seen favouring direct aspiration for the speed of the procedure (Table 1).

Predictors of success with aspiration

Blanc et al.[13] sought to determine the predictors of a successful aspiration technique in the anterior circulation. They performed a retrospective analysis of prospectively gathered data and included 347 patients treated with aspiration as the initial technique. They saw that aspiration was successful in achieving recanalization of TICI 2b–3 in 55.6% (193/347) with a median of two passes. They noted that rescue treatment was required in 40% of patients (138/347). The majority of patients with successful reperfusion using aspiration first had clots located in the MCA although it is not clear whether this refers to the M1 segment, the M2 segment or both. The authors suggest that this may be due to an optimised ratio between the size of the vessel and the aspiration catheter that leads to better ingestion of the clot. Whilst this seems plausible and is in line with *in vitro* studies published by Nikoubashman et al.,[14,15] this issue is reduced with the use of stent retrievers since they, by design, adapt to the vessel diameter and therefore minimise issues of size. A sub-group analysis of the ASTER trial data comparing the results of patients with M1 clots would help to shed light on whether there is an optimal strategy based on clot location especially given that the majority of patients in this trial had clots that were located in the M1 segment. Lastly, one location where direct aspiration may be safer is the basilar artery, which can avoid perforator occlusions by snowplowing complications during stent deployment. Although not much data is available, there are small preliminary trials showing that direct aspiration is feasible in basilar occlusions.[16]

Strengths and weaknesses

Mechanical thrombectomy with stent retrievers and direct aspiration both have their potential advantages and disadvantages. The direct aspiration approach has a faster punc-

ture-to-recanalization time with a superior cost-effectiveness over stent retriever thrombectomy;[17] however, it may come with the downside of emboli breaking off distally during withdrawal and a greater need for bail-out techniques, which would then have an impact on the cost and the puncture-to-final-recanalization time. Trials currently report the rate of emboli to new uninvolved territories; however, the rate of distal emboli in the affected vessel should be reported as well. In fact, Chueh et al.[18] have shown in an *in vitro* model that the number of emboli is significantly higher in A Direct Aspiration First Pass Technique (ADAPT) thrombectomy compared with stent retriever thrombectomy. There is also evidence that thrombectomy with a stent retriever may result in damage to the endothelium compared to direct aspiration although the significance of this is as yet unknown.[19,20] The choice of adjunctive devices such as the use of a balloon-guide catheter may affect the success rate of thrombectomy and we have yet to see many trials where a balloon guide catheter is used in conjunction with a distal aspiration device. In fact, the poorer clinical outcomes of direct aspiration in RCTs compared to stent retriever trials (Figure 1) may well be due to the absence of balloon guide catheter usage which has a more widespread use in conjunction with stent retrievers. Finally, nowadays larger aspiration catheters such as the ACE 68, Sophia 070, and Navien 072 are routinely used and may be more effective but have yet to be evaluated in randomised clinical trials.

The location of the occlusion matters as well as a smaller artery, such as the distal M1 or M2, is probably a better site for use of the currently available aspiration catheters that can snugly fit into these vessels and exert better suction, if the vessel does not collapse, as compared to terminal ICA where the calibre of the artery, and consequently also the target thrombus, is most likely considerably bigger than the aspiration catheter. Conversely, if the vascular anatomy is tortuous, navigating a stent retriever into the M2 can be challenging. Dragging a stent retriever from M2, which is a much more mobile branch than M1 or ICA termination, into a balloon guide in the cervical ICA can also potentially cause avulsion of small perforators, especially if there is no supporting distal access catheter used as an intermediary, stabilizing the system and providing a better transmission of the pulling force.

The type of pump delivering the suction force may make a difference in the outcomes of the direct aspiration method. The rationale of the ADAPT technique is to engage a clot with a catheter and to establish adherence between clot and catheter with suction force. This force is the product of the cross-sectional area at the catheter tip and the applied pressure gradient. However, clot stripping and fragmentation with consecutive distal embolization may be potentially important mechanisms that may occur unnoticed. In this case, it is not the force at the catheter tip, but the flow through the aspiration catheter, which is important to allow for clot ingestion and to prevent clot embolisation. Ideally, this flow needs to be strong enough to overcome any anterograde flow around the guide catheter as well as the cross flow from a patent anterior communicating artery. This is to minimise any risk of distal embolization with withdrawal of the clot during thrombectomy.[21] A recent study has shown that the best reverse flow is achieved with a manual syringe and a Dominant Flex (Medela, Baar, Switzerland) suction pump and least strong with the Penumbra MAX aspiration pump.[15,22] The clinical significance of this difference in flow remains to be seen in further studies.

Clot characteristics are important in the choice of method of thrombectomy. Thrombus size and composition are key factors in determining susceptibility to mechanical manipulation and the degree of successful recanalization. It determines the forces of

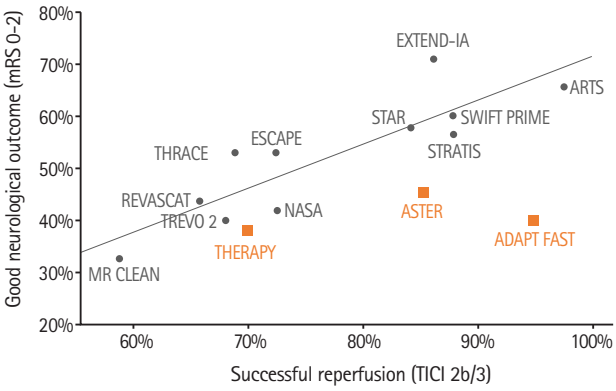

Figure 1. Relationship between successful reperfusion and good functional outcomes in the various thrombectomy trials. mRS, modified Rankin Scale; TICI, treatment in cerebral infarction; MR CLEAN, Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands; REVASCAT, Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; TREVO 2, Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke 2; THRACE, Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; NASA, North American Solitaire Stent-Retriever Acute Stroke; THERAPY, The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial; STAR, Solitaire Thrombectomy for Acute Revascularization; SWIFT PRIME, Solitaire FR With the Intention For Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; STRATIS, Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke; ASTER, Direct Aspiration First Pass Technique for Thrombectomy Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke; ARTS, Aspiration-Retriever Technique for Stroke; ADAPT FAST, A Direct Aspiration, First Pass Technique for the Endovascular Treatment of Stroke.

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friction and adhesion between the thrombus and the vessel wall and determines the extent that the stentretriver struts can indent on the thrombus. Fibrin-rich thrombi have a much higher coefficient of static friction than red-cell rich thrombi and are more vulnerable to compression from each thrombectomy attempt, which increases the friction of the thrombus.[23-25] Larger thrombus sizes also increases the friction and adhesion forces resulting from the larger surface area between the thrombus and vessel. The age and stage of the organization of the thrombus plays a role as well. A fibrin-rich thrombus which has been given time to evolve is firm and adherent, making it a challenge for both conventional stent retrievers and aspiration approaches. In these types of situation, a balloon guide catheter to break the pressure gradient created by the water-hammer effect of systolic blood pressure, or an intermediate catheter to pin the thrombus against the stentretriver, can be effective. Newer stent retrievers designed to capture rather than penetrate the thrombus may fare better as well as larger bore aspiration catheters to engulf the clot whole. A recent sub-analysis of the ASTER trial suggested that imaging markers reflecting clot characteristics could help determine which method to use. The presence of a susceptibility vessel sign on T2* gradient gradient echo sequence on magnetic resonance imaging scans were associated with better recanalization using a stentretriver. In occlusions without a susceptibility vessel sign, direct aspiration and stentretriver recanalization were not significantly different.[26]

Future aspiration studies

In light of the current evidence which has been presented, the American Heart Association/American Stroke Association guidelines for 2018 recommended that direct aspiration as a first line is a "class 2B" strength of recommendation with a B-R level of evidence.[27] While the European guidelines have yet to be updated, they still cite the evidence for direct aspiration as weak.[28,29] With comparison of direct aspiration versus stent retriever as a first approach (COMPASS) trial on the verge of publication, it seems as if we are at the precipice of a new understanding of the advantages and disadvantages of direct aspiration thrombectomy. Future studies can ride on these current ones to accurately calculate a sample size and if not prohibitively expensive, superiority trials to move the field forwards should be aimed for rather than non-inferiority. The current excellent recanalization rates with devices also means that better recanalization rates is a target with diminishing returns. We should instead look to how these devices function for distal emboli in the same territory or other factors which can reduce the proportion of patient's who achieve successful recanalization but yet do not achieve mRS 0–2.

It seems evident that the best treatment for patients is to achieve full recanalization (TICI 3) in the first attempt.[30] Repeat attempts inevitably destabilize the thrombus and will increase the number of downstream emboli. Moreover, repeat attempts increase the time to recanalization, and will thereby have a negative effect on neurological outcome. Future analyses to evaluate recanalization techniques should therefore consider "first-pass TICI 3" rates.[30]

A final but important point is that many thrombectomy device trials tend to report mTICI recanalization rates which include both the initial attempt and the use of rescue devices. It is difficult to then tease out what is the actual efficacy of a certain device. Future studies should include the recanalization rates for the initial device only, before any rescue device has been used, especially if the rescue device is the primary one in the other arm of the study.

Conclusions

While the evidence is building that direct aspiration is a viable method for thrombectomy, we need to be clear that currently there is no robust evidence that direct aspiration is superior or even comparable to the use of stent retrievers. Nonetheless this field is a moving target and with the advent of large bore aspiration catheters, results are improving. The initial results of the COMPASS trial has been presented and the upcoming full publication results will hopefully shed some new light on this contentious issue.[31] Finally, these techniques may not have to be mutually exclusive and either method could be superior in a particular anatomical scenario or occlusion type. Future research to determine the optimum appropriate subgroups for each method is needed.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2018.02026.

Disclosure

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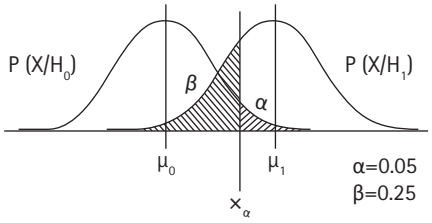
Supplementary material

Fundamental equations[8]

Parameter	Superiority trial	Inferiority trial
Purpose	Intervention is 'better' than control	Intervention is 'not worse' than control
H0 (null hypothesis)	$H_0: \mu_I - \mu_C = \delta$	$H_0: \mu_I - \mu_C = \delta$ Or $H_0: \mu_C - \mu_I = \delta$
Meaning	Intervention is better than control by a clinically admissible margin, delta	Intervention is worse than control by a clinically admissible margin, delta
H1 (alternative hypothesis)	$H_1: \mu_I - \mu_C > \delta$	$H_1: \mu_I - \mu_C > -\delta$
Meaning	Intervention is better than control by at least delta (a clinically admissible margin)	Intervention is NOT worse than control by delta (a clinically admissible margin), and can be better
Test statistic	$z = \frac{(d-\delta)}{\sigma}$	$z = \frac{(d-\delta)}{\sigma}$
Difference	Difference in effectiveness, $\mu_I - \mu_C$	Difference in effectiveness, $\mu_I - \mu_C$
N, sample size	$N = 2 \times \left[\frac{z_{1-\alpha} + z_{1-\beta}}{\delta - \delta_0}\right]^2 \times s^2$	$N = 2 \times \left[\frac{z_{1-\alpha} + z_{1-\beta}}{\delta_0}\right]^2 \times s^2$

Type 1 error, type 2 error, power



α Type I error: rejecting the null hypothesis when it's actually true usually 0.05, usually 2-sided

β Type II error: unable to reject H0 when it should be rejected

Power = 1 – β, usually set to 0.8

ASTER trial calculations

δ	Expected clinical difference – 15%
δ_0	Clinically significant difference – 5%
α	0.05
β	0.20
$z_{1-\alpha}$	1.645
$z_{1-\beta}$	0.842
N_{CS}	Sample size, clinical superiority
N_{NI}	Sample size, non-inferiority

ASTER, Direct Aspiration First Pass Technique for Thrombectomy Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke.

Sample size calculations[9]

$$\frac{N_{CS}}{N_{NI}} = \frac{2 \times \left[\frac{z_{1-\alpha} + z_{1-\beta}}{\delta - \delta_0}\right]^2 \times s^2}{2 \times \left[\frac{z_{1-\alpha} + z_{1-\beta}}{\delta_0}\right]^2 \times s^2}$$

$$\frac{N_{CS}}{N_{NI}} = \frac{\cancel{2\times}\left[\frac{z_{1-\alpha} + z_{1-\beta}}{\delta - \delta_0}\right]^2 \cancel{\times s^2}}{\cancel{2\times}\left[\frac{z_{1-\alpha} + z_{1-\beta}}{\delta_0}\right]^2 \cancel{\times s^2}}$$

$$\frac{N_{CS}}{N_{NI}} = \frac{[\delta_0]^2}{[\delta - \delta_0]^2}$$

$$\frac{N_{CS}}{N_{NI}} = \frac{[0.05]^2}{[0.15 - 0.05]^2}$$

$$\frac{N_{CS}}{N_{NI}} = \frac{[0.05]^2}{[0.1]^2}$$

$$\frac{N_{CS}}{N_{NI}} = \frac{0.0025}{0.01}$$

$$\frac{N_{CS}}{N_{NI}} = \frac{25}{100} = \frac{1}{4}$$

$$N_{NI} = 4 \times N_{CS}$$

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