Influence of trial design, heterogeneity and regulatory environment on the results of clinical trials: An appraisal in the context of recent trials on acute stroke intervention

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Abstract

The outcome of randomized controlled trials can vary depending on the eligibility criteria of the patients entering into the trial, as well as the heterogeneity of the eligible population and/or the interventions. If the subject population and/or interventions are heterogeneous, the final outcome of the trial depends on the degree of concordance of effects of the subgroups of interventions on the subgroups of the subject population. The considerations that go into the calculation of sample size and determination of the study stopping rules also would affect the nature of the outcome of the study. In this paper we try to examine these phenomena with respect to the recent trials on endovascular therapy in acute ischemic stroke.

Key Words

Heterogenity in clinical trials, discordant subgroups, endovascular acute stroke intervention, SYNTHESIS Expansion, IMS III, MR Rescue, SWIFT

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The recently published Solitaire With the Intention For Thrombectomy (SWIFT)[1] and the Diffusion and Perfusion Imaging evaluation for Understanding of Stroke Evolution 2 (DEFUSE 2)[2] studies draw interesting comparison with the results of Local versus Systemic Thrombolysis for acute Ischemic Stroke (SYNTHESIS Expansion),[3] Interventional Management of Stroke (IMS-III)[4] and Mechanical Retrieval and Recanalisation of Stroke Clots Using Embolectomy (MR RESCUE).[5] While the SWIFT study that compared the stent retriever solitaire with the 'standard of care' Merci mechanical thrombectomy device showed superior outcome to the tune of 25% absolute risk reduction in modified Rankin scale (mRS) of 2 or less in favor of Solitaire, the DEFUSE 2 showed that magnetic resonance imaging (MRI) based risk profiling based on diffusion-perfusion mismatch can predict favorable outcome in patients undergoing endovascular therapy with an odds ratio of 8.8. In contrast, SYNTHESIS Expansion and IMS-III did not find any greater benefit in patients undergoing endovascular therapy. The MR RESCUE trial failed to show benefit of favorable diffusion-perfusion mismatch pattern in predicting response to endovascular therapy. In this paper, we argue that the discordance of the results of these studies warrants closer scrutiny of the methodological difference between these trials.

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Overview of the Trials

To give an overview, between October 2012 and March 2013, six studies were published on the topic of acute ischemic stroke intervention: SYNTHESIS Expansion, IMS III, MR RESCUE, SWIFT, TREVO II and DEFUSE 2.

SYNTHESIS Expansion[3] was a randomized control trial (RCT) evaluating the efficacy of endovascular therapy against intravenous tissue plasminogen activator (IV tPA) in acute ischemic stroke patients presenting within 4.5 hours of onset where IV tPA is deemed appropiate or those patients within 6 hours of onset of stroke where IV thrombolysis is considered possible. There were no additional clinical or imaging criteria for the selection other than those used in selection of patients for IV tPA in the National Institute of Neurological Disorders and Stroke (NINDS) Recombinant Tissue Plasminogen Activator Stroke trial (NINDS trial) criteria. The study found that endovascular therapy is not better than standard therapy with IV tPA.

IMS-III[4] was a RCT in which the patients who presented within 3 hours of onset of acute ischemic stroke were randomized to endovascular therapy in addition to IV tPA or IV tPA alone. The eligibility criteria were similar to that of the NINDS trial except that the National Institutes of Health Stroke Scale (NIHSS) score need to 10 or more or eight or more if there was imaging evidence of occlusion in internal carotid artery, proximal middle cerebral artery (M1) or basilar artery. The trial was prematurely stopped because of futility due to absence of difference between the groups.

MR RESCUE[5] evaluated whether risk stratification based on diffusion-perfusion mismatch pattern would predict favorable outcome in patients undergoing mechanical thrombectomy in large vessel anterior circulation stroke within 8 hours of onset. The study population was randomized between mechanical thrombectomy and standard medical care. The study did not show that neuroimaging was able to better identify patients who benefit from endovascular therapy.

SWIFT[1] was a non-inferiority RCT comparing the newer generation stent retriever Solitaire with the United States Food and Drug Administration (US-FDA) approved embolectomy device Merci. The eligible population was acute ischemic stroke with angiographically confirmed proximal cerebral artery occlusion, treatable by thrombectomy within 8 hours of onset of stroke. Inclusion criteria included NIHSS score between 8–30 hours and ineligibility or failure to respond to IV tPA. While the primary outcome was successful recanalization without rescue treatment and no symptomatic hemorrhage, the secondary outcome included good neurological outcome at 90 days defined as mRS of 2 or less or NIHSS score improvement 10 or more. The study found, of interest to the present discussion, that patients randomized to the Solitaire arm had good neurological outcome with an absolute risk reduction of 25%.

TREVO 2,[6] similar to SWIFT, was a non-inferiority trial comparing the newer stent retriever Trevo with Merci. The inclusion criteria was adults (18-85 years) presenting with acute ischemic stroke within 8 hours of onset with an angiographically confirmed proximal cerebral artery occlusion (ICA, M1/M2 segments of MCA and basilar and/or vertebral artery), amenable to endovascular therapy. Patients needed to have NIHSS score of 8-29, and to be ineligible to IV tPA or have had failure of treatment with IV tPA. The primary efficacy end point was recanalization rate, and the secondary efficacy end point included 90-day good outcome defined as mRS two or less. The study found that clinical outcome was better in Trevo group with an absolute risk reduction of 18%.

DEFUSE 2 was a prospective cohort study that evaluated the utility of MRI based diffusion perfusion mismatch in identifying patients who were likely to improve with endovascular intervention. It used an image-reconstruction software to generate quantitative diffusion and perfusion weighted MRI lesion maps with a processing time of 4-7 minutes. Follow-up MRI scan assessed reperfusion and was defined as 50% reduction in the volume of the lesion on perfusion-weighted MRI. The primary outcome was 8 or more improvement on NIHSS between baseline and day 30 or a score of 0-1 at day 30. The secondary endpoint was mRS score two or less at day 90. The study found that the adjusted odds ratio for favourable clinical response associated with reperfusion was 8.8 (95% confidence interval 2.7-29) in the patients with significant diffusion-perfusion mismatch (the target mismatch group), and 0.2 [95% confidence interval (CI) 0.0-1.6] in the patient group with no target mismatch. Reperfusion effected favorable clinical outcome at 90 days in the target mismatch group Odds Ratio (OR) 4, 95% CI 1.3-12.2], but not in the group without target mismatch (OR 1.9, CI 0.2-18.7). The study showed that reperfusion alone did not effect better clinical outcome. Only when reperfusion was associated with target mismatch did the endovascular intervention tend to yield favorable clinical outcome. This difference in better outcome in patients with target mismatch did not decrease with duration of onset of stroke.

Synthesis Expansion

In the report on SYNTHESIS Expansion, the authors mention as the rationale of their study, the poor generalizability of the results of Prolyse in Acute Cerebral Thromboembolism II (PROACT II) and Middle Cerebral Artery Embolism Local Fibrinolytic Therapy (MELT) trials.[3] The authors, here, imply the highly selective population of middle cerebral occlusion studied in PROACT II[7] and MELT.[8] According to the authors the selective nature of the study population would affect the 'generalizability' of the study.

To contextualize, PROACT II was a RCT comparing efficacy of intra-arterially (IA) administered recombinant prourokinase in angiographically ascertained middle cerebral artery (MCA) occlusion within 6 hours after the onset of stroke. It found a statistically significant 15% absolute risk reduction for having favourable mRS of 2 or less at 90 days in patients who were randomised to the prourokinase arm. The MELT was a RCT conducted between 2000-2005 that used the opportunity that was available due to delayed regulatory approval for intravenous tPA in Japan. It randomized patients with MCA territory occlusion within 6 hours of onset of symptoms with intra-arterially administered urokinase. The study did not achieve its objective because it was stopped prematurely as IV tPA became available as a standard of care in Japan by October 2005. The study result was statistically non-significant and inconclusive as only 57% of the calculated sample size was enrolled. The United States-FDA did not give approval for IA prourokinase based on PROACT II result, as it required one more phase III trial in the same direction. Another confirmatory phase III study on the topic was not forthcoming because the concerned manufacturer thought that it was commercially non-feasible.[9] However, US-FDA approved embolectomy devices like Merci and Penumbra based on uncontrolled trials studying recanalization rates and clinical outcome (recanalization rates with the devices and differences in the clinical outcome in patients with and without recanalization) as the regulatory requirement for devices was different from that for drugs. The SYNTHESIS Expansion investigators lament that there is no 'clinical equipoise' among stroke specialists with respect to these interventions, and that it is very difficult to conduct a trial on the question, because clinicians almost 'seem to know' what is the best in acute stroke management. The lead authors of the SYNTHESIS

Expansion, in an earlier paper, argue that this 'impression of the best practice' is a myth.[10]

As if to mitigate the issue of 'generalizability' of PROACT II and MELT, the investigators of SYNTHESIS Expansion made the study agent as heterogeneous as possible. The interventions in SYNTHESIS Expansion range from IA therapy with tPA to various mechanical devices as diverse as Merci, Penumbra, Trevo and Solitaire. They qualify this diversity of interventions as a 'pragmatic' design, simulating the real life practice.[3]

The SYNTHESIS Expansion authors calculated the sample size based on their own pilot study, the SYNTHESIS Pilot.[11] Synthesis pilot was a randomized control trial that compared IV tPA with IA tPA. The calculated sample size for Synthesis pilot was 350. This was based on the presumption of 15% absolute difference between the two treatment groups. However, the study was terminated when only 58 patients were randomized. The authors state that the study was stopped, as the analysis of the data was required to "access a grant for an expansion phase of the study". Although there was a favorable trend, the result of SYNTHESIS Pilot was nonsignificant when the parameter for favorable response was mRS 1 or less. However, the result was statistically significant with a huge effect size (OR 4.56; 95% CI 1.2-17.37) when the outcome parameter was considered mRS two or less. The wide CI of 1.2-17.37 in the study reflected the sample size of study (N = 54) as the study enrolled only 14% of the calculated sample size.

In designing the SYNTHESIS Expansion, the authors assumed an absolute difference of 15% between the patients, similar to the magnitude of effect detected in SYNTHESIS Pilot. This is a huge effect size for a study comparing two active agents. To make a comparison, IV tPA in NINDS trial had an absolute risk reduction (ARR) of 13%, and a number needed to treat (NNT) of 7.6 using mRS 1 or less as a favorable outcome.[12] However, in the NINDS trial the control was placebo, while in SYNTHESIS Pilot it an active agent, IV tPA. It is noteworthy that very few therapeutic agents have shown such phenomenal effect size in stroke medicine. We would argue that given the fact that the sample size is calculated based on such a remarkable outcome of SYNTHESIS Pilot, it is unreasonable to allow drastic change in the composition of the study population or interventions.

Heterogenity of Interventions and the NIHSS Scores

In the SYNTHESIS Expansion, however, the nature of the interventions and the biological homogeneity of the study group are significantly altered. While in Synthesis pilot only two patients underwent mechanical thrombectomy using devices (2/25; 8%), in Synthesis Expansion, 20% of the patients underwent device mediated mechanical thrombectomy. There is also no homogeneity in the types of mechanical thrombectomy devices used. In the study, Solitaire was used in 18 patients, and Trevo and Merci was employed in five patients each. This is notwithstanding the fact that, there was, until recently, no equivalence or non-inferiority data on the comparative efficacy of various devices (Synthesis Expansion was conducted between 2008 and 2012; the non-inferiority trials on Solitaire and Trevo were published in August 2012).

The average NIHSS of Synthesis Pilot was 17, while that of Synthesis Expansion is 13. In two studies that showed outcome favoring IA thrombolysis, PROACT II trial, on IA prourokinase as well in an observational study[13] comparing IA versus IV thrombolysis on patients with dense MCA sign, the average NIHSS score was 17. We have evidence from angiography-corroborated studies that higher NIHSS score reflect more proximal location of the occlusion.[14] The relationship between positive intervention studies and higher NIHSS score can be deduced from this observation. It is conceivable that the disadvantage of the time lag required for endovascular intervention over IV thrombolysis is offset only when the lesion is more proximal such that IV thrombolysis alone would prove ineffective. In such a scenario, comparing IV thrombolysis with endovascular intervention without stratifying the lesion based on severity score is bound to yield negative results, because in those patients with distal lesion, endovascular therapy may well be detrimental.

SWIFT Trial and the Significance of Heterogeneity of Interventions

The results of SWIFT illustrate the importance of the issue of heterogeneity in SYNTHESIS Expansion and IMS-III. SWIFT compares the stent retriever Solitaire with standard of care mechanical thrombectomy device Merci in a non-inferiority trial. The results show that Solitaire is not only non-inferior to Merci, but is superior with an absolute risk reduction between the intervention to the extend of 25% for the outcome mRS two or less, giving a NNT of four.[1] Here, it needs to be noted that Merci is not a device approved based on a controlled trial, but based on a single arm observational study that regarded recanalization rate and clinical outcome in patients with and without recanalization.[15] From a purely statistical point of view, the result of SWIFT can be interpreted as demonstrating the superiority of solitaire over Merci and in the context of a trial involving two active agents, this could be as well be a case of Merci being inferior to the hypothetical placebo, had such a controlled trial been done. While the latter scenario is highly improbable, in the absence of a definitive controlled trial one cannot completely exclude such a possibility. Indeed, interpreting the significance of the outcome of a non-inferiority trial when a controlled trial on the comparator is not available creates a host of problems. Had the SWIFT trial result been just non-inferior or worse still, non-inferior and inferior (two of the five possible outcomes of a non-inferior trial, Figure 1), the regulatory environment that enabled a non-inferiority trial without an original controlled trial, would have facilitated a 'bio-creep' phenomenon[16] that would evoke highly uncertain extrapolations.

Bio-Creep in Non-Inferiority Trials

'Bio-creep' is the natural outcome of the design characteristics of non-inferiority trials. In non-inferiority trials, the objective is to show that the study agent is not 'much worse' than the comparator. The margin of difference that can be considered as 'not much worse' is the interval of 'non-inferiority'. The lower end of the confidence interval of the non-inferiority study should not touch or extend beyond this predetermined point to call the study agent 'non-inferior'. If the CI extends beyond this limit, the study agent would be deemed 'not non-inferior'. If the

lower end of CI is not only above the non-inferiority margin, but also above the point of no effect of the forest plot, the study agent would be deemed 'superior'. If the CI straddles both the non-inferiority margin and the line of no effect, the study would be considered inconclusive to prove or disprove 'non-inferiority'. Thus, depending upon the disposition of the CI with respect to this predetermined point and the point-of-no-effect, there can be five possible outcomes for a non-inferiority trials: superior, non-inferior, non-inferior and inferior, not non-inferior and non-inferiority not shown [Figure 1]. If an agent B is found to be non-inferior (but not 'superior') to a comparator A, the study would have conceded a margin of non-inferiority, up to which the study agent would be considered 'non-inferior'.

Now, if the agent B is subsequently compared with an agent C in another non-inferiority trial, a yet another 'margin of non-inferiority' has to be considered. If this new agent C is also found to be just non-inferior (again not 'superior'), to another agent D, a further margin of non-inferiority would be conceded. If this process goes on, at one point the cumulative margin of non-inferiority conceded would be so substantial that the later agents may well be inferior to the placebo. Bio-creep (or techno-creep for devices) is the jargon to this phenomenon of 'sliding standards'.

In the context of SWIFT study, if another device is developed by yet another manufacturer and compared in a non-inferiority trial with the Solitaire, the significance of the results would be almost undecipherable. This would be more so if a wider non-inferiority margin is employed, and the result is non-inferior or non-inferior and inferior. While the 'biocreep' phenomenon is described in the context of sequential and indirect non-inferiority trials against an initial agent that has been verified by a controlled trial, the scenario of non-inferiority trial without an initial comparator that is verified by controlled trial is almost unprecedented. Indeed, the terminology of 'biocreep' would be insufficient to explain the situation. In the SWIFT study whether the solitaire device can be extrapolated to be better than a hypothetical placebo is something that cannot be settled as a matter of debate. The only conclusion from the SWIFT is that Solitaire is better than

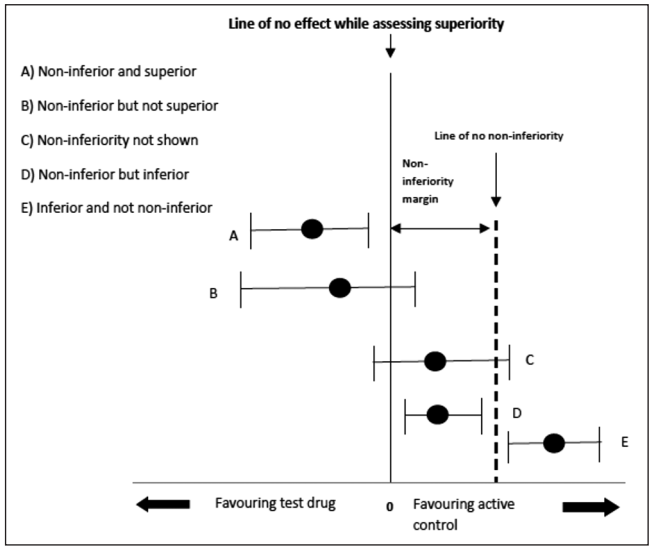

Figure 1: Possible outcomes of non-inferiority trial

Merci. There is no empirical 'controlled' proof that Merci is better than placebo or the standard medical care. The outcomes of SYNTHESIS Expansion, IMS-III and MR RESCUE further complicate this question because both these trials have shown that 'endovascular therapy' (whatever that means) is no better than the comparator IV tPA or standard therapy.

Heterogenity of Interventions

In both SYNTHESIS Expansion and IMS-III, the study agent 'endovascular therapy', is a heterogeneous collection of intervention ranging from IA tPA to Merci, Penumbra, Trevo and Solitaire. Solitaire was used in 2.8% of the total number of patients who used device mediated mechanical thrombectomy in IMS-III trial, and in 10.9% of patients who underwent intervention in SYNTHESIS Expansion trial. The SYNTHESIS Expansion authors note this deficiency when they state that the new generation devices like stentrievers are infrequently used in their study, and their wider use could provide better benefit. Authors of IMS-III also have a similar opinion. IMS-III was terminated when about 72% of the patients were enrolled based on futility analysis done during interim review. However, in their final report, the authors propose that a larger study sufficiently powered to test the efficacy of the intervention in subgroup of patient with severe stroke might show efficacy. Here, the question that remains unanwered is why the investigators did not take into account this important subgroup, when it was decided to terminate the study prematurely. One possibility is that the data of improved efficacy of stentreivers vis-à-vis thromboectomy devices may not have been known when these studies were initiated. However, it is unrealistic that the investigators thought that all endovascular therapies ranging from intra-arterial tPA to various mechanical thrombectomy devices as a unitary whole while designing the trial. We think this is direct consequence of the regulatory standards that gave approval to first generation embolectomy devices Merci and Penumbra without a controlled study against the standard therapy. The outcome of MR RESCUE unties this knot in all detail.

MR RESCUE in a randomized control trial compared the embolectomy with standard of care and evaluated whether preintervention imaging of penumbral pattern would be able to identify patients who are likely to benefit from the relevant therapy. This study was conducted between 2004-2011 and used the first generation embolectomy devices the Merci retriever and the Penumbra system. The study did not find benefit for the penumbral imaging in predicting favourable response. It also did not find difference between those patients who underwent embolectomy versus those who underwent standard of care. While the main objective of the study was to evaluate the use of imaging for identifying candidates for endovascular intervention, in effect, it became a controlled trial evaluating the efficacy of the first generation embolectomy devices against the standard of care. The study result questions, in retrospect, the prudence of US-FDA's approval of first generation embolectomy devices based on the 'surrogate outcome' of recanalization rates and uncontrolled clinical outcome data. It also brings the issue of 'bio-creep' when subsequent non-inferiority trials are done using the unproven 'standard of care'.

Discordant Subgroups

The outcome of SWIFT and MR RESCUE underscores the possibility of the presence of multiple subgroups with varying efficacy in both IMS-III and SYNTHESIS Expansion. We would argue that if there are multiple interventions with varying efficacy, the presence of a minority intervention/population with phenomenal efficacy would be annulled by a majority intervention with mediocre or no effect. Thus, even if Solitaire had phenomenal efficacy, it would not be evident in the trial, because it is a minority intervention in the trial.

To illustrate this with a thought experiment, let us assume that a controlled trial is conceived for comparing the 'sweetness' of fruits and roots. Let's also consider that by some quirk of chance the representative of fruits chosen were apples, oranges, and grapes and that of roots is sweet potato. Here, if the proportion of grapes were higher than apples and oranges, the remarkable sweetness of apples would be annulled by the overwhelming sourness of grapes. The final outcome of such a study would be that the 'fruits' group is no better than 'roots' group on the composite outcome of 'sweetness'. Here, if sample size of the study had been calculated for all 'fruits', then the ability of the study to demonstrate the effect of the subgroups apples, oranges and grapes would be compromised, especially if there is an imbalance between the proportion of apples and grapes. IMS-III demonstrates an exactly similar issue in the trial design. In the absence of data on the subgroup differences between different type of interventions, IMS-III investigators based futility analysis on primary outcomes without figuring out the important subgroup difference in the category of interventions adapted in the study as 'endovascular therapy'. They prematurely stopped the trial on the basis of 'futility' of achieving the trial predetermined trial endpoints, potentially compromising the ability of study for conducting a statistically meaningful subgroup analysis of the subgroups identified by the results of trials like SWIFT and TREVO 2.

However, IMS-III, had, in contrast to SYNTHESIS Expansion, addressed the issue of NIHSS score and had included only patients with NIHSS 10 or more [or 8 or more if there is angiographic evidence of proximal lesion on computed tomography (CT) or MR angiography]. The only issue was that the NIHSS score defining the eligibility could have been still higher. Indeed, in the IMS-III results, the subgroup with NIHSS score ≥ 20 had very wide confidence interval. The confidence interval of patients who were treated within 120 minutes ranged from 0.60-5.21, while that of patients treated after 120 minutes ranged from 0.28-3.39. This is in contrast to the estimate of patients with NIHSS score between 8-19 (0.81-1.68 in patients treated within 120 minutes and 0.61-1.26 for patients treated after 120 minutes). Thus, for the patient group with lower NIHSS score the estimate was more precise, while in the patient group with higher NIHSS score the estimate was less precise. In the latter group, one end of the confidence interval was further into the side favouring endovascular therapy (5.21). This indicated highly variable responses in the subgroup of patients with higher NIHSS score. It also indicates that if the same size was more in this group, the confidence interval would have closed in and the final estimate would be in the side favoring endovascular therapy. Here, given the dissimilarity of efficacy of various types of devices evident with SWIFT and TREVO 2 results, the importance of subgroup heterogeneity determining the final outcome of the study is very much clear.

We hypothesize that the issue of subgroups with discordant outcomes is a general problem plaguing all clinical trials. It is expected to give uncertain results when the degree of heterogeneity of the population and/or intervention is not known at the initiation of the trial. IMS-III and Synthesis Expansion, being constrained by the lack of controlled clinical efficacy trials on the mechanical thrombectomy device, lumped them all as similar kind of interventions with presumably similar efficacy. It is only fortuitous that the investigators could identify this issue from the evidence made available by SWIFT and TREVO 2 studies. However, in many areas in medicine such subgroup interactions may not be evident at all. This is especially so in trials done in diseases defined purely phenotypically, without any definite pathological markers suggesting nosographic uniformity of the disease. In fact, in many such diseases (e.g.Idiopathic Parkinson's disease), the very existence of pathological subgroups would be hard to understand. In all such situations, a negative randomized control trial is only an absence of evidence, and not evidence of absence, as physicist and cosmologist Carl Sagan famously articulated with respect to the absence of evidence of the extra-terristerial intelligence.

Conclusion

In conclusion, the outcomes of recent trials of endovascular therapy are more related to the nature of the design of these trials, than a true reflection of what these trials had aimed at their initiation. It also reflects on the domino effect of regulatory regimes that short-cut scientific scrutiny by approving devices on 'surrogate' markers than by rigorous clinical end-points that are usually insisted for newly introduced drugs. Stroke trials, given the mechanistically simple nature of the disease, help us to decipher this phenomenon in reasonable detail. We could only guess the magnitude of effects of the 'yet unknown' subgroups in clinical trials on diseases where pathogenic pathways are extremely complex, and where simple mechanistic reasoning is generally unrewarding.

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