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Association of Time of Day When Endovascular Therapy for Stroke Starts and Functional Outcome

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Neurology® 2021;96:e1124-e1136. doi:10.1212/WNL.0000000000011449

Abstract

Objective
To investigate the association between endovascular therapy (EVT) start time in acute ischemic stroke (AIS) and midterm functional outcome.

Methods
This retrospective cohort study included all patients with AIS treated with EVT from 2 stroke center registries from January 2012 to December 2018. The primary outcome was the score on the modified Rankin Scale (mRS) and the utility-weighted mRS (uw-mRS) at 90 days. A proportional odds model was used to calculate the common odds ratio (OR) as a measure of the likelihood that the intervention at a given EVT start time would lead to lower scores on the mRS (shift analysis).

Results
A total of 1,558 cases were equally allotted into 12 EVT start time periods. The primary outcome favored EVT start times in the morning at 08:00–10:20 and 10:20–11:34 (OR, 0.53; 95% confidence interval [CI], 0.38 to 0.75; $p < 0.001$; OR, 0.62; 95% CI, 0.44 to 0.87; $p = 0.006$, respectively), while it disfavored EVT start times at the end of the working day at 15:55–17:15 and 18:55–20:55 (OR, 1.47; 95% CI, 1.03–2.09; $p = 0.034$; OR, 1.49; 95% CI, 1.03–2.15; $p = 0.033$). Symptom onset to EVT start time was significantly higher and use of IV tissue plasminogen activator significantly lower between 10:20 and 11:34 ($p < 0.004$ and $p = 0.012$, respectively).

Conclusion
EVT for AIS in the morning leads to better midterm functional outcome, while EVT at the end of the work day leads to poorer midterm functional outcome. Difference in baseline factors, standard workflow, and technical efficacy metrics could not be identified as potential mediators of this effect.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article. The Article Processing Charge was funded by the authors.

Glossary

AIS = acute ischemic stroke; **CI** = confidence interval; **EVT** = endovascular therapy; **mRS** = modified Rankin Scale; **mTICI** = modified Treatment in Cerebral Ischemia; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **sICH** = symptomatic intracranial hemorrhage; **TOAST** = Trial of ORG 10172 in Acute Stroke Treatment; **tPA** = tissue plasminogen activator; **uw-mRS** = utility-weighted modified Rankin Scale score.

Research on occupational accidents indicates that the risk of accidents while working increases as a function of number of hours at work.[1–3] Hänecke and colleagues reported an exponential increase in occupational accidents after the 9th hour of work.[4] Although most countries officially define the work day as 8 hours, many doctors experience working hours well beyond 9 hours due to the need for 24-hour patient care coverage.[5,6] Neurointerventionists and the rest of the stroke management team are currently feeling the effects of changes in acute ischemic stroke (AIS) management,[7] due in part to the mounting level of evidence from several large randomized controlled studies since 2015 that demonstrated the value of endovascular therapy (EVT) for first-line and delayed treatment.[8–17] The significant increase in the number of EVT-eligible patients has proportionally increased the emergency case load for the neurointerventionists as well as the support staff in the stroke unit, which extends the number of hours at work and could be a potential source of fatigue.[18] The need to examine the effects of doctor fatigue on the midterm outcome of treated patients was recognized and reported in the literature.[19] Current data on midterm functional outcome in patients treated during work hours vs after hours is limited, requiring more robust studies to elucidate the effects on patients treated at different times of the day.[20] We sought to investigate the association between EVT performed by presumed fatigued neurointerventionists and the stroke unit staff after standard working hours and the midterm neurologic outcome in treated patients.

Methods

Patient Population

We used 2 institutional databases—the acute stroke registry and analysis of Lausanne (ASTRAL) from Lausanne University Hospital, Switzerland, and the stroke registry from University Hospital of Bern, Switzerland—to retrospectively include all adult patients with AIS who received EVT, either as thromboaspiration or mechanical thrombectomy according to institutional guidelines, from January 2012 to December 2018. For patient selection, we used the following inclusion criteria: AIS secondary to a large vessel intracranial occlusion, CT-based multimodal imaging performed within 24 hours of last proof of good health showing occlusion of an intracranial vessel amendable to EVT, and brain angiography of good quality showing results following recanalization. Extracranial internal carotid artery occlusion or symptomatic stenosis without intracranial occlusion were excluded.

Both hospitals feature a comprehensive stroke center accredited by the Swiss Federation of Clinical Neurosocieties Swiss Stroke Committee mainly based on recommendations of the Swiss Stroke Society and European Stroke Organisation. Stroke team composition was similar between the centers and included an onsite neurologist trainee, on-call stroke attending neurologist, onsite attending anesthesiologist, and on-call attending interventional neurologist at all times including standard working hours, nighttime, and weekends. Imaging protocol and EVT criteria were based on local institutional guidelines and were applied in the same way regardless of admission day or time. For the University Hospital of Bern, MRI is performed during nighttime and daytime and there are no differences in its availability. Indications for EVT are standardized according to an institutional operating procedure scheme. For Lausanne University Hospital, a dedicated emergency MRI is available 24 hours a day, 7 days a week. It prioritizes stroke cases and there are no differences in its availability during nighttime and weekends relative to daytime. Indications for EVT are identical to those mentioned in the operating procedures of the University Hospital of Bern. Transfer patients were generally not reimaged unless transfer times were greater than 1.5 hours or the patient severely deteriorated after thrombolysis. In these 2 situations, perfusion CT/MRI was repeated prior to EVT.

Both centers have between 4 and 6 interventional neuroradiologists in order to provide 1 on-call physician per center working in 24-hour shifts covering 5 to 7 days per month. Approximately 5 EVTs are performed at Lausanne University and 7 at University Hospital of Bern per week. During EVT, operators work almost exclusively independently, with 1 angiography suite technician working in 8-hour shifts providing technical and material support. Endovascular trainees are often present during EVT, but do not participate as primary or secondary operators. Finally, a wide array of stent retriever devices are used in these centers to perform EVT, including, but not limited to, Trevo (Stryker, Kalamazoo, MI), Solitaire (Medtronic, Irvine, CA), Embotrap (Cerenovus, Galway, Ireland), Catch (Balt Extrusion, Montmorency, France), and Tiger (Rapid Medical, Yokneam, Israel).

Data Collection

Stroke time onset or last time seen without symptoms, groin puncture time, and recanalization time were recorded for each patient. The EVT start time was considered the operator's groin puncture time. A disproportionate number of EVTs were performed during normal working hours, making analysis at fixed time intervals with unequal cohort sizes a potential source of bias. As a result, patients were divided into 12 cohorts containing the same number of patients according to EVT start time, beginning at 08:00, the start of the work day, until 07:59 the following day.

Table 1 Patient Characteristics and Cardiovascular Risk Factors

	Total	08:00–10: 20 (n = 127)	10:20–11: 34 (n = 127)	11:34–12: 40 (n = 127)	12:40–13: 37 (n = 127)	13:37–14: 41 (n = 127)	14:41–15: 55 (n = 127)	15:55–17: 15 (n = 127)	17:15–18: 55 (n = 127)	18:55–20: 55 (n = 127)	20:55–22: 57 (n = 127)	22:57–02: 07 (n = 127)	02:07–07: 58 (n = 131)
Age, y	71.1 (62.4–82.0)	67.6 (57.7–78.7)[a]	70.8 (62.8–81.4)	73.6 (66.3–82.1)	71.1 (62.3–82.1)	75.0 (69.4–85.7)	72.7 (65.0–82.1)	70.9 (62.4–82.1)	70.4 (60.6–83.0)	70.2 (59.2–81.1)	69.9 (59.9–81.2)	72.2 (63.7–81.7)	68.9 (60.1–79.2)
Female sex	794/1,527 (52.0)	72 (56.7)	75 (59.5)	62 (50.4)	62 (48.8)	58 (45.7)	57 (44.9)	60 (47.2)	69 (54.3)	68 (53.5)	61 (48.0)	70 (55.1)	78 (59.5)
Atrial fibrillation	630/1,398 (45.1)	40 (33.6)	46 (39.0)	51 (43.6)	59 (49.6)	65 (54.2)	60 (52.2)	46 (40.7)	54 (46.6)	49 (43.4)	48 (43.2)	57 (49.1)	55 (45.5)
Smoking	413/1,500 (27.5)	38 (30.2)	34 (27.0)	31 (24.6)	32 (25.6)	31 (24.8)	33 (27.5)	38 (30.9)	30 (24.0)	35 (27.8)	34 (27.4)	40 (31.8)	37 (28.9)
Diabetes	298/1,506 (19.8)	22 (17.5)	30 (23.8)	21 (16.9)	16 (12.8)	23 (18.3)	26 (20.6)	28 (22.6)	26 (20.8)	30 (24.2)	30 (23.8)	23 (18.3)	23 (18.0)
Hyperlipidemia	1,025/ 1,515 (67.7)	86 (67.7)	82 (65.1)	95 (74.8)	82 (65.1)	92 (73.0)	83 (67.5)	84 (67.2)	85 (66.9)	84 (66.7)	72 (57.6)	86 (67.7)	94 (72.3)
Hypertension	1,153/ 1,542 (74.7)	85 (66.4)[b]	88 (67.7)	108 (82.4)	96 (73.3)	105 (82.7)	100 (78.7)	99 (76.7)	96 (73.9)	93 (72.7)	93 (73.2)	101 (79.5)	89 (69.5)

Data are mean (interquartile range) or n (%).
[a] $p = 0.002$, calculated using 1-way analysis of variance.
[b] $p = 0.025$, calculated using 1-way analysis of variance.

Table 2 Stroke Characteristics

	Total	08:00–10:20 (n = 127)	10:20–11: 34 (n = 127)	11:34–12: 40 (n = 127)	12:40–13: 37 (n = 127)	13:37–14: 41 (n = 127)	14:41–15: 55 (n = 127)	15:55–17: 15 (n = 127)	17:15–18: 55 (n = 127)	18:55–20: 55 (n = 127)	20:55–22: 57 (n = 127)	22:57–02: 07 (n = 127)	02:07–07: 58 (n = 131)	*p* Value
NIHSS at admission[a]	14.8 (9.0–20.0)	14.4 (8.0–19.0)	13.1 (7.0–17.0)	16.0 (10.5–20.0)	14.7 (9.0–20.0)	15.5 (10.0–21.0)	13.4 (7.0–19.0)	15.0 (9.0–20.0)	14.7 (8.5–19.5)	15.0 (8.0–19.0)	15.1 (9.0–19.0)	14.8 (8.0–19.0)	16.3 (11.0–19.0)	0.051
ASPECTS[b]	7.8 (7–10)	8 (7–9.5)	8 (7–9)	7.8 (6–10)	8.2 (7–10)	8 (7–9)	7.9 (7–10)	7.9 (6–10)	7.8 (7–9)	7.9 (7–10)	7.6 (7–9)	7.9 (7–9.5)	7.2 (6–9)	0.400
IV tPA[c]	792 (53.8)	60 (50.9)	49 (40.8)	62 (51.2)	73 (58.4)	67 (55.4)	71 (57.3)	76 (60.3)	75 (60.5)	68 (54.4)	59 (48.0)	75 (62.5)	57 (45.2)	0.012[g]
TOAST[d]														0.197
1	213 (14.2)	14 (11.1)	18 (14.4)	20 (15.8)	21 (16.8)	14 (11.5)	15 (12.0)	28 (22.4)	21 (16.5)	20 (16.0)	14 (11.3)	15 (11.9)	13 (10.2)	
2	638 (42.4)	48 (38.1)	45 (36.0)	52 (40.9)	61 (48.8)	64 (52.5)	61 (48.8)	50 (40.0)	48 (37.8)	47 (37.6)	54 (43.6)	55 (43.7)	53 (41.4)	
4	157 (10.4)	21 (16.7)	16 (12.8)	9 (7.1)	11 (8.8)	9 (7.4)	10 (8.0)	8 (6.4)	13 (10.2)	19 (15.2)	11 (8.9)	10 (7.9)	20 (15.6)	
5	488 (32.4)	42 (33.3)	45 (36.0)	46 (36.2)	31 (24.8)	35 (28.7)	39 (31.2)	38 (30.4)	44 (34.6)	38 (30.4)	45 (36.3)	45 (35.7)	40 (31.3)	
Prestroke mRS[e]														0.833
0–2	1,349 (89.5)	118 (94.4)	109 (87.9)	111 (87.4)	110 (88.0)	109 (88.6)	109 (88.6)	111 (89.5)	113 (89.7)	117 (92.9)	109 (87.9)	109 (88.6)	115 (89.8)	
3–5	158 (10.6)	7 (5.6)	15 (12.1)	16 (12.6)	15 (12.0)	14 (11.4)	14 (11.4)	13 (10.5)	13 (10.3)	9 (7.1)	15 (12.1)	14 (11.4)	14 (11.4)	
uw-mRS[f]	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	9.9 (10.0–10.0)	0.833
Onset to EVT start time, min	305 (178–350)	306 (152–435)	335 (169–422)	312 (178–330)	282 (170–274)	313 (192–323)	312 (164–347)	299 (166–357)	288 (166–334)	294 (184–324)	266 (169–304)	273 (200–314)	376 (245–462)	0.004[h]
Admission to EVT start time, min	102 (65–117)	97 (62–103)	96 (61–105)	87 (58–113)	85 (54–112)	95 (54–115)	98 (59–117)	110 (67–115)	110 (70–117)	106 (73–119)	93 (71–115)	110 (64–133)	133 (84–134)	0.001[h]

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; EVT = endovascular therapy; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; TOAST = Trial of ORG 10172 in Acute Stroke Treatment; tPA = tissue plasminogen activator; uw-mRS = utility-weighted modified Rankin Scale score.
Data are mean (interquartile range) or n (%).
[a] Scores on the NIHSS range from 0 to 42. Scores increase as a function of neurologic deficit.
[b] ASPECTS ranging from 0 to 10.
[c] IV treatment with tPA was used up to 4.5 hours after symptom onset: 1,473 patients analyzed.
[d] TOAST classification of subtypes of acute ischemic stroke are defined as follows: 1, large artery atherosclerosis; 2, cardioembolism; 3, small vessel occlusion; 4, stroke of other determined etiology; and 5, stroke of undetermined etiology: 1,505 patients analyzed.
[e] Scores on the mRS: 0, no symptoms; 1, no clinically significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; 6, death: 1,498 patients analyzed.
[f] Score on uw-mRS ranges from 0 (death) to 10 (no symptoms or disability).
[g] *p* Value calculated using χ^2.
[h] *p* Value calculated using 1-way analysis of variance.

Table 3 Occlusion Site

	Total	08:00–10:20 (n = 127)	10:20–11:34 (n = 127)	11:34–12:40 (n = 127)	12:40–13:37 (n = 127)	13:37–14:41 (n = 127)	14:41–15:55 (n = 127)	15:55–17:15 (n = 127)	17:15–18:55 (n = 127)	18:55–20:55 (n = 127)	20:55–22:57 (n = 127)	22:57–02:07 (n = 127)	02:07–07:58 (n = 131)
Vertebral artery	18 (1.2)	1 (0.8)	0 (0)	2 (1.7)	1 (0.8)	1 (0.9)	0 (0)	5 (4.3)	2 (1.6)	1 (0.8)	1 (0.8)	2 (1.7)	2 (1.7)
Basilar artery	21 (1.5)	2 (1.6)	1 (0.8)	1 (0.8)	3 (2.5)	2 (1.7)	0 (0)	2 (1.7)	1 (0.8)	3 (2.5)	2 (1.7)	3 (2.5)	1 (2.5)
Intercranial internal carotid artery[a]	319 (22.1)	23 (18.9)	26 (21.3)	25 (20.8)	29 (23.8)	29 (24.8)	21 (18.6)	19 (16.4)	26 (21.0)	34 (27.9)	30 (24.8)	23 (19.2)	34 (27.6)
First segment of middle cerebral artery	679 (47.1)	61 (50.0)	58 (47.5)	62 (51.7)	55 (45.1)	56 (47.9)	56 (49.6)	55 (47.4)	68 (54.8)	54 (44.3)	59 (48.8)	51 (42.5)	44 (35.8)
Second segment of middle cerebral artery	272 (18.9)	24 (19.7)	28 (23.0)	24 (20.0)	23 (18.9)	23 (19.7)	18 (15.9)	30 (25.9)	16 (12.9)	19 (15.6)	18 (14.9)	26 (21.7)	23 (18.7)
Third segment of middle cerebral artery	14 (1.0)	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)	0 (0)	2 (1.8)	0 (0)	2 (1.6)	2 (1.6)	2 (1.7)	1 (0.8)	1 (0.8)
Fourth segment of middle cerebral artery	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
First segment of anterior cerebral artery	4 (0.3)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	2 (1.6)	0 (0)	0 (0)	0 (0)
Second segment of anterior cerebral artery	4 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.9)	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.8)	1 (0.8)
First segment of posterior cerebral artery	104 (7.2)	10 (8.2)	6 (4.9)	5 (4.2)	10 (8.2)	4 (3.4)	14 (12.4)	5 (4.3)	7 (5.6)	7 (5.7)	9 (7.4)	11 (9.2)	16 (13.0)
Second segment of posterior cerebral artery	6 (0.4)	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.9)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.7)	1 (0.8)

Data are n (%); 1,442 patients analyzed; p value of 0.51 was calculated using χ^2.
[a] Patients who had occlusion of intracranial internal carotid artery (carotid terminus) may have also had thrombus extension into the first segment of either the anterior or the middle cerebral artery, or both.

Table 4 Unadjusted and Adjusted Association Between Endovascular Therapy (EVT) Start Time and Long-term Neurologic Outcome

	mRS score at 90 days[a]								Reduction in mRS score at 90 days[c]		Mortality at 90 days
EVT start time	0	1	2	3	4	5	6	Utility-weighted mRS score at 90 days[b]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[d]	OR (95% CI)
08:00–10:20 (n = 127)	15 (12.0)	32 (25.6)	35 (28.0)	13 (10.4)	9 (7.2)	5 (4.0)	16 (12.8)	6.6 (6.5–9.1); $p < 0.001$[e]	0.51 (0.37–0.70); $p < 0.001$[e]	0.53 (0.38–0.75); $p < 0.001$[e]	0.52 (0.28–0.90); $p = 0.028$[e]
10:20–11:34 (n = 127)	20 (16.5)	25 (20.7)	20 (16.5)	13 (10.4)	16 (13.2)	7 (5.8)	19 (15.8)	6.0 (3.3–9.1); $p = 0.008$[e]	0.63 (0.46–0.88); $p = 0.006$[e]	0.62 (0.44–0.87); $p = 0.006$[e]	0.71 (0.40–1.20); $p = 0.223$
11:34–12:40 (n = 127)	14 (11.5)	18 (14.8)	18 (14.8)	23 (18.9)	13 (10.7)	6 (4.8)	30 (24.5)	5.2 (0.0–9.1); $p = 0.709$	1.03 (0.74–1.43); $p = 0.853$	0.76 (0.54–1.07); $p = 0.123$	0.86 (0.52–1.37); $p = 0.534$
12:40–13:37 (n = 127)	10 (8.4)	21 (17.7)	21 (17.7)	16 (13.5)	19 (16.0)	6 (5.0)	26 (21.8)	5.2 (0.0–9.1); $p = 0.677$	1.02 (0.73–1.42); $p = 0.919$	1.01 (0.71–1.43); $p = 0.950$	0.93 (0.55–1.51); $p = 0.773$
13:37–14:41 (n = 127)	13 (10.8)	19 (15.8)	17 (14.2)	23 (19.2)	9 (7.5)	10 (8.3)	29 (24.2)	5.1 (0.0–9.1); $p = 0.862$	1.08 (0.77–1.50); $p = 0.656$	0.93 (0.65–1.32); $p = 0.675$	0.83 (0.50–1.35); $p = 0.471$
14:41–15:55 (n = 127)	12 (10.1)	19 (16.0)	26 (21.9)	23 (19.3)	8 (6.7)	5 (4.2)	26 (21.9)	5.6 (0.0–9.1); $p = 0.353$	0.87 (0.62–1.21); $p = 0.407$	1.12 (0.78–1.59); $p = 0.539$	1.06 (0.63–1.73); $p = 0.825$
15:55–17:15 (n = 127)	11 (9.2)	16 (13.3)	20 (16.7)	10 (8.3)	16 (13.3)	8 (6.7)	39 (32.5)	4.4 (0.0–7.6); $p = 0.017$[e]	1.46 (1.05–2.05); $p = 0.025$[e]	1.47 (1.03–2.09); $p = 0.034$[e]	1.78 (1.21–2.79); $p = 0.013$[e]
17:15–18:55 (n = 127)	12 (9.8)	19 (15.5)	23 (18.7)	17 (13.8)	12 (9.8)	8 (6.5)	32 (26.0)	5.0 (0.0–8.4); $p = 0.275$	1.09 (0.79–1.52); $p = 0.596$	1.09 (0.77–1.54); $p = 0.629$	1.20 (0.74–1.91); $p = 0.447$
18:55–20:55 (n = 127)	9 (7.8)	13 (11.2)	23 (19.8)	12 (10.3)	18 (15.5)	9 (7.8)	32 (27.6)	4.5 (0.0–7.6); $p = 0.086$	1.42 (1.01–1.99); $p = 0.042$[e]	1.49 (1.03–2.15); $p = 0.033$[e]	1.08 (0.65–1.73); $p = 0.773$
20:55–22:57 (n = 127)	11 (8.9)	22 (17.9)	17 (13.8)	19 (15.5)	20 (16.3)	6 (4.9)	28 (22.8)	5.1 (0.0–9.1); $p = 0.712$	1.06 (0.76–1.47); $p = 0.736$	1.24 (0.87–1.77); $p = 0.226$	1.04 (0.62–1.68); $p = 0.879$
22:57–02:07 (n = 127)	10 (8.5)	19 (16.1)	23 (19.5)	14 (11.9)	14 (11.9)	6 (5.1)	32 (27.1)	4.9 (0.0–7.6); $p = 0.557$	1.12 (0.80–1.57); $p = 0.495$	1.24 (0.86–1.78); $p = 0.243$	1.28 (0.78–2.05); $p = 0.312$
02:07–07:58 (n = 131)	8 (6.7)	15 (12.5)	24 (20.0)	19 (15.8)	16 (13.3)	8 (6.7)	30 (25.0)	4.8 (0.0–7.6); $p = 0.245$	1.28 (0.92–1.78); $p = 0.152$	1.15 (0.80–1.65); $p = 0.453$	1.02 (0.61–1.64); $p = 0.947$

Abbreviations: CI = confidence interval; mRS = modified Rankin Scale; OR = odds ratio.
Data are mean (interquartile range) or n (%).
[a] Scores on the mRS range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Distribution of scores at 90 days for EVT start times in the overall trial population.
[b] The utility-weighted mRS scale ranges from 0 (death) to 10 (no symptoms or disability).
[c] The measurement of effect was a cumulative logistic-regression OR (shift analysis).
[d] Controlling for age, symptom onset to EVT start time, age, NIH Stroke Scale score, modified Treatment in Cerebral Ischemia score, and prestroke mRS score.
[e] Significant.

Time periods varied between cohorts, with those during the day shorter and those at night longer. To perform a multivariate analysis and eliminate confounding factors, the following patient characteristics were recorded: age, sex, atrial fibrillation, smoking, diabetes, hypertension, and hyperlipidemia, as well as stroke characteristics including NIH Stroke Scale (NIHSS) score at admission, prestroke modified Rankin Scale score (mRS), Alberta Stroke Program Early CT Score (ASPECTS), occlusion site, prestroke utility-weighted mRS score (uw-mRS), concomitant IV tissue plasminogen activator (tPA), Trial of ORG 10172 in Acute Stroke Treatment (TOAST) mechanism type, symptom onset to EVT start time, admission to EVT start time, and occlusion site; and defined as large artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined etiology, or stroke of undetermined etiology.[21] The EVT characteristics reported included the following: modified Treatment in Cerebral Ischemia (mTICI) score, number of EVT passes, symptomatic intracranial hemorrhage (sICH), and uw-mRS at 90 days post-EVT.[22,23]

Primary and Secondary Outcomes

The primary outcome of the study was the score on the mRS at 90 days after EVT, which was assessed by trained personnel who were unaware of the EVT start time. The mRS is a graded interval scale (range, 0 [no symptoms] to 6 [death]) for the assessment of neurologic functional disability. Secondary outcomes included EVT start to recanalization interval time, mTICI score, number of EVT passes, and rate of sICH.

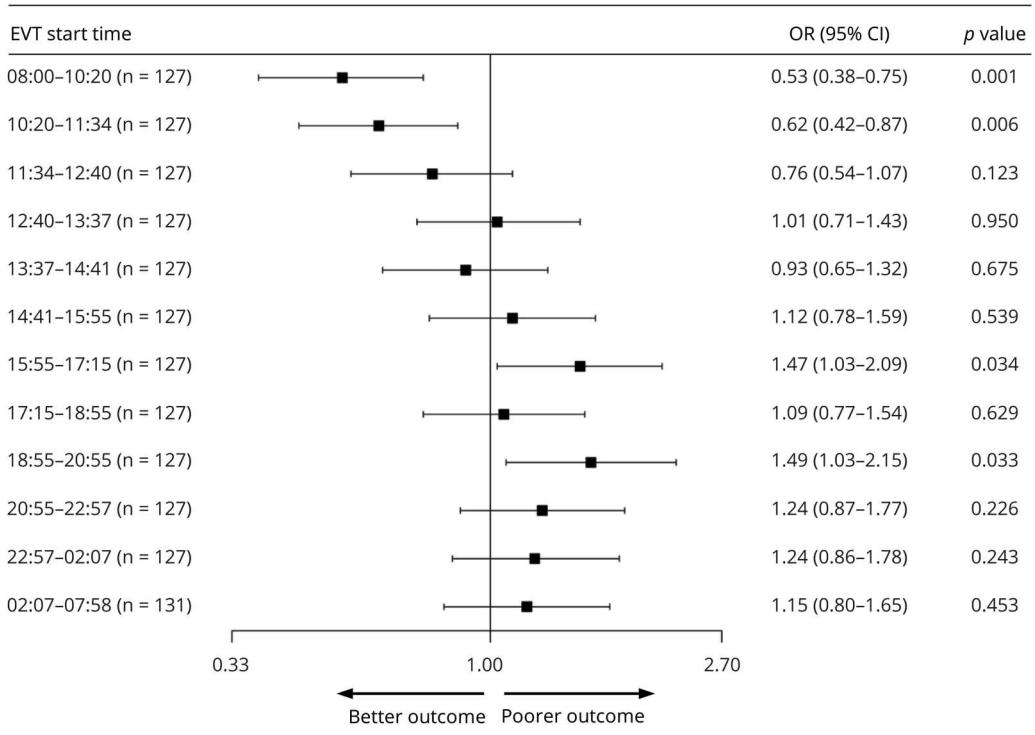
Statistical Analyses

Our analyses were performed to detect a shift in the distribution of scores on the mRS at 90 days between each EVT start time, with scores of 5 (bedbound with severe disability) and 6 (death) combined due to comparable patient-centered outcome and with the assumption that the differential effect would lead to a common odds ratio (OR) (indicating the odds of improvement of 1 point on the mRS) of 0.6 for positive effects and 1.4 for negative effects.[24]

Comparisons of baseline characteristics between cohorts were conducted using a one-way analysis of variance for continuous variables of interest (age, NIHSS at admission, onset to EVT start time, number of EVT passes, baseline EVT start to recanalization time, and uw-mRS at 90 days). Chi-square analysis was conducted for categorical variables of interest (atrial fibrillation, hypertension, smoking, diabetes, hyperlipidemia, IV tPA, TOAST, baseline mTICI, and sICH). Continuous variables are presented using mean and interquartile range. Categorical variables are presented as frequencies with percentages. Significance was set at $p < 0.05$.

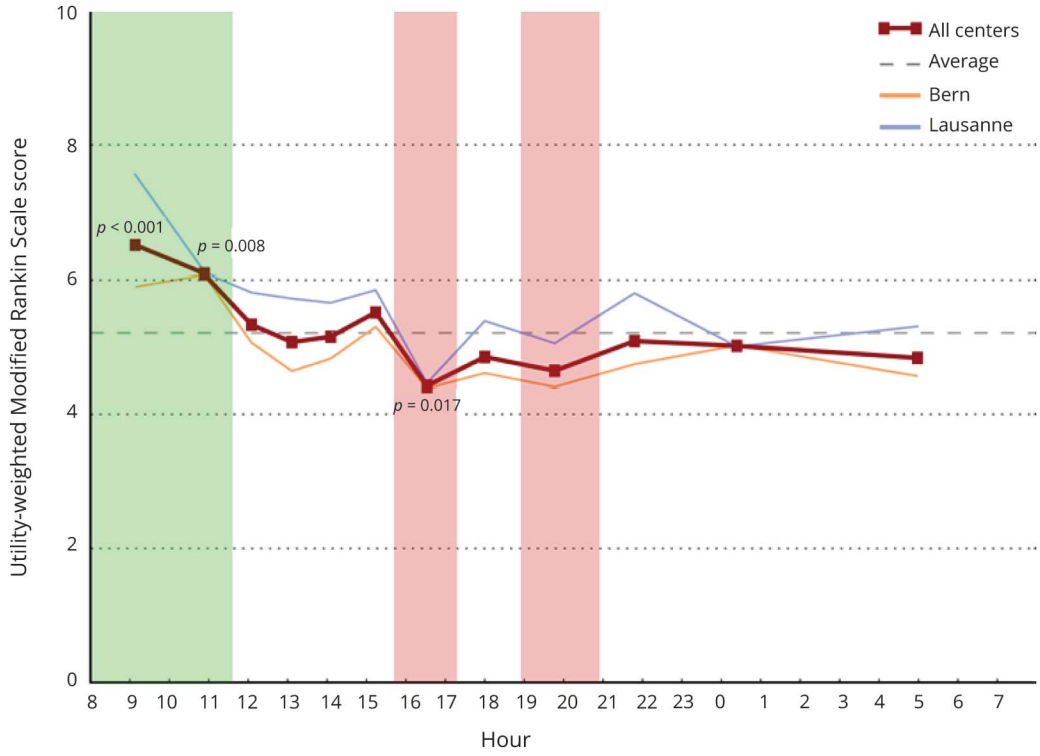
Detection of statistically significant variables was performed by a univariate analysis using an unpaired *t* test comparing 1

Figure 1 Analysis of the Primary End Point



The forest plot shows the effect size in the primary end point (common odds ratio for improvement on the modified Rankin Scale at 90 days, analyzed according to ordinal logistic regression and adjusted for age, symptom onset to endovascular therapy (EVT) start time, age, NIH Stroke Scale score, modified Treatment in Cerebral Ischemia score, and prestroke modified Rankin Scale score) across all EVT start time cohorts. There are significant differences in the morning cohorts at 08:00–10:20 and 10:20–11:34, suggesting better functional outcome at 3 months, as well as in the end of work day cohorts at 15:55–17:15 and 18:55–20:55, suggesting poorer functional outcome at 3 months. CI = confidence interval; OR = odds ratio.

Figure 2 Scores on the Utility-Weighted Modified Rankin Scale at 90 Days for Each Stroke Center as a Function of Endovascular Therapy Start Time



Data are organized into 12 equally sized cohorts over 24 hours starting at 8:00. Higher scores indicate better functional outcome. Green shading corresponds to cohorts with favorable functional outcome at 3 months; red shading corresponds to cohorts with poorer functional outcome at 3 months.

cohort to all other reference cohorts, then subsequently repeated for other cohorts. Significance was set at $p < 0.05$.

Adjusted estimates of effect were selected according to clinical relevance and adjusted for age, symptom onset to EVT start time, age, NIHSS score, mTICI score, hypertension, and prestroke mRS score. The assessment of heterogeneity of EVT start time effect was performed with the inclusion of multiplicative interaction terms. Significance was set at $p < 0.05$.

Statistical analyses were performed using Anaconda version 5.3.1 (Anaconda, Austin, TX) for Python 2.7 linked via module Rpy2 with R version 3.5.1ci (R Foundation, Vienna, Austria). For the primary end point, an ordinal multivariate logistic regression was performed with proportional OR. To perform it, a Vector Generalized Linear and Additive Models (VGLM/VGAM) library was used in R. The confounding factors added into the model were selected by clinical relevance. Noncollinearity was verified using tolerance metric in the R package "olsrr." All variables had a tolerance greater than 0.2 with the lowest tolerance calculated at 0.23. This confirmed our clinical assumption of no collinearity between variables.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the local institutional review board of each hospital under the auspices of the Swiss ethics committees for research involving humans (Swissethics). No informed consent was required according to the legislation.

Data Availability

Individual deidentified participant data, related documents such as study protocol, and statistical analysis will be shared on request from any qualified investigator for 3 years after the date of publication.

Results

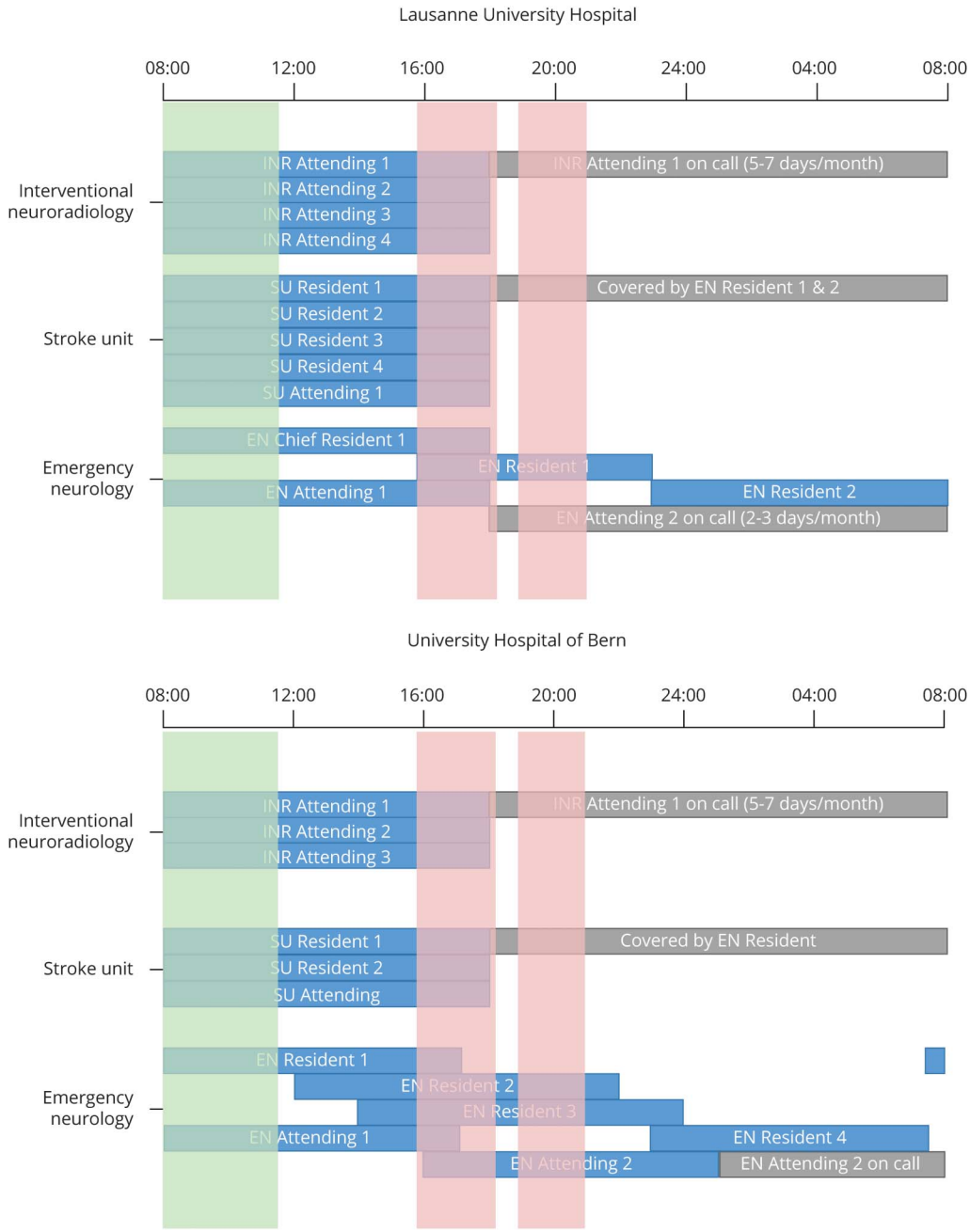
A total of 1,574 consecutive EVT procedures meeting selection criteria were selected for review, with 991 cases derived from University Hospital of Bern, of which 660 were direct presentations (66%), and 581 from Lausanne University Hospital, of which 490 were direct presentations (83%). Sixteen cases were lost to follow-up as no information on midterm functional neurologic status was available. The 1,558 cases available for analysis were distributed according to EVT start time into equal size patient cohort time periods, each containing 127 to 131

Table 5 Efficacy Outcomes

	Total	08:00–10: 20 (n = 127)	10:20–11: 34 (n = 127)	11:34–12: 40 (n = 127)	12:40–13: 37 (n = 127)	13:37–14: 41 (n = 127)	14:41–15: 55 (n = 127)	15:55–17: 15 (n = 127)	17:15–18: 55 (n = 127)	18:55–20: 55 (n = 127)	20:55–22: 57 (n = 127)	22:57–02: 07 (n = 127)	02:07–07: 58 (n = 131)	*p* Value
mTICI[a]														0.0682
3	734/ 1,526 (48.1)	51 (40.2)	62 (48.8)	66 (52.0)	62 (48.8)	61 (48.0)	60 (48.0)	62 (48.8)	55 (43.3)	58 (45.7)	72 (56.7)	55 (43.3)	70 (53.4)	
2b	528/ 1,526 (34.6)	58 (45.7)	43 (33.9)	37 (29.1)	37 (29.1)	45 (35.4)	50 (40.0)	41 (32.3)	46 (36.2)	37 (29.1)	36 (28.4)	52 (40.9)	38 (29.0)	
0–2a	264/ 1,526 (17.3)	18 (14.2)	22 (17.3)	24 (18.9)	20 (15.8)	21 (16.5)	15 (12.0)	24 (18.9)	26 (20.5)	32 (25.2)	19 (15.0)	20 (15.8)	23 (17.6)	
sICH	118/ 1,476 (8.0)	5 (4.1)	10 (7.9)	9 (7.3)	8 (6.7)	10 (8.3)	9 (7.3)	13 (10.5)	7 (5.6)	9 (7.6)	10 (8.2)	10 (8.1)	18 (14.3)	0.374
EVT start to recanalization time, min	58.0 (29–75)	56.1 (25–80)	59.9 (31–75)	65.9 (30–90)	60 (34–72)	57.7 (31–74)	55.4 (30–68)	58.9 (27–81)	52.0 (29–67)	52.0 (29–67)	50.4 (25–65)	59.7 (28–80)	57.8 (30–86)	0.282

Abbreviations: EVT = endovascular therapy; mTICI = modified Treatment in Cerebral Ischemia; sICH = symptomatic intracranial hemorrhage,
Data are mean (interquartile range) or n (%).
[a] mTICI score: 2b or 3 indicates successful reperfusion.

Figure 3 Shift Schedules for Physicians in Interventional Neuroradiology (INR), Stroke Unit (SU), and Emergency Neurology (EN)



Data are organized into 12 equally sized cohorts over 24 hours starting at 8:00. Green shading corresponds to cohorts with favorable functional outcome at 3 months; red shading corresponds to cohorts with poorer functional outcome at 3 months.

patients. The cohorts were as follows: 08:00–10:20, 10:20–11:34, 11:34–12:40, 12:40–13:37, 13:37–14:41, 14:41–15:55, 15:55–17:15, 17:15–18:55, 18:55–20:55, 20:55–22:57, 22:57–02:07, and 02:07–07:58.

Demographics, Cardiovascular Risk Factors, and Stroke Characteristics

A description of the demographics and cardiovascular risk factors for each patient cohort is shown in table 1. No inhomogeneity was detected in patient cohorts relating to demographics and cardiovascular risk factors with the exception of age; a small, yet statistically significant younger population was observed in the morning 08:00–10:20 cohort ($p = 0.002$). The absolute difference of mean age between patients in this cohort relative to the mean of all patients included in the study was 3.5 years. Fewer patients in this cohort were hypertensive ($p = 0.025$). A description of stroke characteristics for each patient cohort is shown in table 2. Stroke characteristics were similarly homogenous with

the exception of symptom onset to EVT start time, IV tPA use, and admission to EVT start time. Onset to EVT start time was significantly longer between 10:20–11:34 and 02:07–07:58 and significantly shorter between 20:55–22:57 and 22:57–02:07 (p = 0.004). IV tPA was used less frequently between 10:20–11:34 and 02:07–07:58 (p = 0.012). Admission to EVT start time was significantly longer between 02:07 and 07:58. A description of stroke occlusion site is shown in table 3. Distribution of stroke occlusion site was homogenous among all cohorts.

Primary End Point, EVT Start Time, and Midterm Functional Outcome

Table 4 describes the univariate and multivariate analyses investigating the relationship between the EVT start time and mRS, uw-mRS, and mortality at 90 days. Analysis of the primary end point showed a common OR (indicating the odds of improvement of 1 point on the mRS) of 0.53 (95% confidence interval [CI], 0.38 to 0.75, p < 0.001) and of 0.62 (95% CI, 0.44 to 0.87, p = 0.006) favoring EVT with start times in the morning at 08:00–10:20 and 10:20–11:34 as well as 1.47 (95% CI, 1.03 to 2.09, p = 0.034) and 1.49 (95% CI, 1.03 to 2.15, p = 0.033) at 15:55–17:15 and 18:55–20:55, respectively, disfavoring EVT at start times at the end of the work day. Figure 1 shows the effect size in the primary end point across all EVT start time cohorts. There was a higher uw-mRS at 90 days, signifying better functional outcome, in patients with EVT performed between 08:00 and 10:20 (5.9; 95% CI, 3.3 to 9.1, p < 0.001) as well as EVT performed between 10:20 and 11:34 (5.2, 95% CI, 0.0 to 9.1, p = 0.008) and significantly lower uw-mRS, signifying poorer functional outcome, in patients treated at 15:55–17:15 (5.0; 95% CI, 0.0 to 8.4, p = 0.017). Figure 2 depicts the uw-mRS at 90 days as a function of time period cohort for both stroke centers. Similar trends in functional outcome are observed in each stroke center.

The proportion of patients with mRS of 0–2 at 90 days was 37.6% and 37.2% when EVT start times were between 08:00–10:20 and 10:20–11:34, respectively, vs only 22.5% and 19.0% for EVT start times at 15:55 and 18:55–20:55. Mortality at 90 days was lower in the morning in 12.8% patients with EVT start time at 08:00–10:20 (OR, 0.52; 95% CI, 0.28–0.90; p = 0.028) and higher at the end of the work day in 32.5% of patients when EVT start times were 15:55–17:15 (OR, 1.78; 95% CI, 1.21–2.79; p = 0.013).

Secondary End Points, EVT Procedural Characteristics

Table 5 describes the univariate analysis of EVT characteristics in all time period cohorts. mTICI score, number of EVT passes, presence of sICH, and EVT start to recanalization time were not significantly different.

Discussion

The main finding of the present study is that midterm functional outcome and mortality after EVT in AIS varied according to the start time of thrombectomy. EVT performed in the morning, 08:00–10:15, yielded good functional outcomes, whereas EVT performed after the ninth hour of work, 15:55–17:15, led to poorer functional outcomes. The outcome from EVT performed at nighttime is not significantly worse than that of EVT performed during the day. The difference observed does not seem to be caused by differences in baseline characteristics or due to difference in standard measures of interventional efficacy and safety at different time points.

EVT is a procedure requiring a high degree of vigilance and reflex developed after several years of specialized training, which may become impaired due to extended working hours.[25] Patients admitted out of normal work hours are less likely to be managed according to current operational guidelines, leading to poorer short-term outcomes than those of patients admitted during normal work hours.[26] We hypothesized that EVT performed outside of the work day or at night would lead to poorer midterm functional outcome because of doctor fatigue. The link between fatigue and performance remains controversial, with some studies failing to demonstrate any correlation between extended working hours and doctor performance or safety outcomes.[27] A systematic literature review by Gates and colleagues[19] suggests that evidence for possible association of doctor fatigue with performance is varied in part because of the use of heterogenous outcome measurements. In stroke management, the outcomes of interest are midterm functionality graded on the mRS and uw-mRS, a patient-centered scale that measures benefit of a given intervention to the patient.[23] We studied effect on mRS as a function of EVT start time. Assuming that the on-call neurointerventionist begins the work day between 07:00 and 08:00, our study suggests that at the start of the work day, between 08:00 and10:31, technical performance is optimal in a rested and vigilant doctor, leading to the significantly higher uw-mRS at 90 days or better midterm functional outcome observed. However, the analyses of the secondary end points measuring technical performance did not reveal higher rates of complete recanalization, fewer numbers of EVT passes, faster procedure times, or lower rates of sICH. Notably, in this cohort, symptom onset to EVT start times were significantly longer and on average beyond 4.5 hours. This may suggest that many patients in this cohort met the stricter EVT requirements and thus had relatively better collateral circulation and smaller core infarct sizes, which could be a potential source of selection bias. Any possible inhomogeneity between cohorts cannot be corroborated because these 2 stroke characteristics were not recorded in the majority of patients in the 2 institutional databases used in this study. We hypothesize that in the morning cohorts, an increased number of patients with stroke of unknown onset with limited infarct core size due to good collateralization were selected for EVT and thus had a higher probability of favorable midterm functional outcome. These patients were statistically younger than other cohorts, thus had better leptomeningeal collateral circulation and better hemodynamic variables with hypothetically small core size volumes. This

cannot be substantiated in this study because infarct volume size was not available for analysis in this dataset.[28,29] Also, only 66.4% patients at 08:00–10:15 were hypertensive, compared to a frequency of 74.7% for all groups. Whereas concomitant hypertension in AIS is associated with poorer outcome and therefore could in part explain better outcome in the morning cohorts, we do not observe a statistically poorer outcome in cohorts with higher frequency hypertension. Any inhomogeneity in rates of hypertension among the cohorts cannot solely explain, according to the applied statistical model, the difference in midterm functional outcome.[30] Moreover, this could also indicate that a large number of patients were deemed unsuitable, but possibly could have benefitted from EVT.

Conversely, EVTs performed between 15:55 and 17:15, after a 9-hour work day, were associated with higher mRS at 90 days or poorer midterm functional outcome. Although our multivariate analysis showed significantly higher mRS at 90 days, intermediate outcome measurements that have predictive effects on midterm functional outcome, like mTICI, number of EVT passes, and rate of sICH, were not significantly altered in this time period.[31–33] Moreover, EVT start to recanalization time, a measure of technical skill and rapidity, was not significantly different between time period cohorts. We therefore hypothesize that other factors independent of doctor fatigue, such as stroke team shift changes or hampered performance from other collaborators such as emergency neurologist or support staff in the stroke unit, may contribute to poor functional outcome. Figure 3 shows the work shifts for interventional neuroradiology, stroke unit, and emergency neurology physicians at both centers.

The observed outcome decline between 15:55 and 17:15 was only transient, with values of uw-mRS at 90 days actually increasing after 17:15, at the end of the standard work day in our 2 hospitals. Admission to groin puncture delays were significantly longer at night, which has been previously reported.[34,35] Corroborating the findings of the MR CLEAN (Multicenter Randomized Clinical *Trial*of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry, this delay was not appreciable in our analysis regarding clinical outcome. We conjecture that working conditions for EVT paradoxically improves during the evening or night and may maintain good technical performance and offset fatigue partially because of less work burden or distractions. Studies on work-related injuries as a function of the number of hours worked showed a transient, yet significant increase after the 9th hour of work, but a nonsignificant risk thereafter or at nighttime.[4,36] The results of this study show similar findings regarding functional outcome and highlights similar trends in both stroke centers included in this study.

The repercussions of the burgeoning demand for EVT due to recent paradigm shifts of AIS management on neurointerventionists and the stroke unit staff remains controversial.[25] Previously, AIS stroke management was limited to IV thrombolysis, requiring knowledge but not depending on technical skill. Nowadays, the complexities involved in EVT during AIS management pose challenges to neurointerventionists, anesthetists, and stroke unit staff faced with increasing caseload, extended working hours, and more on-call duties. Our data show differences in outcome warranting further investigation of current workplace conditions for EVT in AIS on patient outcome.

One of the weaknesses of this study is that many of the confounding variables cannot be controlled in the analyses, such as variability in a doctor's skill, training level, or overall stroke unit performance. For example, interruptions of activity related to shift changes, patient transferring, and diagnostic examinations during the day may decrease the amount of time for direct patient care in certain cohorts, leading to adverse effects prior to or following EVT. Any potential difference may also be observed between the hospitals included in this study, as Lausanne University Hospital performs fewer EVTs than University Hospital of Bern. Nevertheless, the subgroup analysis of uw-mRS at 90 days for each hospital reveals similar trends as a function of EVT start time, most notably at 15:54 to 17:15. Moreover, the addition of center variables, such as hospital site or weekday vs weekend, to the logistic regression did not affect results. Perfusion imaging data and infarct core size score were not available for analysis and inhomogeneity in these characteristics among the cohorts may explain differences in clinical outcome. Other limitations include the fact that this study is retrospective and includes patients with AIS treated by EVT from 2012, an era when EVT was less standardized.

EVT for patients with AIS performed in the morning between 08:00 and 10:20 leads to better midterm functional outcome at 90 days, despite having a statistically longer symptom onset to EVT start time delay, whereas EVT performed at the end of the working day, between 15:54 and 17:15, leads to poorer neurologic outcome. Additional prospective study data are required to support our findings and further analysis regarding causal relation is warranted.

Study Funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* July 24, 2019. Accepted in final form October 28, 2020.

Appendix Authors

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Steven D. Hajdu	Lausanne University Hospital, Switzerland	Designed and conceptualized study, data analysis, drafted and revised the manuscript for intellectual content

Continued

Appendix *(continued)*

Name	Location	Contribution
Johannes Kaesmacher	University Hospital of Bern, Switzerland	Designed and conceptualized study, data analysis, drafted and revised the manuscript for intellectual content
Patrik Michel	Lausanne University Hospital, Switzerland	Major role in acquisition of data, interpreted the data
Gaia Sirimarco	Lausanne University Hospital, Switzerland	Interpreted the data, revised the manuscript for intellectual content
Jean-Francois Knebel	Lausanne University Hospital, Switzerland	Performed statistical analysis
Bruno Bartolini	Lausanne University Hospital, Switzerland	Major role in acquisition of data
Christoph C. Kurmann	University Hospital of Bern, Switzerland	Major role in acquisition of data
Francesco Puccinelli	Lausanne University Hospital, Switzerland	Major role in acquisition of data
Pascal J. Mosimann	University Hospital of Bern, Switzerland	Major role in acquisition of data
Christophe Bonvin	Sion Hospital, Switzerland	Major role in acquisition of data
Marcel Arnold	University Hospital of Bern, Switzerland	Major role in acquisition of data
Julien Niederhäuser	Nyon Regional Hospital, Nyon, Switzerland	Major role in acquisition of data
Ashraf Eskandari	Lausanne University Hospital, Switzerland	Interpreted the data
Pasquale Mordasini	University Hospital of Bern, Switzerland	Major role in acquisition of data
Jan Gralla	University Hospital of Bern, Switzerland	Major role in acquisition of data, study design
Urs Fischer	University Hospital of Bern, Switzerland	Designed and conceptualized study, data analysis, drafted the manuscript for intellectual content
Guillaume Saliou	Lausanne University Hospital, Switzerland	Designed and conceptualized study, data analysis, drafted the manuscript for intellectual content

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