

**Outcome, efficacy and safety of endovascular thrombectomy in ischemic stroke according to time to reperfusion: Data from a multicenter registry.**

**Running title: Effect of time to reperfusion in MT**

Thomas Raphael Meinel<sup>a\*</sup>, Johannes Kaesmacher MD<sup>a,b\*</sup>, Pasquale Mordasini MD<sup>b</sup>, Pascal J Mosimann MD<sup>b</sup>, Simon Jung MD<sup>a</sup>, Marcel Arnold MD<sup>a</sup>, Mirjam Rachel Heldner<sup>a</sup>, Patrik Michel MD<sup>c</sup>, Steven D. Hajdu MD<sup>d</sup>, Marc Ribo MD<sup>e</sup>, Manuel Requena MD<sup>e</sup>, Christian Maegerlein MD<sup>f</sup>, Benjamin Friedrich MD<sup>f</sup>, Vincent Costalat MD<sup>g</sup>, Amel Benali MSc<sup>g</sup>, Laurent Pierot MD<sup>h</sup>, Matthias Gawlitza MD<sup>h</sup>, Joanna Schaafsma MD<sup>i</sup>, Vitor Mendes Pereira MD<sup>i</sup>, Jan Gralla MD<sup>b\*</sup> and Urs Fischer MD<sup>a\*</sup>

**a** Department of Neurology, University Hospital Bern, Inselspital, University of Bern, Bern, Switzerland

**b** University Institute of Diagnostic and Interventional Neuroradiology, University Hospital Bern, Inselspital, University of Bern, Bern, Switzerland

**c** Department of Neurology, CHUV Lausanne, Lausanne, Switzerland

**d** Department of Radiology, CHUV Lausanne, Lausanne, Switzerland

**e** Department of Neurology, Department of Neurology, Vall d'Hebron University Hospital, Barcelona, Spain.

**f** Department of Diagnostic and Interventional Neuroradiology, Klinikum rechts der Isar, Technical University Munich, Munich, Germany

**g** Department of Neuroradiology, CHU Montpellier, Montpellier, France

**h** Department of Neuroradiology, CHU Reims, Reims, France

**i** Department of Neurology, Toronto Western Hospital, Toronto, ON, Canada

**10** Joint Department of Medical Imaging, Toronto Western Hospital, Toronto, ON, Canada

\* These authors contributed equally

***ONLINE SUPPLEMENT***

## Supplementary Tables

### Supplementary Table I – BEYOND-SWIFT overview

Center	N	Time period	LVO anterior circulation (ICA, M1, M2)	Lost to follow-up (mRS day 90)	ASPECTS available (LVO anterior circulation)	% ASPECTS ≤5 (LVO anterior circulation)	% MRI as initial imaging modality	ASPECTS grading	Admission and 24h NIHSS	mRS at 90 days	mTICI grading	EC approval	Responsible EC
Inselspital Bern, University Hospital Bern, University of Bern, Bern, Switzerland	966	2010-2017	91.8% (888/966)	5.6% (54/966)	863/888	176/863 (20.4%)	50.6% (487/963)	Research fellow blinded to clinical data	Board certified stroke neurologists	Stroke neurologists on scheduled clinical visits. Structured telephone interviews if the patient was unable to attend (either by physician or mRS certified stroke nurse).	Operator-measured	Yes	Kantonale Ethik Kommission Bern
Toronto Western Hospital - University Health Network, University of Toronto, Toronto, Canada	60	2014-2017	88.3% (53/60)	0% (0/60)	53/53	1/53 (1.9%)	1.7% (1/60)	Prospective, by neuroradiologist	Board certified stroke neurologists	Clinical visits at the university hospital. For patients still in rehabilitation facilities, a mRS certified nurse schedules telephone interviews.	Operator-measured	Yes	IRB Toronto
Klinikum rechts der Isar, Technical University Munich, Munich, Germany	206	2009-2017	74.3% (153/206)	18.4% (38/206)	151/153	0/153 (0%)	2.4% (5/206)	Retrospective by neuroradiologist	Board certified stroke neurologists	mRS was evaluated either by face-to-face assessments (by stroke neurologists) or standardized telephone interviews (by certified study nurses).	Operator Measured	Yes	Ethikkommission der medizinischen Fakultät der Technischen Universität München
University Hospital Vall d'Hebron, Barcelona, Spain	419	2010-2017	85.7% (359/419)	20.0% (84/419)	319/360	4/319 (1.3%)	0% (0/491)	Prospective, by neurologist/neuroradiologist on call	Board certified stroke neurologists	Stroke neurologists on scheduled clinical visits. Structured telephone interviews if unable to attend.	Operator Measured	Yes	CEIC H. Vall d'Hebrond
CHUV, Lausanne University Hospital, Lausanne, Switzerland	139	2012-2017	124/139 (89.2%)	26.6% (37/139)	113/124	8/113 (7.1%)	0.1% (1/139)	Consensus stroke neurologist and neuroradiologist (not blinded)	Board certified stroke neurologists	mRS was assessed by Rankin-certified physicians at 3 months in the outpatient clinic, or alternatively through a structured telephone interview by Rankin-certified personnel.	Operator-measured	Yes	Commission Ethique de Recherche, Canton de Vaud
Montpellier CHU, University Hospital Montpellier, Montpellier, France	149	2015-2017	97.3% (145/149)	4.0% (6/149)	109/145	23/109 (21.1%)	82.1% (96/117)	Operator-measured	Board certified stroke neurologists	Stroke neurologists on scheduled clinical visits. Structured telephone interviews if unable to attend.	Operator-measured	Yes	CNIL Comité National Informatique et Liberté
CHU Reims, University Hospital Reims, Reims, France	108	2013 - 2017	90.7% (98/108)	0% (0/108)	96/98	38/96 (39.6%)	92.6% (100/108)	Retrospective, certified neuroradiologist	Board certified stroke neurologists	Stroke physician on clinical visits at university hospital or remote outpatient center.	Retrospective, certified neuroradiologist	Yes*	IRB Reims University Hospital, Champagne-Ardenne University.
<b>Total</b>	<b>2046</b>												

\*Ethics committee votum was waived due to the entirely retrospective nature of data collection

**Supplementary Table 2** - association of symptom onset to reperfusion time (TTR)

considering only patients with TTR of > 6hours and > 7 hours for sensitivity purposes

<b>Outcome</b>	<b>TTR &gt; 6 hours Adjusted odds ratio (95%-CI)</b>	<b>TTR &gt; 7 hours Adjusted odds ratio (95%-CI)</b>
mRS 0-1 at three months	0.859 (0.761 – 0.969)	0.813 (0.696 – 0.950)
mRS 0-2 at three months	0.909 (0.831 – 0.993)	0.925 (0.831 – 1.028)
mRS 0-3 at three months	0.958 (0.894 – 1.027)	0.987 (0.915 – 1.066)
Reperfusion at intervention (mTICI ≥2B)	1.110 (0.991 – 1.245)	1.159 (0.990 – 1.357)
mRS at three months (shift)	1.060 (1.002 – 1.121)	1.051 (0.987 – 1.120)
Non hemorrhagic worsening at 24 hours	1.090 (0.988 – 1.201)	1.072 (0.944 – 1.217)
Mortality at three months	1.015 (0.930 – 1.108)	0.968 (0.857 – 1.094)
Symptomatic intracranial hemorrhage ECASS II definition	0.961 (0.794 – 1.165)	0.904 (0.647 – 1.263)

**Table II** – Analysis was done using time to reperfusion information in minutes, but association of TTR per hour increase with outcome data comparing patients with large vessel occlusion in the anterior circulation is reported. Analysis was done using multivariable binary or ordinal logistic regression analysis adjusting for prespecified confounders outlined in the methods section for TTR per hour increase except aOR for successful reperfusion which was analyzed without successful reperfusion as variable.

mRS: modified Rankin Scale, mTICI: modified treatment in cerebral ischaemia, ECASS II: European Co-operative Acute Stroke Study-II definition

### Supplementary Table 3 - Association of Symptom Onset to Groin Puncture Time

Comparing Patients with Large Vessel Occlusion.

Outcome	Unadjusted odds ratio (95%-CI)	Adjusted odds ratio (95%-CI)
mRS 0-1 at three months	0.948 (0.908 – 0.989)	0.954 (0.903 – 1.007)
mRS 0-2 at three months	0.967 (0.935 – 0.999)	0.991 (0.952 – 1.031)
mRS 0-3 at three months	0.976 (0.948 – 1.006)	0.992 (0.958 – 1.028)
Reperfusion at intervention (mTICI $\geq$ 2B)	0.954 (0.923 – 0.987)	0.952 (0.915 – 0.991)
mRS at three months (shift)	1.025 (0.999 – 1.052)	1.007 (0.979 - 1.037)
Non hemorrhagic worsening at 24 hours	1.015 (0.972 – 1.059)	0.989 (0.935 – 1.047)
Mortality at three months	1.012 (0.982 – 1.044)	0.984 (0.941 – 1.028)
Symptomatic intracranial hemorrhage ECASS II definition	0.998 (0.942 – 1.056)	1.022 (0.960 – 1.087)

**Table III** – Analysis was done using time from symptom onset to groin puncture (STG) in minutes, but association of STG per hour increase with outcome data comparing patients with large vessel occlusion in the anterior circulation is reported. Analysis was done using multivariable binary or ordinal logistic regression analysis adjusting for prespecified confounders outlined in the methods section for STG per hour increase except aOR for successful reperfusion which was analyzed without successful reperfusion as variable.

mRS: modified Rankin Scale, mTICI: modified treatment in cerebral ischaemia, ECASS II: European Co-operative Acute Stroke Study-II definition

**Supplementary Table 4** – Numbers and percentages of patients in strata of symptom onset to reperfusion time.

Strata of onset to reperfusion

		Frequency	Percent	Valid percent	Cumulated percent
	61-120 min	27	1.5	1.8	1.8
	121-180 min	165	9.0	11.3	13.1
	181-240 min	304	16.6	20.8	33.9
	241-300 min	324	17.7	22.2	56.1
	301-360 min	248	13.5	17.0	73.1
	361-420 min	165	9.0	11.3	84.4
	421-480 min	74	4.0	5.1	89.5
	481-540 min	30	1.6	2.1	91.5
	541-600 min	20	1.1	1.4	92.9
	>600 min	104	5.7	7.1	100.0
	total	1461	79.7	100.0	
missing	System	371	20.3		
total		1832	100.0		

**Supplementary Table 5** – Center-specific aOR for good functional outcome at 90 days

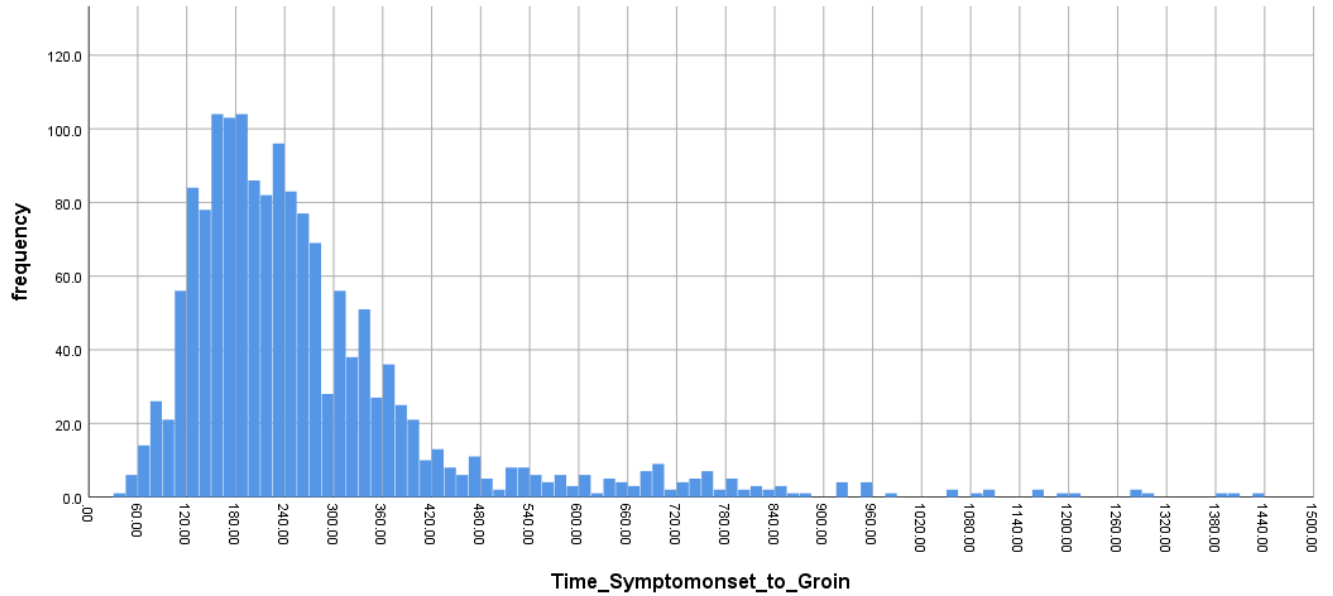
<b>Outcome mRS 0-2</b>	<b>Unadjusted odds ratio (95%-CI)</b>	<b>Adjusted odds ratio (95%-CI)</b>
Center 1	0.932 (0.889 – 0.977)	0.901 (0.853 – 0.970)
Center 2	0.903 (0.725 – 1.124)	1.927
Center 3	0.781 (0.592 – 1.030)	0.618 (0.319 – 1.199)
Center 4	1.004 (0.903 – 1.116)	0.973 (0.851 – 1.113)
Center 5	0.858 (0.746 – 0.988)	0.908 (0.744 – 1.109)
Center 6	0.798 (0.593 – 1.073)	1.577 (0.831 – 2.994)

**Table 4** – Analysis was done using time to reperfusion information in minutes, but association of TTR per hour increase with outcome data comparing patients with large vessel occlusion in the anterior circulation is reported. Analysis was done using multivariable binary or ordinal logistic regression analysis adjusting for prespecified confounders outlined in the methods section for TTR per hour increase.

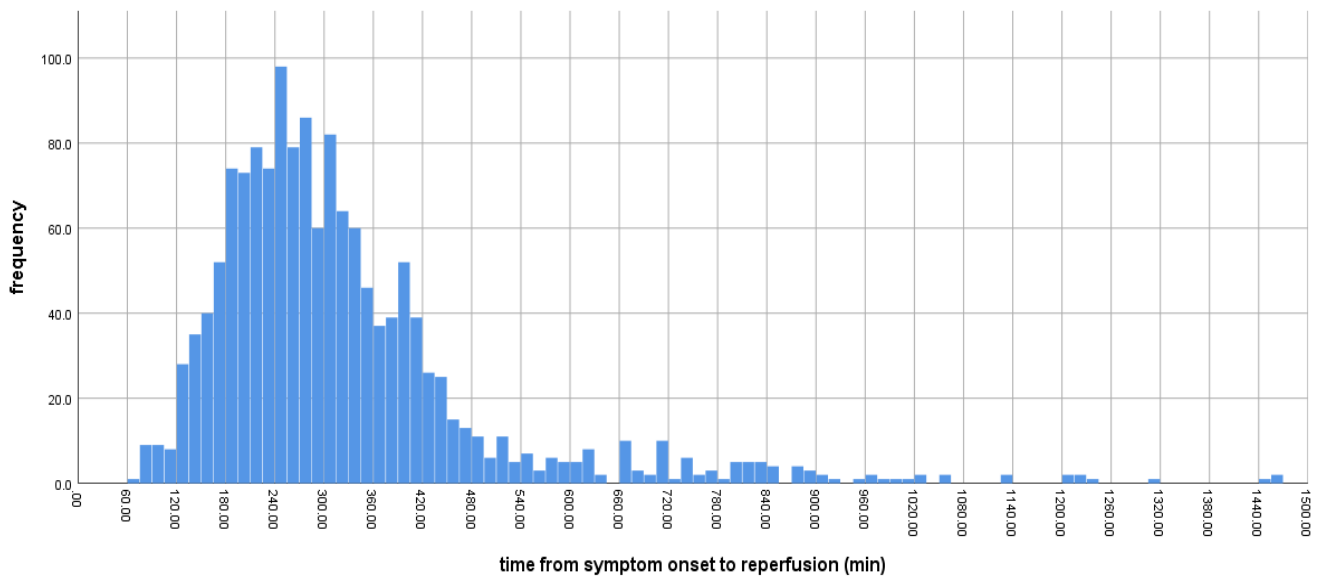
mRS: modified Rankin Scale

*Supplementary Figures*

**Supplementary Figure Ia**– Distribution of symptom onset to groin puncture time (STG, n=1560) and symptom onset to reperfusion time (TTR, n=1461).



**Ia**



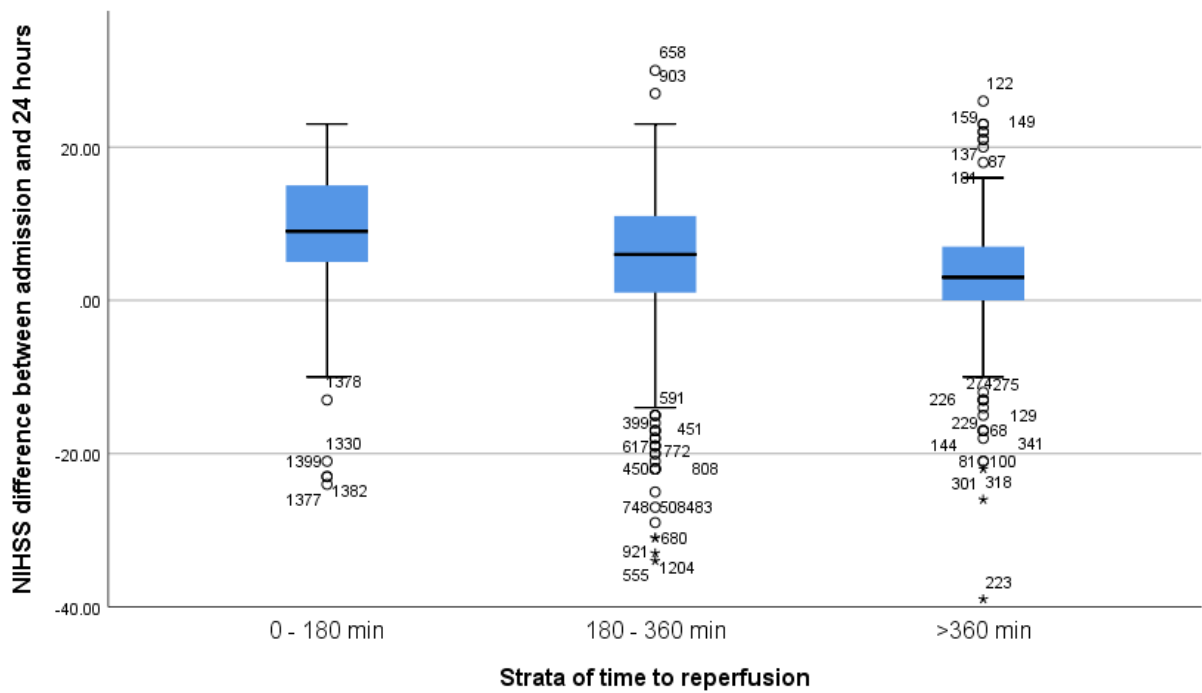
**Ib**

Ia) Median STG was 225 minutes (interquartile range 164-313). Additionally and not shown in the diagram, one patient had a STG of 2377 min (=40 hours) and one patient had a STG of 4667 min (=78hours).

Ib) Median TTR was 280 minutes (interquartile range 217-375). Additionally and not shown in the diagram, one patient had a TTR of 2665 min (=44 hours).

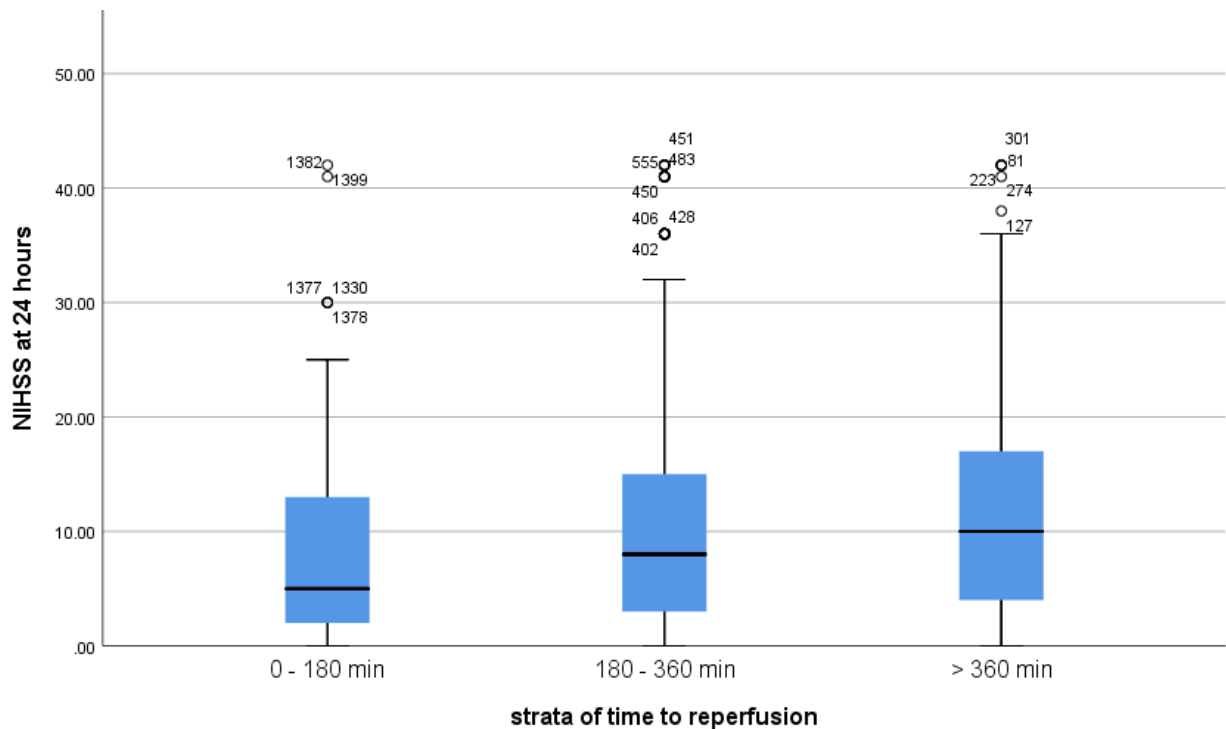


**Supplementary Figure II** –  $\Delta$ NIHSS (admission- 24h) stratified according to TTR



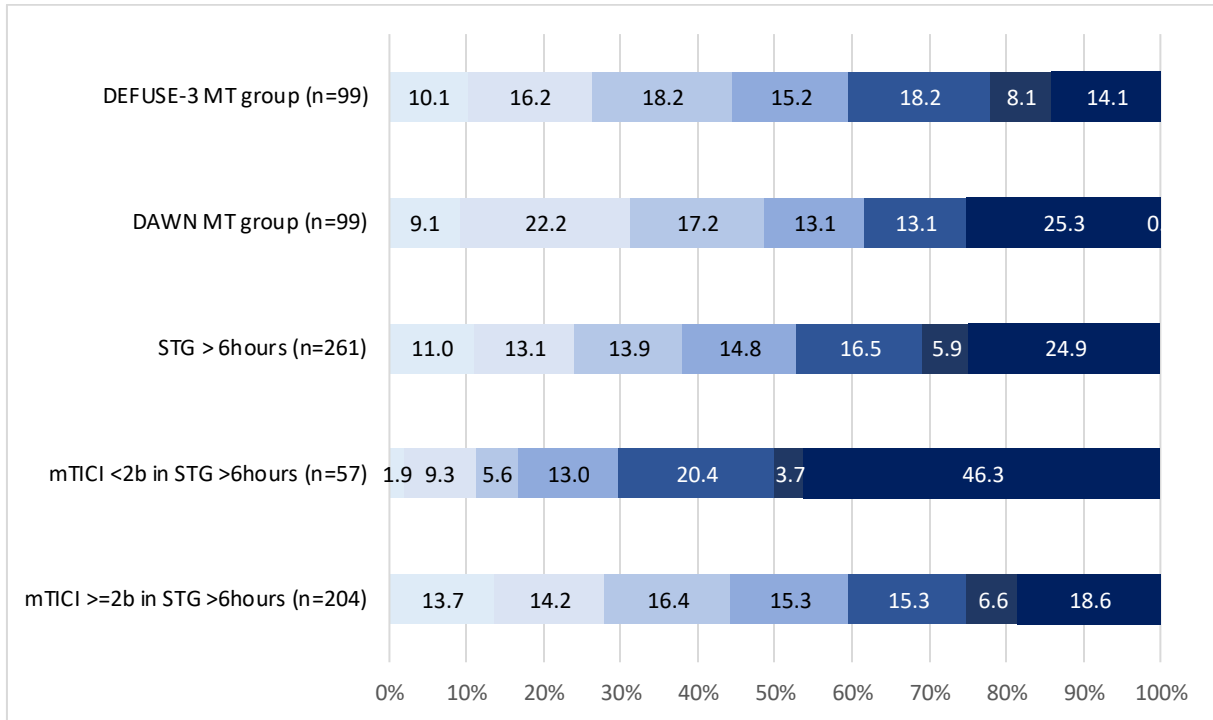
Median  $\Delta$ NIHSS was 9 (interquartile range: 5-15) in TTR 0-180 min, 6 (interquartile range 1-11) in TTR 180 – 360 min and 3 (interquartile range 0-7) in TTR >360 min ( $P < .001$ ).

**Supplementary Figure III** – NIHSS at 24 hours stratified according to TTR



Median NIHSS was 5 (interquartile range: 2-13) in TTR 0-180 min, 8 (interquartile range 4-15) in TTR 180 – 360 min and 10 (interquartile range 4-17) in TTR >360 min ( $P < .001$ ).

**Supplementary Figure IV** –Distribution of modified Rankin scale scores at three months, according to reperfusion status after thrombectomy, in patients with symptom onset to groin time of more than six hours.



In patients with time from symptom onset to groin of more than six hours, the rates of long-term mRS 0-1 or mRS 0-2 and mortality were roughly comparable to DAWN and DEFUSE-3 MT patients. In the DAWN trial, mRS 5 and 6 were combined in one category. Numbers indicate percent of mRS category.

mRS: modified Rankin scale, mTICI: modified treatment in cerebral ischaemia.

