R2: Association between time to reperfusion and outcome is primarily driven by the time from imaging to reperfusion.

Cover title: Workflow Metrics and Likelihood of Good Outcome

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Abstract

Background and Purpose

A progressive decline in the odds of favorable outcome as time to reperfusion increases is well known. However, the impact of specific workflow intervals is not clear.

Methods

We studied the mechanical thrombectomy group(n=103) of the prospective, randomized REVASCAT trial. We defined 3 workflow metrics: time from symptom onset-to-reperfusion(OTR), time from symptom onset-to-CT(OCT), and time from CT-to-reperfusion(CTR). Clinical characteristics, core lab-evaluated ASPECTS and 90 day outcome data were analyzed. The effect of time on favorable outcome (modified Rankin scale 0-2) was described via adjusted odds ratios for every 30-minute delay.

Results

Median admission NIHSS was 17.0(14.0-20.0), reperfusion rate was 66% and rate of favorable outcome 43.7%. Mean(SD) workflow times were as follows: OTR:342(107)min; OCT:204(93)min; CTR:138(56)min. Longer OTR time was associated with a reduced likelihood of good outcome (OR for 30 minutes delay: 0.74; 95%CI:0.59-0.93). The OCT time did not show a significant association with clinical outcome (OR:0.87; 95%CI:0.67-1.12) while the CTR interval showed a negative association with favorable outcome (OR:0.72; 95%CI:0.54-0.95). A similar subgroup analysis according to admission ASPECTS showed this relationship for OTR time in ASPECTS<8 patients (OR:0.56; 95%CI:0.35-0.9) but not in ASPECTS>=8 (OR:0.99;95%CI: 0.68-1.44).

Conclusion

Time to reperfusion is negatively associated with favorable outcome, being CTR, as opposed to OCT, the main determinant of this association. In addition, OTR was strongly associated to outcome in patients with low ASPECTS scores but not in patients with high ASPECTS scores. .

Clinical trial registration

REVASCAT Trial substudy:

https://clinicaltrials.gov/ct2/show/NCT01692379

NCT01692379

Timely reperfusion of salvageable brain is the fundamental principle underlying reperfusion therapies for stroke[1, 2]. Several studies have demonstrated the progressive decrease in the odds of favorable long term outcome as time to reperfusion increases[3, 4]. The most common studied time metric is time from symptom-onset to reperfusion, however other time intervals[5] have been defined and their specific impact on outcome has been described[6].

While the overall time interval from onset to reperfusion is known to be a critically important predictor of outcomes, a breakdown of various workflow intervals according to level of impact on clinical outcomes has not yet been described. Knowledge of such differential influence of various workflow intervals on clinical outcomes is important as strategies focused on reducing those intervals that have highest relationships to clinical outcomes to the minimum would likely yield highest gains in terms of outcomes. Time from onset to reperfusion represents a chronology based indicator while time from imaging (assuming indication to treat is based on imaging evidence of small core) to reperfusion reflects a physiology based indicator. We sought to determine the specific relationship of different workflow metrics with clinical outcomes in a randomized trial of mechanical thrombectomy for acute stroke.

Methods

The REVASCAT trial investigated the effects of mechanical thrombectomy with Solitaire device compared to best medical therapy alone in patients with acute stroke due to major arterial occlusion in the anterior circulation within 8 hours from symptom onset. Main study design, patients characteristics and results were published elsewhere[7, 8]. For the purpose of this analysis we studied the mechanical thrombectomy group (n=103). The main inclusion criteria for this trial were: anterior circulation strokes in which endovascular treatment could be started < 8 hours from symptom onset, Alberta Stroke Program Early CT Scores[9] (ASPECTS) score ≥7 on pre-randomization CT and identification of a major vessel occlusion (Tandem ICA/MCA, Terminal ICA, M1-MCA). We defined 3 workflow metrics: 1- time from symptom onset to reperfusion, 2- time from symptom onset to the CT scan qualifying the patient for randomization, 3- time from CT scan to reperfusion. Time of reperfusion was defined as the time when complete recanalization (TICI2b-3) was

achieved. For those patients who did not achieve complete recanalization or those who recanalized between CTA and first angiogram (n=5) we used the time of end of procedure. Qualifying ASPECTS scores for enrollment in REVASCAT were obtained by local investigators (stroke neurologists and neuroradiologists) who prior to starting enrollment in REVASCAT had undergone additional training in ASPECTS score reading. However, the ASPECTS scores used for purposes of trial reporting were centrally adjudicated scores by an independent core lab blinded to clinical data.

The primary outcome was the severity of disability at 90 day, according to the centrally adjudicated modified Rankin scale scores. For this substudy a favorable outcome was defined as mRS 0-2.

Statistical analysis

Statistical analyses were obtained using SAS 9.3 software. Categorical variables are presented as absolute values and percentages, and the continuous variables are presented as mean, ± standard deviation if symmetrically distributed, or median [interquartile intervals] otherwise. The effect of time on good clinical outcome is described via odds ratios for every 30-minute delay. All patients allocated to the revascularization arm, including those who did not achieve revascularization, were included in the analysis. To account for possible confounding factors, such less severe patients recruited at longer arrival times, analyses have been adjusted both for minimization variables (age and baseline NIHSS) and for the intravenous use of alteplase. We studied the impact of the time intervals on the whole population and repeated the analysis for patients with ASPECTS <8 or ASPECTS ≥ 8 on admission CT scan evaluated by the independent central corelab. A probability value <0.05 was considered significant for all tests. Model goodness of fit was assessed via the Hosmer and Lemeshow test.

Results

103 patients were randomized to the thrombectomy arm, 55% male, mean age 65.7±11.3. Median admission NIHSS was 17.0 (14.0–20.0) and median ASPECTS value on initial CT scan was 7.0 (6.0–9.0). Complete recanalization was achieved in 66% of patients and the rate of favorable outcome was 43.7%.

Median workflow times were as follows: 1- time from symptom onset to reperfusion: 342 +/- 107 min, 2- time from symptom onset to CT-scan: 204 +/- 93 min, 3- time from CT-scan to reperfusion 138 +/- 56 min (figure 1). Additional baseline characteristics and workflow times are showed in table 1. OTR was 28.4 minutes shorter for patients with NIHSS ≥ 17 (329.4 ±104 vs. 357.8 ±111.1).

Longer time from symptom to reperfusion was associated with a reduced likelihood of good outcome (adjusted OR for 30 minutes delay intervals: 0.74; 95%CI: 0.59-0.93). Overall, the odd of achieving a good outcome was reduced by 26% for every 30 minutes delay in reperfusion.

When we analyzed the effect of time in each interval (table 2, figure 2) we observed a clear difference between both sub-intervals. While in the initial interval, a longer time from symptom onset to imaging, did not show an impact on final outcome (OR 0.87; 95% CI: 0.67-1.12), in the second interval, a longer time from imaging to reperfusion, showed a significant negative association (OR: 0.72; 95%CI: 0.54-0.95) (figure 3).

Analysis according to admission ASPECTS

For those patients with an ASPECTS<8 on pre-treatment CT-scan (n=53, 51.5%) a longer time from symptom to reperfusion was also associated with a reduced likelihood of good outcome (OR:0.56; 95% CI: 95%CI: 0.35-0.9). The probability of achieving a good outcome was reduced by 44% for every 30 minutes delay in reperfusion. When we looked for the consistency of these results in each time frame, we found completely overlapping intervals with those observed in the whole population analysis [onset-to-imaging (OR:0.77; 95%CI: 0.47-1.27) and imaging to reperfusion (OR:0.50; 95% CI: 0.28-0.88)] supporting the idea of a similar relationship between time and outcome in each time interval (table 1). For every 30 minutes delay the odds of achieving a good outcome were reduced by 27% in the symptom to imaging interval and by 50% in the imaging to reperfusion interval (figure 3). As fewer cases are included in this subgroup analysis, both intervals are wider, loosing statistical signification in the former.

For patients showing an ASPECTS ≥8 on admission (n=50, 48.5%) the association between good outcome and time in the different intervals was inconsistent and closer to the OR=1 of no relationship: onset to reperfusion (OR: 0.99; 95% CI:0.68-1.44), onset to imaging (OR: 1.19; 95%:0.75-1.88) and imaging to reperfusion(OR: 0.81; 95% CI: 0.5-1.31) (figure 3).

Discussion

In line with previous studies, our findings confirm a progressive decline of the probabilities of regaining a good functional outcome as time to reperfusion increases, overall a 26% decrease for every 30 minutes delay. The stronger association with time as compared with previous similar studies[4] may be due to the fact that unlike those studies we did not exclude from the analysis those patients who did not achieve recanalization after the procedure.

Our study however aimed to describe the specific relationship of two different intervals. While the time elapsed from symptom initiation to the admission CT scan was not associated with a clear decrease in the odds of good outcome in the treated patients, the second interval, CT scan to reperfusion, showed a clear negative relationship with the odds of good recovery.

These findings could be explained by the fact that in our study, the favorable outcome endpoint for this analysis was dichotomized into good (mRS 0-2) or poor (mRS 3-6). Since infarct volume has been shown to be strongly associated with outcomes [1], at least theoretically, each individual will achieve a good outcome if reperfusion occurs before crossing the "infarct volume threshold of no return to independent level of activity" after which the outcome will be unfavorable regardless of recanalization. By convention, the term favorable and unfavorable outcome refers to mRS 0-2 vs mRS 3-6 even though different degrees of disability exist within the "unfavorable" category that may favor those who experience recanalization. REVASCAT was designed to maximize the chance of a good outcome in patients who reperfuse and therefore an ASPECTS cut-off of 7 or more was chosen, acting de facto as a screening imaging method meant to detect any patient who surpassed "the infarct volume threshold" at the moment of imaging with consequent exclusion from enrollment in the trial. This fact explains the flat appearance of the curve in this initial time interval because

most patients who may have caused the curve to decline were excluded by the CT-scan (ASPECTS) screening. It is likely that the small association between time to CT and outcomes was driven by those patients enrolled in REVASCAT who had low ASPECTS scores. In other words, the fact that the curve is nearly flat confirms that the REVASCAT imaging selection criteria were sufficient to allow accurate patient selection in most patients.

Our findings do not mean that time does not have an impact on outcome before CT-scan is performed. The positive impact of shortening this initial interval (pre hospital and in hospital pathways) cannot be measured in this group of treated patients, but a reduction in time to CT would very likely result in an increase in the number of eligible patients who would benefit from thrombectomy because the earlier the time point from symptoms onset relative to imaging the higher the likelihood of a higher ASPECTS score [10].

The second studied interval, time from CT-scan to reperfusion did show a clear negative association with the probability of good outcome. As we adjusted for main known prognosis factors, and we tried to minimize the risk of selection bias by including also patients who couldn't be recanalized, the interpretation of this relationship as causal is, at least, plausible. In this case the positive impact of decreasing the CT-to-reperfusion interval is easy to quantify: +28% likelihood of favorable outcome for each 30 minutes reduction.

When analyzing according to initial ASPECTS, in patients with lower scores (ASPECTS<8) we observed the expected negative association of time and outcome in the initial interval. This may be due to the fact that the lower ASPECTS score group represents patients with poorer baseline collaterals who will experience rapid growth of ischemic core prior to reperfusion. More sophisticated imaging techniques such as those used in EXTEND IA [11] (size of Tmax > 6s lesion) or ESCAPE[12] (collateral imaging) may more precisely identify those patients with fast core growth who have a low likelihood of return to independent level of functioning in the absence of immediate reperfusion. Whether endovascular reperfusion therapies, unless feasible within the shortest period of time should be withheld in these patients awaits clarification from future randomized trials. However, this group represents a subgroup of patients particularily sensitive to time to reperfusion and every effort should be made to repefuse the brain in the timeliest possible manner. While tempting to more precisely characterize the status of collateral flow, this group of patients may represent the group where treatment decisions should be made with the minimum available information (ASPECTS score) in

order to save precious time to reperfusion. On the other hand the same analysis among patients presenting with an ASPECTS≥8 did not show a clear association between time in any of the studied intervals, and outcome. A likely explanation would be an increased proportion of patients with good collateral flow supplying the ischemic penumbra despite major arterial occlusion, favoring high ASPECTS scores and a lower rate of core growth. Since time becomes less relevant in this scenario our results might also indicate that in cases with an unknown time from onset a compatible favorable CT-scan (ASPECTS>8) might be used to select patients who will benefit from thrombectomy or at least may allow some time for advanced imagin g studies confirming favorable physiology (mismatch) based upon which definitive treatment decision can be made [13]. This contention however, needs to be confirmed by future trials.

The strength of our data consists in prospective pre-specified data collection including time intervals (onset to CT and CT to reperfusion) and core lab adjudicated ASPECTS. This is the first prospectively collected dataset analyzing granular time intervals as they relate to outcome with pre-specified imaging criteria. The main limitation is the sample size that does not provide sufficient power for highly reliable subgroup analysis. Therefore our findings await confirmation from larger, pooled datasets of prospectively collected acute endovascular stroke cases. The REVASCAT trial unfortunately did not include a screening log that prospectively recorded all patients excluded due to a large ischemic lesion on qualifying neuroimaging. This information could have been very valuable to quantify the number of patients that could have benefited from thrombectomy if the symptoms-to-CT interval was decreased. Future studies related to workflow metrics should record patients excluded after neuroimaging.

Conclusion

Time to reperfusion has a negative impact in favorable outcome, although differently reflected in each interval. While reducing the symptom to imaging time might increase the number of eligible patients for effective thrombectomy, reducing the time from CT to reperfusion would increase the positive impact of

thrombectomy performed in those patients selected for therapy. Our results enforce the convenience to design interventions to reduce revascularization times.

Disclosures

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Table 1:

Patients characteristics at baseline and measured workflows

Variable	Thrombectomy group (N = 103)
Mean age ±SD — yr	65.7±11.3
Male sex — no. (%)	55 (53.4)
NIHSS score: Median (IQR)	17.0 (14.0–20.0)
Treatment with intravenous alteplase — no. (%)	70 (68.0)
Median ASPECTS value (IQR)	7.0 (6.0–9.0)
ASPECTS 8-10 — no. (%)	50 (48.5%)
Location of intracranial occlusion on CTA or MRA — no./total no. (%)*.	
Terminal internal carotid artery with involvement of M1	26/102 (25.5)
M1	66/102 (64.7)
Single M2	10/102 (9.8)
Ipsilateral cervical carotid occlusion — no. (%)	19/102 (18.6%)
No occlusion on initial angiogram — no. (%)	5 (4.85%)
Modified Thrombolysis in Cerebral Infarction 2b/3 after procedure-no.(%)	67 (65.7%)
Workflow times	
Median time from stroke onset to groin puncture (IQR) — min	269 (201–340)
Median time from hospital arrival to groin puncture (IQR) — min	109 (85, 163)
Median time from imaging to groin puncture (IQR) — min	67 (47, 84)
Median time from groin puncture to revascularization (IQR) — min(n=92)	59 (36, 95)

(*The location of the occlusion was not available in 1 patient in the intervention group)

Table 2

Adjusted and unadjusted odds ratios for 30 minutes delay in each time interval for all patients, patients with ASPECTS<8 and patients with ASPECTS≥8. (ASPECTS: Alberta Stroke Program Early CT scores)

		OR for 30 minutes delay (95% CI)		
		All patients	*ASPECTS<8*	*ASPECTS≥ 8*
Time from symptom to revascularization	Unadjusted	0.95 (0.85-1.06)	0.87 (0.73-1.03)	1.05 (0.9-1.24)
	Adjusted	0.74 (0.59-0.93)	0.56 (0.35-0.90)	0.99 (0.68-1.44)
Time from symptom to imaging (minutes)	Unadjusted	0.99 (0.87-1.13)	0.91 (0.75-1.11)	1.10 (0.92-1.32)
	Adjusted	0.87 (0.67-1.12)	0.77 (0.47-1.27)	1.19 (0.75-1.88)
Time from imaging to revascularization (minutes)	Unadjusted	0.83 (0.66-1.03)	0.72 (0.5-1.05)	0.92 (0.69-1.23)
	Adjusted	0.72 (0.54-0.95)	0.5 (0.28-0.88)	0.81 (0.50-1.30)

Figure 1

The figure shows the studied intervals and the observed times

Figure 2

Forest plot for the relationship between the 3 different interval times with dichotomized modified Rankin Scale at 90 days (0-2 vs. 3-6) in all patients and according to baseline ASPECTS. Adjusted analyses were made for age, baseline NIHSS and IV tPA.
(ASPECTS: Alberta Stroke Program Early CT scores, OTR: onset to reperfusion, OCT: onset to CT, CTR: CT to reperfusion)

Figure 3

Probabilityof mRS 0-2 according to time for different studied timeframes in all patients, in patients with admission ASPECTS<8 and in patients with admission ASPECTS≥8 . (mRS: modified Rankin Scale, ASPECTS: Alberta Stroke Program Early CT scores)
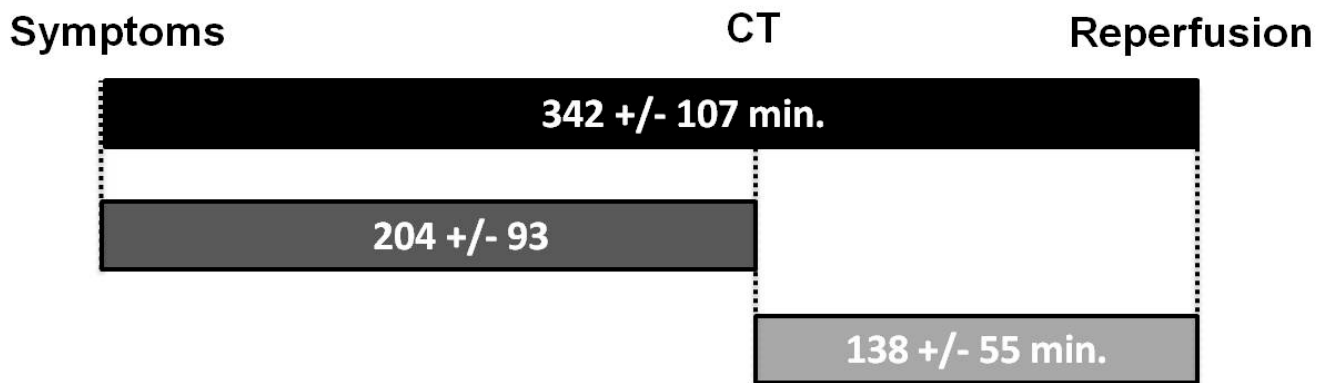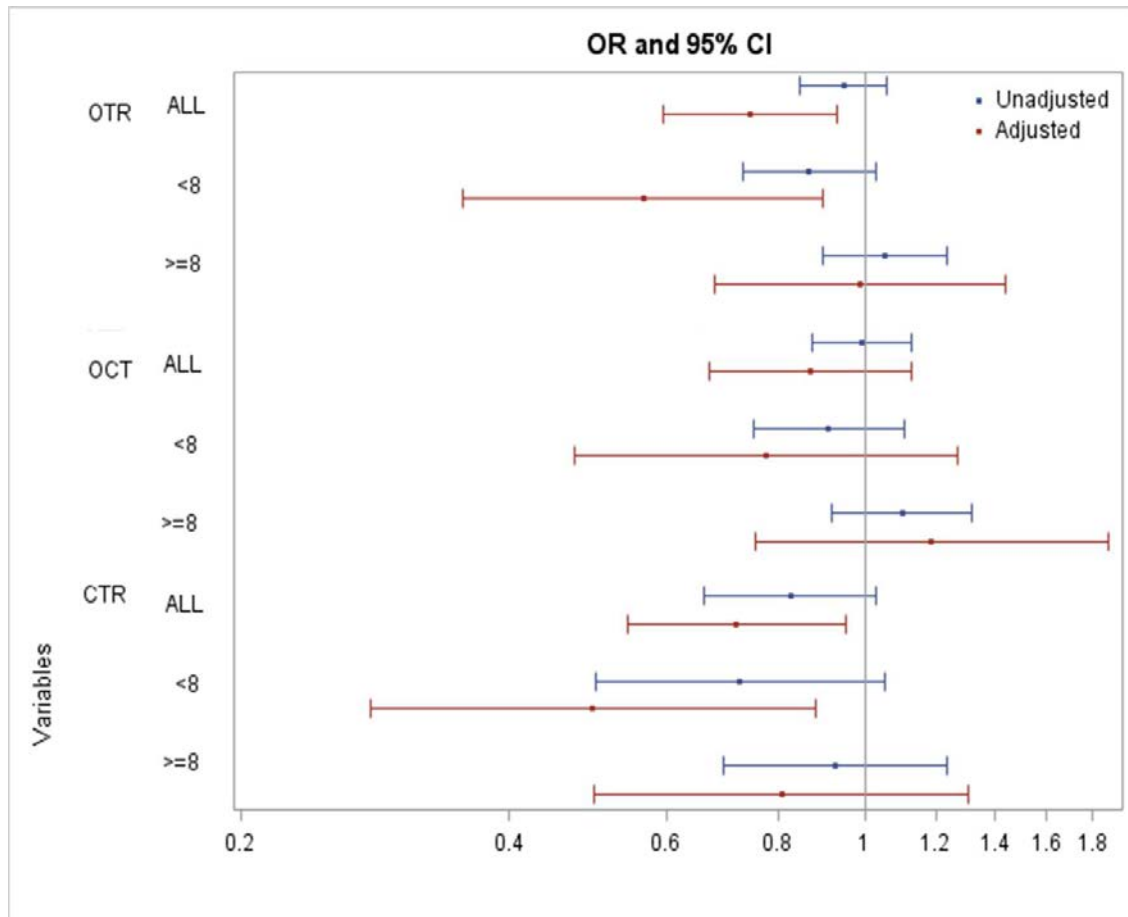
Figure 1

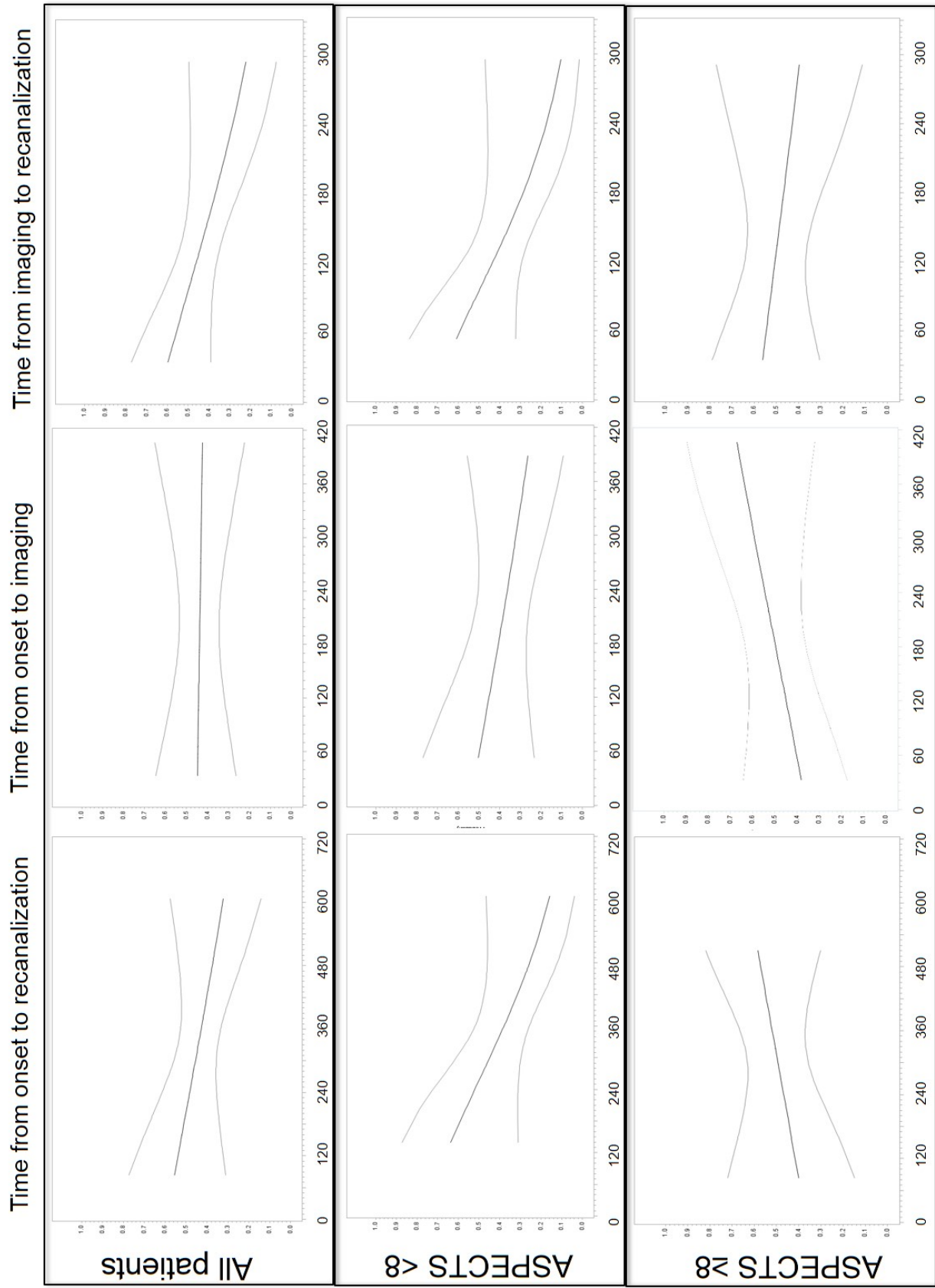Symptoms — CT — Reperfusion

342 +/- 107 min.

204 +/- 93

138 +/- 55 min.

Figure 2

OR and 95% CI

Figure 3

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Apendix

The REVASCAT investigators

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