ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

BRIEF COMMUNICATION

Association of the time of day of EVT with clinical outcomes and benefit from successful recanalization after stroke

Vanessa Granja Burbano[1,2,*], Teresa A. Wölfer[1,2,*], Naomi Vlegels[1], Fanny Quandt[3], Hanna Zimmermann[4], Johannes Wischmann[5], Lars Kellert[5], Thomas Liebig[4], Konstantinos Dimitriadis[1,5], Jeffrey L. Saver[2,6], Steffen Tiedt[1,2] & for the GSR investigators

[1]Institute for Stroke and Dementia Research (ISD), LMU University Hospital, LMU Munich, Munich, Germany
[2]Consortium International pour la Recherche Circadienne sur l'AVC (CIRCA), Munich, Germany
[3]Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[4]Institute of Neuroradiology, LMU University Hospital, LMU Munich, Munich, Germany
[5]Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany
[6]Department of Neurology and Comprehensive Stroke Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

Correspondence
Steffen Tiedt, Institute for Stroke and Dementia Research, LMU University Hospital, LMU Munich, Feodor-Lynen-Straße 17, Munich 81377, Germany. Tel: +49 89 4400 46171; Fax: +49 89 4400 46113; E-mail: steffen.tiedt@med.uni-muenchen.de

Received: 30 June 2023; Accepted: 4 August 2023

Annals of Clinical and Translational Neurology **2023; 10(10): 1917–1923**

doi: 10.1002/acn3.51877

*These authors contributed equally.

Abstract

Experimental and neuroimaging studies suggest an influence of the time of day on acute infarct growth, but whether this could inform patient selection for acute treatments is uncertain. In a multicenter cohort of 9357 stroke patients undergoing endovascular treatment, morning treatment (05:00–10:59) was associated with lowest 90-day mRS scores (adjusted odds ratio, 1.27 [95% CI, 1.08–1.47]; $p = 0.004$). The association between successful recanalization and outcome was stronger in morning compared to evening-treated patients ($p_{ia} = 0.046$) with treatment benefit persisting until 24 h for morning-treated compared to 11.5 h for evening-treated patients suggesting that the time of day might inform patient selection for EVT.

Introduction

Experimental stroke studies suggest an influence of the time of day of acute treatment on treatment efficacy and outcome.[1,2] Cellular circadian clocks tightly regulate the response to ischemia including cell death and collateral flow.[3,4] While a recent study identified an association between time of day and hyper-acute infarct progression in large-vessel occlusion stroke patients,[5] it remains uncertain whether this finding also extends to clinical outcomes and benefit from endovascular treatment (EVT). We sought to determine whether the time of day of EVT is associated with clinical outcome and the benefit from successful recanalization.

Methods

The analytical methods can be obtained from the corresponding author. The underlying data can be obtained upon request after approval of the ethics committee and all participating centers.

Patients and outcomes

We retrieved data from 13,082 patients from the German Stroke Registry—Endovascular Treatment (GSR, ClinicalTrials.gov Identifier: NCT03356392), an ongoing, academic, prospective, multicenter registry in Germany.[6] Patients were recruited in 29 centers between July 2015 and December 2021. GSR inclusion criteria were a diagnosis of acute ischemic stroke due to large-vessel occlusion of the anterior or posterior circulation (including the distal M2 segment of the middle cerebral artery but not beyond), EVT initiation, and age ≥18 years without exclusion criteria. For this study, we excluded patients if time of day of onset or of EVT (i.e., flow restoration) was not available ($N = 3725$). The primary end point was the 90-day modified Rankin Scale (mRS) score distribution.

Secondary outcomes included the rate of functional independence (mRS 0–2) at 90 days and discharge, the mRS score distribution at discharge, and 24-h National Institutes of Health Stroke Scale (NIHSS) scores. All analyses were performed with patients treated between 2015 and 2019 ($N = 5025$) while patients treated in 2020 or 2021 ($N = 4332$) were analyzed for independent replication of the primary end point analysis.

Statistical analysis

Patients were grouped into four 6-h time-blocks (morning: 05:00–10:59; midday: 11:00–16:59; evening: 17:00–22:59; night: 23:00–4:59; Fig. 1A) based on either the time of day of flow restoration (primary analysis) or the time of symptom onset (secondary analysis) following the time segment analysis recommendations of the Leducq network on Circadian Effects in Stroke.[7] If not otherwise indicated, patients from one group were compared to all other patients. For unwitnessed onset stroke, time of onset was considered to be the midpoint between last seen well and time of recognition.[8] For the primary endpoint analysis, we used a multivariable ordinal logistic regression model adjusted for age, prestroke mRS score, time from onset to admission, admission during working hours (Monday–Friday 8:00–17:00), admission NIHSS score, intravenous alteplase treatment, the time from admission to flow restoration and the final modified Thrombolysis in Cerebral Infarction (mTICI) score. For secondary endpoint analyses, we used univariable and multivariable linear (for the 24-h NIHSS score) or binomial logistic (for functional independence at 90 days and discharge) regression models adjusted for the same set of variables. To assess the relation between outcome and time as a continuous variable, we applied sinusoidal regression. The relation between clinical outcome and time to treatment or status of recanalization was assessed using multivariable logistic regression models adjusted for the same set of variables. Interactions were tested using a multiplicative interaction term (e.g., time group*time to treatment). Complete case analysis was performed without imputations.

Results

Stroke patients (median [IQR] age, 76 years [65–82], 50% female, Table 1) showed a peak of onset at 09:30 and of flow restoration at 14:00 (Fig. 1A). Stratifying patients to 6-h time-blocks resulted in mildly larger groups for onset in morning and midday, and a substantially larger group for flow restoration during midday (Fig. 1B). Patients treated in the morning were younger, less likely to be female and to receive intravenous alteplase treatment, and showed longer times from onset to flow restoration when compared to other times of the day. There was no difference between time groups with regard to adverse events following EVT (Table 1).

In univariable analyses, treatment during the morning was associated with lower mRS scores at 90 days (odds ratio [OR], 1.33; 95% CI, 1.15–1.55; $p < 0.001$; Fig. 1C). Sinusoidal regression analyses which showed large overlap with a data-driven local polynomial regression fit (Fig. 1D) mapped the time of day of treatment with best outcomes to 07:12 ($p < 0.001$, Fig. 1E). Morning treatment was also associated with a higher rate of functional independence at 90 days (OR, 1.35; 95% CI, 1.14–1.61; $p < 0.001$) and discharge (OR, 1.40; 95% CI, 1.19–1.65; $p < 0.001$), lower mRS scores at discharge (OR, 1.40; 95% CI, 1.21–1.61; $p < 0.001$), and lower NIHSS scores at 24 h (OR, 5.14; 95% CI, 2.12–12.45; $p < 0.001$). For comparison, the time of day of onset was not associated with the distribution of mRS scores at 90 days or discharge (Fig. 1F-H).

In multivariable analyses, morning treatment was associated with lower mRS scores at 90 days in both the primary sample (adjusted OR [aOR], 1.27; 95% CI, 1.08–1.47; $p = 0.004$; Fig. 1I) and the replication sample (aOR, 1.19; 95% CI, 1.01–1.41; $p = 0.049$; Fig. 1J). This finding was consistent with the results from all secondary analyses (Fig. 2A-D) and in analysis restricted to patients with witnessed onset stroke (aOR, 1.30; 95% CI, 1.02–1.64; $p = 0.04$) or those with complete reperfusion (mTICI 3; aOR, 1.33; 95% CI, 1.01–1.75; $p = 0.043$; Fig. 2E,F) but not in patients without successful recanalization (mTICI 0–2a; aOR, 1.07; 95% CI, 0.55–2.17; $p = 0.81$). Morning treatment remained associated with lower mRS scores at

Figure 1. Association of the time of day of endovascular treatment with clinical outcome at 90 days after stroke. (A) The time of day of stroke onset peaked at 09:30 and the time of day of endovascular treatment (i.e., flow restoration) peaked at 14:00. (B) Stratifying patients to 6-h time-blocks resulted in mildly larger groups for onset in morning and mid-day, and a substantially larger group for flow restoration during mid-day and indicated crossflow between groups of symptom onset and flow restoration. (C) In unadjusted analyses, morning EVT was associated with lower mRS scores at 90 days after stroke compared to patients treated at other times of the day. (D) A sinusoidal fit of the relation of the time of flow restoration with mRS scores 90 days after stroke largely overlapped with a fit derived from unbiased local polynomial regression. (E) Sinusoidal regression analyses mapped the time of day of EVT with best outcomes to 07:12. (F–H) The time of day of symptom onset was not associated with mRS scores at 90 days (F and G) and discharge (H). (I and J) In adjusted analyses, morning EVT was associated with lower mRS scores at 90 days after stroke in the primary cohort (I) and in the independent replication cohort (J). aOR, adjusted odds ratio; EVT, endovascular treatment; mRS, modified Rankin Scale; n.s., not significant; T, time of day.

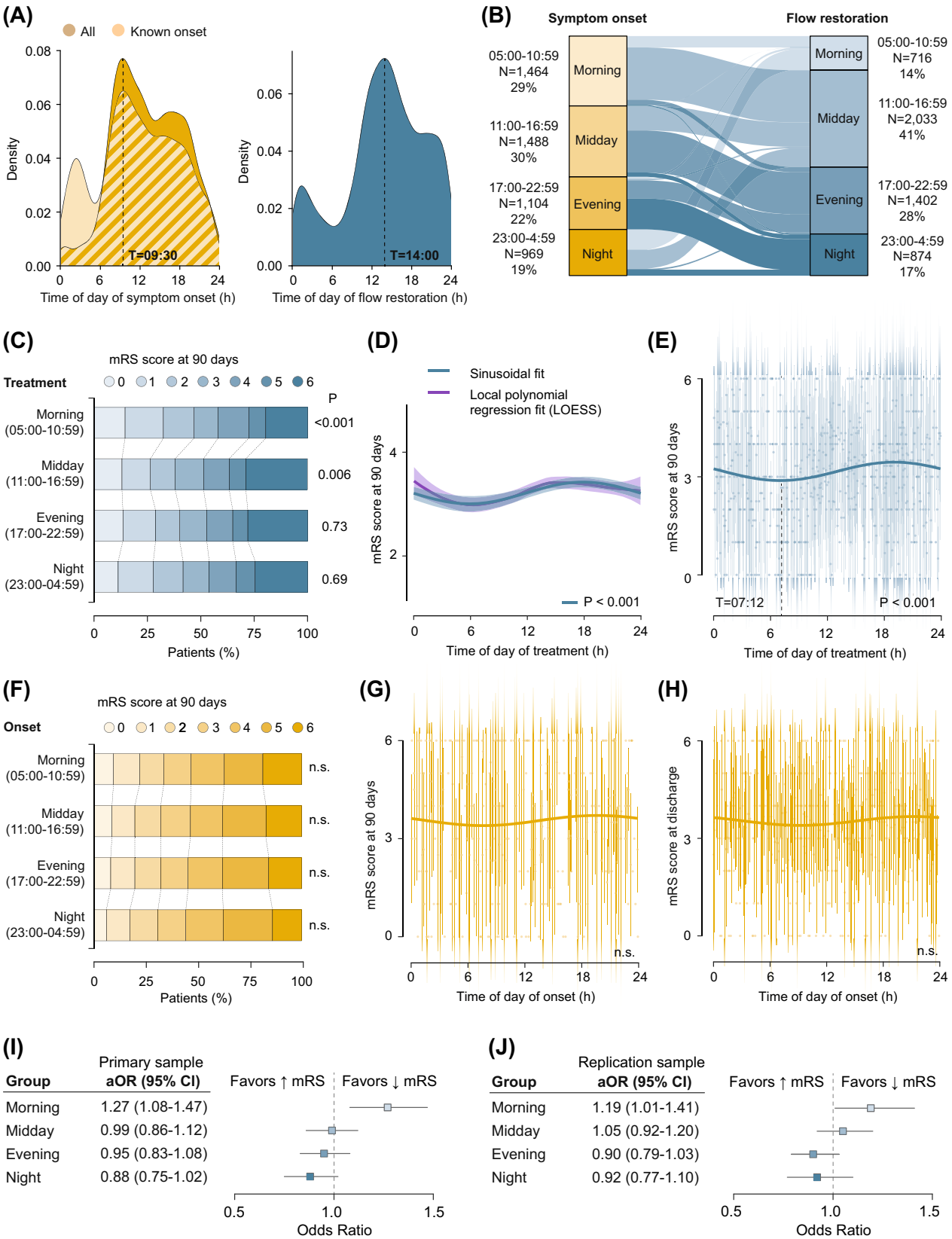


Table 1. Baseline characteristics and procedural metrics of patients treated at different times of the day.

Characteristic	Morning *N* = 716	Midday *N* = 2033	Evening *N* = 1402	Night *N* = 874	*p*
Age, median (IQR) [years]	73 (61–80)	77 (66–83)	76 (66–82)	75 (65–82)	<0.001
Female, No. (%)	320 (45)	1075 (53)	705 (50)	431 (49)	0.002
Hypertension, No. (%)	538 (77)	1510 (77)	1049 (78)	665 (78)	0.88
Diabetes mellitus, No. (%)	156 (22)	457 (23)	281 (21)	180 (21)	0.35
Dyslipidemia, No. (%)	283 (40)	777 (40)	516 (38)	341 (40)	0.72
Atrial fibrillation, No. (%)	292 (42)	820 (42)	578 (43)	375 (44)	0.67
pmRS score >1, No. (%)	129 (19)	428 (22)	262 (20)	120 (14)	<0.001
Baseline NIHSS score, median (IQR)	14 (10–19)	15 (9–19)	15 (9–19)	15 (10–19)	0.84
ASPECTS, median (IQR)	9 (7–10)	9 (7–10)	9 (8–10)	9 (7–10)	0.08
i.v. rt-PA treatment, No. (%)	313 (44)	1011 (50)	812 (58)	507 (58)	<0.001
Unwitnessed onset stroke, No. (%)	402 (56)	699 (34)	355 (25)	236 (27)	<0.001
T [SO → FLR], median (IQR) [h]	5.8 (3.6–7.6)	4.6 (3.3–7.7)	4.4 (3.3–6.1)	5.1 (3.9–6.6)	<0.001
T [ADM → PUN], median (IQR) [min]	65 (44–93)	63 (43–92)	67 (44–94)	71 (44–101)	0.009
First-pass rate, No. (%)	329 (48)	868 (45)	570 (43)	382 (46)	0.21
mTICI 2b/3, No. (%)	673 (95)	1881 (93)	1285 (92)	797 (92)	0.16
EVT-related adverse events					
Any adverse event, No. (%)	91 (13)	299 (15)	211 (15)	143 (16)	0.24
Intracranial hemorrhage, No. (%)	19 (2.7)	59 (2.9)	35 (2.5)	19 (2.2)	0.71
Device malfunction, No. (%)	1 (0.1)	9 (0.4)	4 (0.3)	2 (0.2)	0.70
Clot migration or embolization, No. (%)	24 (3.4)	65 (3.2)	48 (3.4)	30 (3.4)	0.98
Dissection or perforation, No. (%)	12 (1.7)	49 (2.4)	35 (2.5)	21 (2.4)	0.66

ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular treatment; i.v., intravenous; IQR, interquartile range; mTICI, modified Thrombolysis In Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; pmRS, prestroke modified Rankin Scale; rt-PA, recombinant tissue Plasminogen Activator; T [ADM → PUN], Time from admission to arterial puncture; T [SO → FLR], Time from symptom onset to flow restoration.

90 days when additionally adjusting for EVT-related adverse events ($p = 0.006$) or the number of EVTs per center ($p = 0.004$). In comparison with other predictors, morning EVT was similarly related to 90-day outcome as treatment with intravenous alteplase and a 4-h delay of the time to treatment (Fig. 2G).

Further, morning-treated patients showed lower odds to progress one point on the mRS scale per 1-h delay of the time to treatment compared to evening-treated patients (aOR, 95% CI: 0.95 [0.91–0.98] vs. 0.91 [0.89–0.94], $p_{interaction} = 0.046$, Fig. 2H). The association of successful recanalization with functional independence at 90 days was more pronounced in morning- compared to evening-treated patients (aOR, 95% CI: 7.09 [2.54–22.73] vs. 2.29 [1.34–4.03], $p_{interaction} = 0.049$, Fig. 2I). Comparing patients with and without successful recanalization according to their probability for functional independence, we found that the benefit from successful recanalization persisted until 24 h after onset for morning-treated patients while getting lost after 11.5 h for evening-treated patients (Fig. 2J).

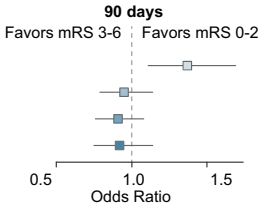
Discussion

In this retrospective multicenter cohort study, EVT between 05:00 and 10:59 was associated with better clinical outcomes compared to EVT at other times of the day across multiple end points, statistical approaches, and subgroup analyses and independent of procedural metrics. The benefit from successful recanalization was greater and longer for morning-treated compared to evening-treated patients, thus potentially opening an avenue for the

Figure 2. Secondary outcomes and benefit from successful recanalization. (A–D) Morning treatment was associated with higher rates of functional independence at 90 days (A) and discharge (B), lower mRS scores at discharge (C), and lower NIHSS scores at 24 h after onset (D). (E and F) Morning treatment was associated with higher likelihood of functional independence at 90 days (E) and discharge (F) in patients with an mTICI score of 3. (G) Morning treatment was similarly related to the rate of functional independence at 90 days compared to treatment with intravenous alteplase and a 4-h delay of the time from onset to treatment. (H) The association between time to treatment and mRS scores at 90 days was weaker in morning- compared to evening-treated patients. (I) The association between successful recanalization and functional independence at 90 days was stronger in morning- compared to evening-treated patients. (J) Predictive margins show that the benefit from successful recanalization persisted until 24 h after onset for morning-treated patients while it was lost after 11.5 h for patients treated in the evening. 95% CI, 95% confidence interval; aOR, adjusted odds ratio; h, hour; mRS, modified Rankin Scale; T, time of day; ΔT, time from onset to treatment.

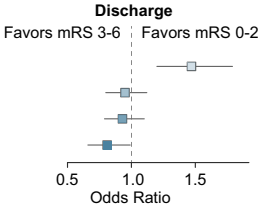
(A)

Treatment group	aOR (95% CI)
Morning (05:00-10:59)	1.37 (1.11-1.69)
Midday (11:00-16:59)	0.95 (0.79-1.14)
Evening (17:00-22:59)	0.91 (0.76-1.08)
Night (23:00-04:59)	0.92 (0.75-1.14)



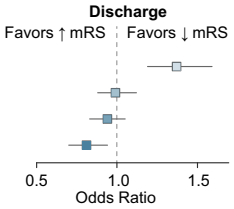
(B)

Treatment group	aOR (95% CI)
Morning (05:00-10:59)	1.47 (1.20-1.79)
Midday (11:00-16:59)	0.95 (0.80-1.12)
Evening (17:00-22:59)	0.93 (0.79-1.10)
Night (23:00-04:59)	0.81 (0.66-0.99)



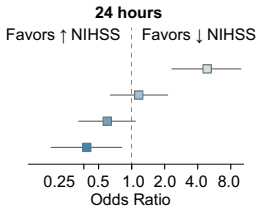
(C)

Treatment group	aOR (95% CI)
Morning (05:00-10:59)	1.37 (1.19-1.59)
Midday (11:00-16:59)	0.99 (0.88-1.12)
Evening (17:00-22:59)	0.94 (0.83-1.05)
Night (23:00-04:59)	0.81 (0.70-0.94)



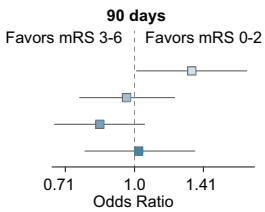
(D)

Treatment group	aOR (95% CI)
Morning (05:00-10:59)	4.88 (2.33-9.90)
Midday (11:00-16:59)	1.16 (0.64-2.13)
Evening (17:00-22:59)	0.60 (0.33-1.08)
Night (23:00-04:59)	0.38 (0.18-0.79)



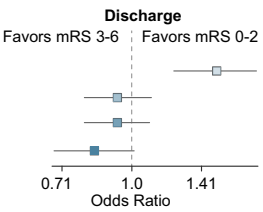
(E) mTICI=3

Treatment group	aOR (95% CI)
Morning (05:00-10:59)	1.33 (1.01-1.75)
Midday (11:00-16:59)	0.96 (0.76-1.22)
Evening (17:00-22:59)	0.84 (0.67-1.05)
Night (23:00-04:59)	1.02 (0.78-1.35)



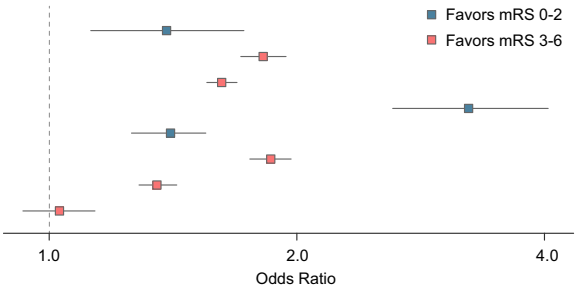
(F) mTICI=3

Treatment group	aOR (95% CI)
Morning (05:00-10:59)	1.52 (1.23-1.85)
Midday (11:00-16:59)	0.93 (0.79-1.10)
Evening (17:00-22:59)	0.93 (0.79-1.09)
Night (23:00-04:59)	0.83 (0.68-1.01)



(G)

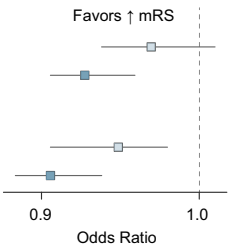
Predictor (90-day functional independence)	aOR (95% CI)
Morning flow restoration	1.39 (1.12-1.72)
Admission NIHSS score (5-point increments)	1.82 (1.71-1.94)
Age (10-year increments)	1.62 (1.52-1.73)
Successful recanalization	3.23 (2.32-4.55)
i.v. alteplase treatment	1.41 (1.19-1.64)
pmRS score	1.86 (1.70-2.03)
ΔT (Onset → flow restoration) [4-hour increments]	1.35 (1.25-1.47)
Admission during working hours	1.03 (0.88-1.20)



(H) Outcome ~ Time to treatment

Treatment group	OR (95% CI)	P
Morning (5:00-10:59)	0.97 (0.94-1.01)	0.048
Evening (17:00-22:59)	0.93 (0.91-0.96)	

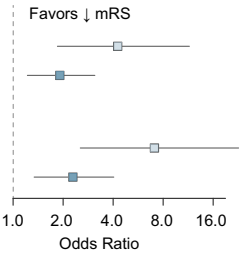
	aOR (95% CI)	
Morning (5:00-10:59)	0.95 (0.91-0.98)	0.046
Evening (17:00-22:59)	0.91 (0.89-0.94)	



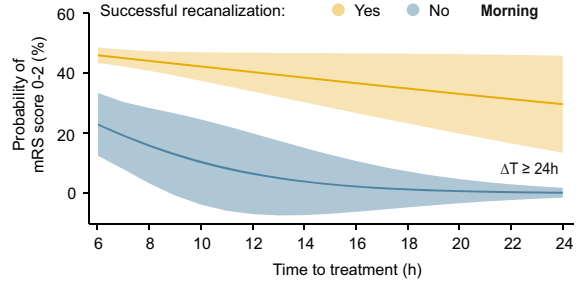
(I) Outcome ~ Successful recanalization

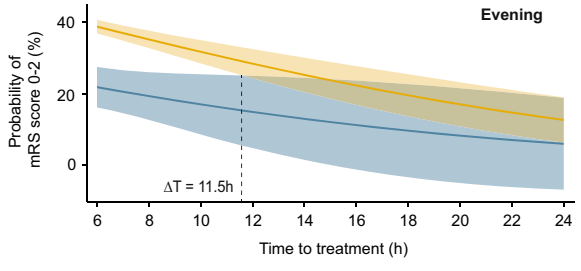
Treatment group	OR (95% CI)	P
Morning (5:00-10:59)	4.26 (1.85-11.5)	0.121
Evening (17:00-22:59)	1.91 (1.22-3.10)	

	aOR (95% CI)	
Morning (5:00-10:59)	7.09 (2.54-22.7)	0.049
Evening (17:00-22:59)	2.29 (1.34-4.03)	



(J)





treatment of particularly morning patients beyond 24 h.[9] Our findings considerably extend beyond earlier studies, which showed heterogeneous results[10–13] and were mostly comparably small and from one or two centers.

Our results from subgroup analyses and from multivariable analyses adjusting for time to treatment and other procedural metrics suggest that the observed effects might be explained by intrinsic human biology, for example, circadian rhythms of neuronal susceptibility to ischemia, mechanisms following reperfusion, and collateral flow,[1,3,4,14] rather than by procedural metrics. Studies are needed to determine how much of these time-of-day effects can be attributed to mechanisms that are diagnostically accessible such as collateral flow. It remains hypothetical to assume that the influence of such diagnostic information on the selection of included patients for EVT was similar between different times of the day.

Our study has several limitations. Due to the retrospective observational cohort design, we cannot exclude that patients were differently selected for EVT at different times of the day. The multivariable regression might not have fully accounted for the baseline differences between patients treated at different times of the day. We also cannot exclude residual confounding by weekday- and time of day-dependent staffing quality and quantity. Lastly, our registry-based dataset lacked information from advanced CT imaging such as on the ischemic core, penumbra, and mismatch ratio. Future studies might investigate whether the observed effects of the time of day on functional outcome could be mediated by differences of infarct progression as assessed by CT perfusion.

In conclusion, this study supports the idea of time-of-day effects on ischemic stroke evolution by identifying better clinical outcomes and longer benefit from successful recanalization for patients treated in the morning. If replicated in other cohorts, these findings might inform the design of clinical trials on EVT and eventually the selection of patients for EVT in routine clinical care.

ACKNOWLEDGEMENTS

J. L. S. and S. T. were supported by a grant from the Leducq foundation (21CVD04: Circadian effects in Stroke). Open Access funding enabled and organized by Projekt DEAL.

AUTHOR CONTRIBUTIONS

VGB, TAW, JLS, and ST contributed to the conception and design of the study and drafted a significant portion of the manuscript or figures. NV, FQ, HZ, JW, LK, TL, KD, and ST contributed to acquisition and analysis of data. A detailed list of the GSR investigators is provided in Table S1.

CONFLICTS OF INTEREST

T. L. consults for Stryker Neurovascular GmbH and has received speaker honoraria from Pfizer, Covidien, Phenox, and Microvention, outside of this study. L. K. has received funding for travel or speaker honoraria from Bayer Vital, Boehringer Ingelheim, Bristol-Meyer-Squibb, Daiichi Sankyo, and Pfizer, outside of this study, and funding for research from Boehringer Ingelheim. J. L. S. reports personal fees outside the submitted work from Phillips, Biogen, BrainsGate, Medtronic, and Rapid Medical. S. T. reports personal fees outside the submitted work from Apollo Alpha. The other authors report no conflicts of interest.

REFERENCES

1. Esposito E, Li W, Mandeville ET, et al. Potential circadian effects on translational failure for neuroprotection. Nature. 2020;582(7812):395-398.
2. Beker MC, Caglayan B, Yalcin E, et al. Time-of-day dependent neuronal injury after ischemic stroke: implication of circadian clock transcriptional factor Bmal1 and survival kinase AKT. Mol Neurobiol. 2018;55(3):2565-2576.
3. Tiedt S, Buchan AM, Dichgans M, Lizasoain I, Moro MA, Lo EH. The neurovascular unit and systemic biology in stroke - implications for translation and treatment. Nat Rev Neurol. 2022;18(10):597-612.
4. Rabinovich-Nikitin I, Lieberman B, Martino TA, Kirshenbaum LA. Circadian-regulated cell death in cardiovascular diseases. Circulation. 2019;139(7):965-980.
5. Reidler P, Brehm A, Sporns PB, et al. Circadian rhythm of ischaemic core progression in human stroke. J Neurol Neurosurg Psychiatry. 2021;94:70-73.
6. Wollenweber FA, Tiedt S, Alegiani A, et al. Functional outcome following stroke thrombectomy in clinical practice. Stroke. 2019;50:2500-2506.
7. Saver JL, Klerman E, Buchan A, et al. Consensus recommendations for standardized data elements, scales, and time segmentations in studies of human circadian/diurnal biology and stroke. Stroke. 2023;54:1943-1949.
8. Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med. 2019;380(19):1795-1803.
9. Sarraj A, Kleinig TJ, Hassan AE, et al. Association of Endovascular Thrombectomy vs medical management with functional and safety outcomes in patients treated beyond 24 hours of last known well: the SELECT late study. JAMA Neurol. 2022;80:172.
10. Wang X, Wang X, Ma J, et al. Association between the time of day at stroke onset and functional outcome of acute ischemic stroke patients treated with endovascular therapy. J Cereb Blood Flow Metab. 2022;42(12):2191-2200.

11. Hajdu SD, Kaesmacher J, Michel PP, et al. Association of time of day when endovascular therapy for stroke starts and functional outcome. Neurology. 2021;97:607.1-607.60607.
12. Ryu WS, Hong KS, Jeong SW, et al. Association of ischemic stroke onset time with presenting severity, acute progression, and long-term outcome: a cohort study. PLoS Med. 2022;19(2):e1003910.
13. Benali A, Moynier M, Dargazanli C, et al. Mechanical thrombectomy in nighttime hours: is there a difference in 90-day clinical outcome for patients with ischemic stroke? AJNR Am J Neuroradiol. 2021;42(3):530-537.
14. Crnko S, Du Pre BC, Sluijter JPG, et al. Circadian rhythms and the molecular clock in cardiovascular biology and disease. Nat Rev Cardiol. 2019;16(7):437-447.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1

