JAMA | Original Investigation

Levodopa Added to Stroke Rehabilitation
The ESTREL Randomized Clinical Trial

Stefan T. Engelter, MD; Josefin E. Kaufmann, MD, PhD; Annaelle Zietz, MD; Andreas R. Luft, MD; Alexandros Polymeris, MD, PhD; Valerian L. Altersberger, MD; Karin Wiesner, PT, MSc; Martina Wiegert, MA; Jeremia P. O. Held, PT, PhD; Yannik Rottenberger, MSc; Anne Schwarz, PT, PhD; Friedrich Medlin, MD; Ettore A. Accolla, MD; Sandrine Foucras, SN; Georg Kägi, MD; Gian Marco De Marchis, MD, MSc; Svetlana Politz, PhD; Matthias Greulich, MD; Alexander A. Tarnutzer, MD; Rolf Sturzenegger, MD, MSc; Mira Katan, MD, MSc; Urs Fischer, MD; Krassen Nedeltchev, MD; Janine Schär, MD; Katrien Van Den Keybus Deglon, PT; Pierre-André Rapin, MD; Alexander Salerno, MD, PhD; David J. Seiffge, MD; Elias Auer, MD; Julian Lippert, MD; Leo H. Bonati, MD; Corina Schuster-Amft, PhD; Szabina Gäumann, MSc; Joelle N. Chabwine, MD, PhD; Andrea Humm, MD; J. Carsten Möller, MD; Raoul Schweinfurther, PhD; Bartosz Bujan, MD; Piotr Jedrysiak, MD; Peter S. Sandor, MD; Roman Gonzenbach, MD; Veit Mylius, MD; Dietmar Lutz, MD; Carmen Lienert, MD; Nils Peters, MD; Patrik Michel, MD; René M. Müri, MD; Sabine Schädelin, MSc; Lars G. Hemkens, MD; Gary A. Ford, MD; Philippe A. Lyrer, MD; Henrik Gensicke, MD; Christopher Traenka, MD; for the ESTREL Investigators

IMPORTANCE Levodopa enhances dopaminergic signaling and may stimulate neuroplasticity, which could potentially enhance motor recovery after stroke. Levodopa is used in stroke rehabilitation despite mixed evidence for its effectiveness.

OBJECTIVE To determine whether levodopa compared with placebo, administered in addition to standardized rehabilitation based on active task-oriented training, is associated with enhanced motor recovery in patients with acute stroke.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, placebo-controlled randomized clinical trial at 13 stroke units and centers and 11 collaborating rehabilitation centers in Switzerland. Between June 14, 2019 (first patient, first visit), and August 27, 2024 (last patient, last visit), 610 patients with acute ischemic or hemorrhagic stroke with clinically meaningful hemiparesis (ie, a total score of ≥3 points on the following National Institutes of Health Stroke Scale items: motor arm, motor leg, or limb ataxia) were randomized 1:1 to receive levodopa or placebo. Statistical analyses were conducted from November 2024 to August 2025.

INTERVENTION Patients received levodopa/carbidopa (100 mg/25 mg; n = 307) or placebo (n = 303) 3 times daily for 39 days, alongside standardized rehabilitation therapy based on active task-oriented training.

MAIN OUTCOMES AND MEASURES The primary outcome was the adjusted mean between-group difference in the Fugl-Meyer Assessment (FMA) total score (range, 0-100 points; fewer points indicate worse motor function; 6-point difference considered patient-relevant) at 3 months.

RESULTS Among the 610 participants (median [IQR] age, 73 [64-82] years; 252 [41.3%] female; median baseline FMA total score, 34 [14-54]), 28 participants died by 3 months, leaving 582 (95.4%) participants eligible for the primary analysis. At 3 months, the median (IQR) FMA total score was 68 (42-85) points in the levodopa group and 64 (44-83) points in the placebo group. The mean difference in the FMA total score between the levodopa and placebo groups was −0.90 points (95% CI, −3.78 to 1.98; *P* = .54). There were 126 serious adverse events in the levodopa group and 129 in the placebo group; the most common was infection (levodopa, n = 55; placebo, n = 44).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, among patients receiving inpatient rehabilitation for acute stroke, levodopa added to standardized rehabilitation did not significantly improve motor function at 3 months compared with placebo plus standardized rehabilitation. These results do not support the use of levodopa as an adjunct to rehabilitation therapy for enhancing motor recovery after acute stroke.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03735901

JAMA. doi:10.1001/jama.2025.15185
Published online September 22, 2025.

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The ESTREL Investigators are listed in Supplement 4.

Corresponding Author: Stefan T. Engelter, MD, Department of Rehabilitation and Neurology, University Department of Geriatric Medicine FELIX PLATTER, University of Basel, Burgfelderstrasse 101, 4055 Basel, Switzerland (stefan.engelter@felixplatter.ch).

Novel therapeutic approaches are needed to improve recovery after stroke.[1,2] Pharmacological interventions have the potential to enhance motor recovery.[3-7] Dopamine modulates motor learning, reward signaling, and brain plasticity,[8-10] rendering levodopa—a precursor to dopamine—a promising candidate for this approach.[3,6]

In 2001, a small randomized clinical trial (RCT) including 53 patients with stroke indicated that levodopa administered in combination with physiotherapy enhanced motor recovery.[11] Although a beneficial effect was not found in subsequent trials,[12-16] levodopa has often been used for this purpose in clinical rehabilitation practice,[17] indicated by an exploratory study across 4 Swiss rehabilitation centers, in which 114 of 464 patients (25%) received levodopa, nearly exclusively with the idea to aid stroke rehabilitation in the absence of an otherwise established indication.[18] A meta-analysis of 6 RCTs including 795 participants[11-16] showed a nonsignificant point estimate favoring levodopa for motor stroke recovery.[19] In the absence of safety concerns, these data indicated that levodopa may hold the potential to enhance motor recovery in patients with stroke.[19]

Given the discrepancy between clinical practice and evidence, the Enhancement of Stroke Rehabilitation With Levodopa (ESTREL) trial was designed after reviewing strengths and weaknesses of the aforementioned levodopa trials and taking into account experiences from studies using selective serotonin reuptake inhibitors as pharmacological enhancement in patients with stroke.[20,21] ESTREL tested levodopa vs placebo applied in addition to standardized rehabilitation therapies based on task-oriented training, formerly referred to as the *principles of motor learning*.[19]

Key Points

Question Does levodopa therapy added to standardized rehabilitation improve stroke recovery compared with standardized rehabilitation alone?

Findings In this randomized clinical trial including 610 participants, motor function at 3 months (measured by the Fugl-Meyer Assessment total score) was not significantly different between the levodopa plus standardized rehabilitation group compared with the placebo plus standardized rehabilitation group (median, 68 points vs 64 points, respectively; adjusted mean between-group difference, −0.90 points).

Meaning These results do not support routine use of levodopa for motor recovery in unselected patients with stroke undergoing rehabilitation.

Methods

Trial Design and Oversight

ESTREL was an investigator-initiated, placebo-controlled, double-blind, multicenter RCT using a parallel-group superiority design to study the benefits and harms of levodopa/carbidopa in addition to standardized rehabilitation therapy to enhance motor recovery after acute stroke. The trial was co-led by the Department of Rehabilitation and Neurology within the University Department of Geriatric Medicine FELIX PLATTER of the University of Basel and the University Hospital Basel. The trial rationale and design have been described previously[19] (see trial protocol in Supplement 1).

The trial was conducted across certified Swiss stroke units and centers and collaborating stroke rehabilitation centers.[19] Ethical and regulatory approval for the study protocol was obtained from the relevant local ethics authorities at each site (lead ethics committee, Ethikkommission Nordwest- und Zentralschweiz; BASEC-ID 2018-02021) and the Swiss Agency for Therapeutic Products (Swissmedic). The study adhered to Swiss regulatory requirements, and written informed consent was obtained from all participants or their legal representatives.

The trial complied with the Good Clinical Practice guidelines of the International Council for Harmonisation E6 and the Declaration of Helsinki.[22] The Department of Clinical Research at the University of Basel performed independent onsite and centralized monitoring. Reporting of the trial follows the CONSORT reporting guideline for RCTs.

The trial steering committee (full list of members in Supplement 3) oversaw the trial design, data collection, and statistical analysis plan. Site investigators were responsible for data collection, and the trial statistician (S.S.) performed the data analysis. The steering committee and investigators confirmed compliance with the trial protocol, the completeness of data, and the appropriate reporting of adverse events. An independent data and safety monitoring committee (full list of members in Supplement 3) monitored safety aspects after enrollment of 200, 400, and 500 participants.

The trial adhered to the protocol, and the results are reported in line with the statistical analysis plan, detailed in Supplement 2. The statistical analysis plan was finalized, signed (on September 27, 2024), and stored under version control at the Department for Clinical Research at the University of Basel before database closure on October 15, 2024.

Participants

Participants were eligible if they had (1) an acute (≤7 days) ischemic (≥24 hours after thrombolysis or thrombectomy, if applicable) or hemorrhagic stroke, (2) leading to a clinically meaningful hemiparesis (ie, scoring a total of ≥3 points on the following National Institutes of Health Stroke Scale [NIHSS] items: motor arm, motor leg, or limb ataxia [distal arm paresis was considered equivalent to 1 of these items and was measured by an additional item derived from the NIHSS Supplementary Scale]) (Supplement 3),[23,24] (3) required in-hospital rehabilitation, (4) were able to participate in rehabilitation, and (5) were previously independent in daily life. eFigure 1 in Supplement 3 lists full eligibility and exclusion criteria.

Trial Treatment

Participants received either active oral treatment with levodopa 100 mg/carbidopa 25 mg or a matching placebo, both administered for 39 days. The study medication

(ie, levodopa/carbidopa and placebo) was provided by Bichsel Pharma. The dosing regimen included 3 phases (with notation reflecting the number of pills or tablets taken in the morning-afternoon-evening): a dose escalation phase (1-0-0 daily on days 1-3 and 1-1-0 daily on days 4-6), a full-dose phase (1-1-1 daily on days 7-34), and a tapering phase (1-1-0 daily on days 35-37 and 1-0-0 daily on days 38-39).[19] The duration of trial treatment was set at a total of 39 days to reflect the usual length of in-hospital rehabilitation in Swiss neurorehabilitation centers and therefore to facilitate the applicability of the study intervention in a controlled inpatient setting. The intervention period also considered prior assumptions on the mechanisms of recovery after stroke and therefore the assumed optimal window of opportunity to enhance recovery through levodopa treatment. If discharge from in-hospital rehabilitation was scheduled before day 39 of the trial treatment, participants were asked to continue the trial treatment as planned, including tapering toward day 39.

Study medication was administered in addition to rehabilitation therapy based on active task-oriented training. To align therapy across centers, it was characterized and standardized in collaboration with Interessengemeinschaft Physiotherapie in der Rehabilitation - Neurorehabilitation (Community of Interests for Physiotherapy in Rehabilitation).[25] As done in routine inpatient rehabilitation in Swiss rehabilitation centers, patients were expected to receive at least 3 sessions of rehabilitative care per day. Ingestion of study medication was not timed to coincide with the rehabilitative therapy sessions but was designed to follow a routine and fixed medication schedule (eg, 3 times daily at fixed time points in the full-dose study phase).

Randomization

Participants were randomly assigned in a 1:1 ratio to either the active treatment or the control group. Randomization was stratified by study center and implemented by the Clinical Trial Unit of the Department of Clinical Research at the University of Basel using a Clinical Data Management application (secuTrial). A computer-generated minimization algorithm with an allocation probability of 80% to the group minimizing imbalance was applied to ensure treatment groups were balanced within each center stratum. No block scheme was used beyond the minimization procedure.

Outcomes

Primary Outcome

The primary outcome was the between-group difference in the motor function Fugl-Meyer Assessment (FMA) total score measured 3 months (±14 days) after randomization. The time point of primary outcome assessment was set at 3 months rather than to the end of study treatment at day 39. This design allowed assessment of whether a potential effect of levodopa treatment would be measurable not only during or close to the intervention but also on a longer-term scale.

The FMA is recommended for assessing changes in motor impairment after stroke[26] and has excellent interrater reliability.[27-30] It comprises 50 items, which are scored as follows: 0 = movement not possible, 1 = partially possible, and 2 = completely possible.[31] The FMA total score ranges from 0 to 100 points, with 66 points allocated to the upper extremity portion and 34 to the lower extremity portion. FMA assessments were conducted by FMA-trained study personnel who had undergone in-person training and refresher sessions provided by 2 FMA experts with academic teaching experience.[19]

Secondary Outcomes

Secondary outcomes were (1) Patient-Reported Outcomes Measurement Information System (PROMIS-29; 7 domains with 4 items each; raw score range, 4-20 points per domain, with higher scores reflecting better functioning in some domains and worse in others; PROMIS-10 Global Health; raw score range, 10-50 points, with higher scores indicating better health[32,33]) and patient-reported assessment of the relevance of motor improvement (2 custom items; interviewer-administered, patient-reported measure [yes/no] assessing perceived improvement and its relevance in daily life; assessed in person during study visits) (Supplement 3), (2) FMA upper and lower extremity scores separately,[31] (3) the FMA total score for the unaffected side,[31] (4) the NIHSS (range, 0-42, with 0 indicating no symptoms and 42 indicating the most severe stroke; higher scores indicate more severe impairment),[34] (5) the modified Rankin Scale (mRS; range, 0-6, with 0 indicating no symptoms and 6 indicating death; higher scores indicate more severe disability),[35] and (6) the Rivermead Mobility Index (range, 0-15, with higher scores indicating greater mobility; based on 15 yes/no items assessing functional mobility, from turning in bed to running),[36] all assessed at 3 months, and (7) the FMA total score at 5 weeks.[31] There were other motor assessments planned to be obtained at a subset of the participating centers and at other preplanned time points (eg, at 6 and 12 months) that are not reported. Details are provided in the trial protocol (Supplement 1). Given the potential for type I error due to multiple comparisons, findings from analyses of secondary end points should be considered as purely exploratory.

Measures of harm were all-cause mortality, recurrent stroke (any), serious adverse events, and prespecified adverse events of interest (ie, possibly related to levodopa therapy, according to prior research) (eTable 9 in Supplement 3).[15]

Sample Size Estimation

The primary analysis aimed to determine the effect of levodopa on motor recovery compared with placebo. We assumed that the FMA scores would follow a normal distribution with an SD of 25 points (derived from a trial of fluoxetine for motor recovery after acute ischemic stroke[20]). Accordingly, a sample size of 548 participants was calculated (80% power, 2-sided significance level of .05) to detect a mean difference of 6 points between the treatment groups at 3 months, considered patient-relevant at the time of trial design.[37,38] Overall, we aimed to enroll 610 participants, accounting for an anticipated dropout rate of 10% (ie, at least 549 patients available for analysis).

Table 1. Baseline Demographic and Clinical Characteristics Stratified by Group

Characteristic	No. (%)	
	Levodopa group (n = 307)	Placebo group (n = 303)
Age, median (IQR), y	72 (62-81)	74 (64-84)
Median age ≥80 y	90 (29.3)	112 (37.0)
Sex		
Female	119 (38.8)	133 (43.9)
Male	188 (61.2)	170 (56.1)
Prior mRS[a] score, median (IQR)	0	0
Medical history		
Hypertension	222 (72.3)	213 (70.3)
Hyperlipidemia	139 (45.3)	152 (50.2)
Diabetes	80 (26.1)	64 (21.1)
Atrial fibrillation	34 (11.1)	61 (20.1)
Smoking	68 (22.1)	59 (19.5)
Coronary heart disease	52 (16.9)	47 (15.5)
Depression	23 (7.5)	18 (5.9)
Dementia	11 (3.6)	9 (3.0)
Movement disorder	6 (2.0)	5 (1.7)
Prior stroke		
Ischemic stroke	39 (12.7)	43 (14.2)
Hemorrhagic stroke	5 (1.6)	6 (2.0)
Prestroke living situation		
Home	302 (98.4)	294 (97.0)
Nursing home	4 (1.3)	5 (1.7)
Other[b]	1 (0.3)	4 (1.3)
Type of stroke		
Ischemic	260 (84.7)	259 (85.5)
Hemorrhagic	47 (15.3)	44 (14.5)
Affected vessel territory[c]		
Anterior cerebral artery	37 (12.1)	31 (10.2)
Middle cerebral artery	230 (74.9)	230 (75.9)
Posterior cerebral artery	27 (8.8)	33 (10.9)
Vertebrobasilar (infratentorial)	63 (20.5)	45 (14.9)
Stroke severity, median (IQR)		
FMA[d] total score on the affected side at randomization	35.0 (14.8-55.3)	33.0 (13.0-52.8)
FMA upper extremity score on the affected side at randomization	20.0 (6.0-35.0)	17.5 (6.0-34.0)
FMA lower extremity score on the affected side at randomization	15.0 (6.0-21.0)	14.0 (7.0-21.0)
NIHSS[e] score at randomization	7 (5-11)	8 (5-10)
mRS score at randomization[a,f]		
0	2 (0.7)	0
1	0	2 (0.7)
2	6 (2.0)	3 (1.0)
3	37 (12.1)	32 (10.6)
4	170 (55.4)	169 (55.8)
5	92 (30.0)	97 (32.0)
Time from stroke onset to randomization, median (IQR), d	3.0 (2.0-5.0)	3.0 (2.0-5.0)

Abbreviations: FMA, Fugl-Meyer Assessment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

[a] mRS scores range from 0 (no symptoms) to 6 (death), with higher scores indicating worse disability.

[b] Defined as any living arrangement outside of private homes or institutional care (eg, assisted living or older adult residences).

[c] Determined by imaging; multiple territories could be affected in each participant.

[d] FMA scores range from 0 to 100 points (upper extremity maximum, 66 points; lower extremity maximum, 34 points), with higher scores indicating better motor function. A baseline total score of approximately 35 points corresponded to moderate to severe motor impairment.

[e] NIHSS scores range from 0 (no stroke symptoms) to 42 (most severe stroke), with higher scores indicating greater neurological deficit. Baseline scores of 7 to 8 points corresponded to moderate stroke severity, typically reflecting partial hemiparesis, mild language or sensory deficits, and some functional dependence.

[f] The majority of trial participants had a score of 4, reflecting moderately severe disability, characterized by inability to walk without assistance and inability to attend to bodily needs without help.

Statistical Analyses

Statistical analyses were conducted from November 2024 to August 2025. The primary analysis followed a treatment policy estimand analyzing participants according to their randomized group. Participants who died before the 3-month assessment were excluded from this analysis (full analysis set). For survivors with missing or incomplete FMA scores at 3 months, multiple imputations with chained equations were applied. A linear regression model was used to analyze the primary outcome, adjusting for baseline FMA total scores and including the treatment group (levodopa vs placebo) as the primary variable of interest. The results were presented as the estimated treatment effect with the corresponding *P* value and 95% CI. The significance threshold was set at α = .05 (2-sided).

We used 7 additional predefined estimands to address the potential impact of the following 5 intercurrent events or factors on outcome assessment: (1) death before the 3-month assessment, (2) serious adverse events causing motor impairment (eg, recurrent stroke or fractures), (3) intake of less than 80% of the study medication, (4) fewer rehabilitation therapies than foreseen in the protocol (ie, <5 rehabilitation sessions per week), and (5) outcome assessments conducted outside the predefined time range (3 months ±14 days) (eTable 2 in Supplement 3).

We performed 2 post hoc analyses on the following estimands: including all participants who died before the 3-month visit, assigning them an FMA score of 0 (the worst possible outcome), and including only participants who received at least 80% of the study medication and attended at least 5 rehabilitation sessions per week (eTable 3 in Supplement 3).

Post hoc, we also repeated the primary analysis dichotomizing our population in participants with FMA scores of 35 or less (severe) vs more than 35 points (mild to moderate impairment) at baseline, applying a categorization used in prior research.[39]

Secondary outcomes were analyzed using regression models with adjustments for baseline measurements. If any component of an outcome assessment was missing, the entire summary score was imputed using multiple imputations. For the mRS, we used an ordinal logistic regression model to estimate the odds of achieving better or worse functional outcomes across mRS categories. Missing data for the mRS and patient-reported assessment of the relevance of motor improvement were not imputed.

A post hoc exploratory plot (eFigure 5 in Supplement 3) was generated to assess treatment-effect heterogeneity across centers, with smaller centers having fewer than 50 participants grouped into a single cluster.

In post hoc analyses, we evaluated potential nonlinearity in the relationship between baseline and 3-month FMA score using spline terms and tested for interactions between baseline FMA score and treatment allocation.

Prespecified analyses were performed as outlined in the statistical analysis plan, which was finalized before database closure. While in line with the general statistical considerations noted in the final version of the trial protocol, the statistical analysis plan also reflects emerging statistical concepts (ie, estimands), which led to differences between the trial protocol and the statistical analysis plan regarding statistical terminology. All statistical analyses were conducted using R version 4.3.1 (R Foundation). The main analysis code is provided in Supplement 5.

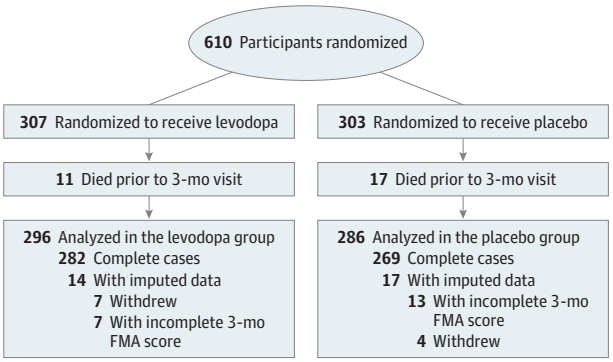
Results

A total of 610 participants were randomized (307 to the levodopa group, 303 to the placebo group) in 13 Swiss stroke units and centers (Supplement 3) between June 14, 2019, and May 21, 2024 (eFigure 3 in Supplement 3). The median (IQR) age was 73 (64-82) years and 252 participants (41.3%) were female (**Table 1**). The median (IQR) NIHSS score at randomization was 7 (5-10). The median (IQR) baseline FMA total score was 34 (14-54) (Table 1) (eTable 1 in Supplement 3).

At 3 months, 28 participants (4.6%; 11 [3.6%] from the levodopa group and 17 [5.6%] from the placebo group) had died, leaving 582 participants (95.4%) eligible for the primary analysis (296 in the levodopa group, 286 in the placebo group) (**Figure 1**).

Participants in the levodopa group underwent a mean (SD) of 79 (35) rehabilitation therapy sessions (mean total duration, 45 [23] hours; 47 [22] sessions based on principles of motor learning). Participants in the placebo group underwent a mean (SD) of 77 (37) rehabilitation therapy sessions (mean total duration, 44 [23] hours; 47 [23] sessions based on principles of motor learning). A total of 252 participants (82.1%) in the

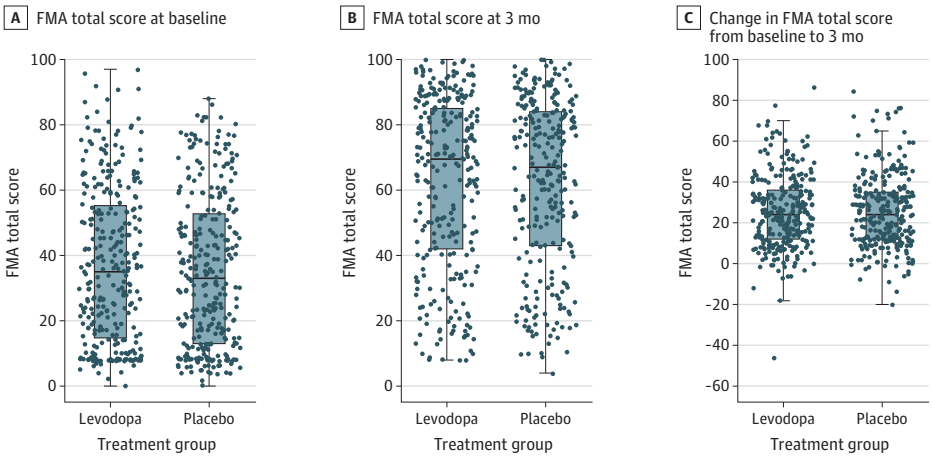
Figure 1. Flow of Participants in a Trial of Levodopa Plus Standardized Rehabilitation Therapy for Recovery After Stroke



The number of individuals approached for participation was not systematically recorded and is therefore not reported.

FMA indicates Fugl-Meyer Assessment.

Figure 2. Dot and Boxplot of Fugl-Meyer Assessment (FMA) Total Scores (Primary Outcome) by Treatment Group



The boxplot displays the primary outcome (FMA total score; range, 0-100) for the levodopa and placebo groups. The horizontal lines indicate the medians, the boxes the IQRs, and the whiskers extend to the most extreme values within 1.5 times the IQR from the lower and upper quartiles (Tukey adjacent values).

Table 2. Adverse Events Stratified by Group

	Events, No.	
	Levodopa group (n = 126)	Placebo group (n = 129)
Serious adverse events		
Infection	55	44
Pulmonary	27	17
Urinary tract	15	15
Abdominal	5	7
Meningoencephalitis/encephalitis	0	2
Unspecified infection	1	2
Other infection	11	9
Stroke	16	19
Ischemic	15	18
Hemorrhagic	1	1
Major extracranial bleeding	5	10
Cardiac event	12	3
Acute coronary syndrome	5	1
Heart failure	5	2
Arrhythmia	2	0
Cancer/malignant neoplasm	4	7
Trauma	4	5
Fall	4	5
Kidney failure	6	2
Epileptic seizure	3	6
Deep vein thrombosis/pulmonary embolism	3	4
Electrolyte disorder	2	2
Fracture	1	3
Traumatic intracerebral hemorrhage	0	0
Other (none of the above)	32	34
Prespecified adverse events of interest[a]	(n = 79)	(n = 67)
Confusion	12	9
Nausea	11	7
Postural hypotension syncope	10	4
Hallucinations	3	10
Depression	6	9
Vomiting	8	5
Arrhythmias	5	3
Dizziness	4	4
Fatigue	4	2
Abnormal dreams	1	3
Anxiety	3	3
Insomnia	1	4
Dry mouth	3	2
Dyskinesia	3	1
Taste disturbances	3	0
Drowsiness (including sudden onset of sleep)	1	0
Psychoses	1	1

[a] Prespecified adverse events of interest were possibly related to levodopa therapy, according to prior research.[15] Data were collected through medical chart review and patient self-report during study visits.

levodopa group and 244 (80.5%) in the placebo group received 80% or more of the study medication.

Primary Outcome

At 3 months, participants in the levodopa group had a median (IQR) FMA total score of 68 (42-85) points compared with 64 (44-83) points for participants in the placebo group. Adjusted for the FMA baseline total score, the mean difference in the FMA total score between the levodopa and placebo groups was −0.90 points (95% CI, −3.78 to 1.98; *P* = .54) (**Figure 2**) (estimand 1 in eTable 2 and eFigure 4 in Supplement 3).

The additional 7 estimand analyses, as well as the post hoc estimand analyses and a post hoc subgroup analysis with dichotomized baseline FMA (≤35 vs >35 points), yielded results similar to the primary analysis (Figure 2) (eTables 2 and 3 and eFigures 4 and 7 in Supplement 3).

Secondary Outcomes

At 3 months, the mean (SD) PROMIS-29 score was 66 (14) points in the levodopa group and 65 (14) points in the placebo group, with an adjusted mean difference of −0.37 points (95% CI, −3.34 to 2.61). For PROMIS-10, the mean (SD) scores were 28 (6) points in both groups, with an adjusted mean difference of 0.18 (95% CI, −0.98 to 1.33). For the patient-reported assessment of relevance of motor improvement, 51 of 276 participants (18%) in the levodopa group and 52 of 270 participants (19%) in the placebo group reported no improvement or no relevant improvement. For the FMA upper extremity score, the mean (SD) scores were 39 (19) points in both groups, with an adjusted mean difference of −0.73 points (95% CI, −2.97 to 1.50). For the FMA lower extremity score, the mean (SD) scores were 23 (7) points in both groups, with an adjusted mean difference of −0.13 points (95% CI, −1.02 to 0.77). For the FMA total score on the unaffected side, the mean (SD) scores were 90 (10) points in the levodopa group and 89 (10) points in the placebo group; the adjusted mean difference was 0.63 (95% CI, −0.72 to 1.99).

For the NIHSS, the mean (SD) scores were 4 (3) points in both groups, with an adjusted mean difference of −0.14 points (95% CI, −0.61 to 0.33). For the Rivermead Mobility Index, the mean (SD) scores were 10 (5) points in both groups, with an adjusted mean difference of −0.33 (95% CI, −1.04 to 0.37). The ordinal logistic regression analysis, evaluating the odds of achieving better functional outcomes across the mRS scale, showed an adjusted odds ratio of 0.93 (95% CI, 0.69-1.23) for levodopa compared with placebo. The median (IQR) mRS score at 3 months was 3.0 (2.0-4.0) in both treatment groups.

At 5 weeks, the mean (SD) scores for the FMA total score were 57 (27) points in the levodopa group and 56 (26) points in the placebo group, with an adjusted mean difference of 0.02 points (95% CI, −2.81 to 2.84) (for secondary outcome results, see eTable 4 in Supplement 3).

Adverse Events

A total of 255 serious adverse events occurred in 177 of 610 participants; 126 in the levodopa group and 129 in the placebo group. The most common serious adverse event was infection (levodopa, n = 55; placebo, n = 44). A total of 146 prespecified adverse events of interest (ie, possibly related

to levodopa therapy, according to prior research[15]) occurred in 115 of 610 participants. Seventy-nine prespecified adverse events of interest were recorded in the levodopa group and 67 in the placebo group. The most common prespecified adverse event of interest in the levodopa group was confusion (n = 12) and in the placebo group, hallucinations (n = 10). Classifications of the serious and prespecified adverse events are described in **Table 2**. Additional information about severity and outcomes of the adverse events can be found in eTables 5 and 6 in Supplement 3.

Additional Post Hoc Analyses

Post hoc analyses revealed a nonlinear association between baseline and 3-month FMA scores; however, this did not impact the primary treatment effect and no interaction between baseline FMA and treatment was detected (eTables 7 and 8 and eFigures 6 and 7 in Supplement 3).

Discussion

In this RCT, levodopa/carbidopa treatment compared with placebo—administered in addition to rehabilitation therapy based on active task-oriented training—showed neither benefit regarding motor recovery nor harm after acute stroke.

The adjusted mean difference in the FMA total score at 3 months was not statistically significant and less than 1 point on a 100-point scale. The frequency of (serious) adverse events or death was similar in both groups. Further, none of the secondary outcomes showed a difference between the treatment groups. These findings are in line with the Dopamine Augmented Rehabilitation in Stroke trial,[15] which showed that walking ability after stroke did not improve in patients treated with levodopa compared with placebo. Study results oppose the idea of a benefit of levodopa-enhanced motor recovery suggested by a recent meta-analysis[19] and do not support the reported practice of using levodopa to enhance stroke rehabilitation.[18]

Although animal studies clearly demonstrated that motor skill learning and recovery after experimental stroke are impaired when dopamine receptors in the primary motor cortex are blocked[40,41] or when the dopaminergic projection from the ventral tegmental area to the motor cortex is destroyed,[42] this trial suggests that in humans, the dopaminergic system cannot be stimulated to enhance recovery. Potential explanations may be that the system is already operating at a ceiling level in the nonstimulated state; the pharmacological stimulation is nonspecifically acting on different, potentially opposing dopaminergic brain systems at the same time; or that after stroke, the dopaminergic system is disrupted,[43,44] leading to downregulation of dopamine receptor genes for at least 1 week.[45] These mechanisms could lead to an insufficient response to exogenous dopamine administration in this setting.

The lack of levodopa treatment effect in this trial contrasts with prior studies in healthy participants, who showed better motor learning performances with levodopa compared with placebo.[46,47] Compared with these healthy individuals, participants in ESTREL were older and had a brain lesion and comorbidities, all of which may have impacted their learning abilities.

Interindividual patient differences could potentially modify the effect of levodopa in enhancing motor recovery. It is possible that some patients might benefit from levodopa-enhanced rehabilitation while others experience harm. This idea is based on the observation of genetic polymorphisms of the dopaminergic system, which influence learning and its modulation by levodopa.[48] To better understand the trial results in the context of the current evidence, subgroup analyses using individual participant data, including previous trials and analyses on recovery trajectories, would be valuable.[49] Incorporating biomarker, genetic variant, and imaging data (including whether or not there is evidence of injury to the dopaminergic system) into these analyses will be useful.[49]

To the study investigators' knowledge, this trial represents the largest RCT to date investigating the benefits and harms of levodopa/carbidopa in motor stroke recovery. A key strength of this study is its execution within established stroke care pathways that strictly adhere to standardized rehabilitation protocols, ensuring consistency in patient care. Additional strengths include high data completeness, with limited loss to follow-up and a focused rehabilitation approach based on active, task-oriented therapy. Further, all additional estimands showed results consistent with the primary estimand, highlighting the robustness of the findings. Using the FMA as the primary outcome is an additional strength, as it is a well-established, validated, and clinically relevant tool for quantifying motor stroke recovery.[26]

Limitations

This study has limitations. First, the study was conducted exclusively in Switzerland, which may limit the generalizability of the findings to different health care systems, rehabilitation practices, and populations with different genetic backgrounds. Second, the interrater reliability of the FMA was not systematically assessed across the entire study population. Third, levodopa serum levels were not measured in this trial, leaving potential interindividual differences in pharmacokinetics unassessed, along with their possible impact on treatment efficacy. Fourth, while concomitant rehabilitative therapy was standardized across study centers, the assessment of the homogeneity of the performed therapy in each center was beyond the means of the trial and thus was not performed. Fifth, the study did not account for genetic variation possibly modifying treatment response.[48] Sixth, while motor recovery is a critical outcome in stroke rehabilitation, it is only one facet of poststroke recovery. It is unclear whether levodopa/carbidopa could have beneficial effects on other poststroke conditions, such as poststroke fatigue or depression, which could impact long-term recovery and quality of life.

Conclusions

Among patients receiving inpatient rehabilitation for acute stroke, levodopa added to standardized rehabilitation did not

significantly improve motor function at 3 months compared with placebo plus standardized rehabilitation. These results do not support the use of levodopa as an adjunct to rehabilitation therapy for enhancing motor recovery after acute stroke.

ARTICLE INFORMATION

Accepted for Publication: August 7, 2025.

Published Online: September 22, 2025. doi:10.1001/jama.2025.15185

Author Affiliations: Department of Rehabilitation and Neurology, University Department of Geriatric Medicine FELIX PLATTER, University of Basel, Basel, Switzerland (Engelter, Kaufmann, Zietz, Wiesner, Wiegert, Gensicke, Traenka); Department of Neurology and Stroke Center, Department of Clinical Research, University Hospital Basel and University of Basel, Basel, Switzerland (Engelter, Kaufmann, Zietz, Polymeris, Altersberger, Wiegert, Katan, Bonati, Lyrer, Gensicke, Traenka); Division of Vascular Neurology and Neurorehabilitation, Department of Neurology, University Hospital of Zurich and University of Zurich, Zurich, Switzerland (Luft, Held, Rottenberger, Schwarz); cereneo Center for Neurology & Rehabilitation, Vitznau, Switzerland (Luft); Stroke Division, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts (Polymeris); Department of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia (Altersberger); Bellevue Medical Group, Zurich, Switzerland (Held); Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, California (Schwarz); Service of Neurology and Stroke Unit, HFR Fribourg–Cantonal Hospital, Fribourg, Switzerland (Medlin, Accolla, Foucras, Humm); University Teaching and Research Hospital, Neurology Department & Stroke Center, HOCH Health Ostschweiz, Kantonsspital St Gallen, St Gallen, Switzerland (Kägi, De Marchis); Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland (Kägi, Müri); Kantonsspital Münsterlingen, Münsterlingen, Switzerland (Politz); Kantonsspital Winterthur, Winterthur, Switzerland (Greulich); NeuroPraxis Zurich GmbH, Zurich, Switzerland (Greulich); Neurology, Cantonal Hospital of Baden, Baden, Switzerland (Tarnutzer); Faculty of Medicine, University of Zurich, Zurich, Switzerland (Tarnutzer); Kantonsspital Graubünden, Departement Innere Medizin, Neurologie, Chur, Switzerland (Sturzenegger); Department of Neurology, University Hospital Bern, University of Bern, Bern, Switzerland (Fischer, Seiffge, Auer, Lippert); Cantonal Hospital of Aarau and Department of Neurology, University of Bern, Bern, Switzerland (Nedeltchev); Department of Neurology and Stroke Center, Klinik Hirslanden, Zurich, Switzerland (Schär, Peters); Acute Neurorehabilitation Unit, Department of Clinical Neurosciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland (Van Den Keybus Deglon); Lavigny Rehabilitation Institution, Lavigny, Switzerland (Rapin); Stroke Center, Service of Neurology, Department of Clinical Neurosciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland (Salerno, Michel); Research Department, Reha Rheinfelden, Rheinfelden, Switzerland (Bonati, Schuster-Amft, Gäumann); School of Engineering and Computer Science, Bern University of Applied Sciences, Biel, Switzerland (Schuster-Amft); Department for Sport, Exercise and Health, University of Basel, Basel, Switzerland (Schuster-Amft); Division of Neurorehabilitation, Fribourg Hospital, Meyriez-Murten, Switzerland (Chabwine, Möller); Laboratory for Neurorehabilitation Science, Medicine Section, University of Fribourg, Fribourg, Switzerland (Chabwine); Rehaklinik Zihlschlacht AG, Zihlschlacht-Sittendorf, Switzerland (Möller, Schweinfurther); Neurorehabilitation, Klinik Lengg Zurich, Zurich, Switzerland (Bujan, Jedrysiak); Research Department, Rehaklinik Bad Zurzach, ZURZACH Care Group, Bad Zurzach, Switzerland (Sandor); Kliniken Valens, St Gallen, Switzerland (Gonzenbach, Mylius, Lutz, Lienert); Gerontechnology and Rehabilitation Group, University of Bern, Bern, Switzerland (Müri); Department of Clinical Research, University Hospital Basel and University of Basel, Basel, Switzerland (Schädelin, Hemkens); Pragmatic Evidence Lab, Research Center for Clinical Neuroimmunology and Neuroscience Basel, (RC2NB), University Hospital Basel and University of Basel, Basel, Switzerland (Hemkens); Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, California (Hemkens); Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom (Ford).

Author Contributions: Drs Engelter and Traenka had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Engelter, Luft, Held, Fischer, Möller, Jedrysiak, Michel, Hemkens, Lyrer, Gensicke, Traenka.
Acquisition, analysis, or interpretation of data: Engelter, Kaufmann, Zietz, Luft, Polymeris, Altersberger, Wiesner, Wiegert, Rottenberger, Schwarz, Medlin, Accolla, Foucras, Kägi, De Marchis, Politz, Greulich, Tarnutzer, Sturzenegger, Katan, Nedeltchev, Schär, Van Den Keybus Deglon, Rapin, Salerno, Seiffge, Auer, Lippert, Bonati, Schuster-Amft, Gäumann, Chabwine, Humm, Möller, Schweinfurther, Bujan, Sandor, Gonzenbach, Mylius, Lutz, Lienert, Peters, Michel, Müri, Schädelin, Hemkens, Ford, Lyrer, Gensicke, Traenka.
Drafting of the manuscript: Engelter, Kaufmann, Sturzenegger, Bujan, Gensicke, Traenka.
Critical review of the manuscript for important intellectual content: Engelter, Kaufmann, Zietz, Luft, Polymeris, Altersberger, Wiesner, Wiegert, Held, Rottenberger, Schwarz, Medlin, Accolla, Foucras, Kägi, De Marchis, Politz, Greulich, Tarnutzer, Sturzenegger, Katan, Fischer, Nedeltchev, Schär, Van Den Keybus Deglon, Rapin, Salerno, Seiffge, Auer, Lippert, Bonati, Schuster-Amft, Gäumann, Chabwine, Humm, Möller, Schweinfurther, Jedrysiak, Sandor, Gonzenbach, Mylius, Lutz, Lienert, Peters, Michel, Müri, Schädelin, Hemkens, Ford, Lyrer, Gensicke, Traenka.
Statistical analysis: Kaufmann, Schädelin, Lyrer, Traenka.
Obtained funding: Engelter, Luft, Michel, Müri, Traenka.
Administrative, technical, or material support: Engelter, Zietz, Luft, Altersberger, Wiesner, Wiegert, Held, Schwarz, Foucras, De Marchis, Politz, Tarnutzer, Nedeltchev, Van Den Keybus Deglon, Lippert, Schuster-Amft, Gäumann, Möller, Schweinfurther, Bujan, Sandor, Gonzenbach, Mylius, Lutz, Peters, Lyrer, Traenka.
Supervision: Engelter, Kaufmann, Zietz, Luft, Polymeris, Altersberger, Held, Medlin, Kägi, De Marchis, Sturzenegger, Katan, Van Den Keybus Deglon, Jedrysiak, Michel, Lyrer, Gensicke, Traenka.
Other - assessments and data: Schweinfurther.
Other - patient recruitment and supervision of internal processes: Sandor.
Other - study design, methodological support: Hemkens.

Conflict of Interest Disclosures: Dr Engelter reported receiving an investigator-initiated research grant to their institution from Swiss National Science Foundation (SNSF) during the conduct of the study. Ms Wiegert reported receiving grants from SNSF during the conduct of the study. Dr Greulich reported receiving personal fees from Novartis, Pfizer AG, and Lundbeck AG outside the submitted work. Dr Katan reported receiving grants from SNSF and Swiss Heart Foundation; and personal fees for serving on the advisory boards of Bristol Myers Squibb, Janssen, AstraZeneca, and Medtronic outside the submitted work. Dr Fischer reported receiving consulting fees to their institution from AbbVie, AstraZeneca, Bayer, Biogen, Boehringer Ingelheim, CSL, and Siemens outside the submitted work; and being the president of the European Stroke Organization, president-elect of Swiss Federation of Clinical Neuro-Societies, and president of the Advanced Training in Neuro-subjects task force at Swiss Neurological Society. Dr Seiffge reported receiving consulting and advisory fees paid to their institution from AstraZeneca; and grants from Swiss Heart Foundation, SNSF, and AstraZeneca outside the submitted work. Dr Bonati reported receiving grants from SNSF outside the submitted work. Dr Humm reported receiving reimbursement from University of Basel for patient recruitment and follow-up during the conduct of the study. Dr Sandor reported serving as a board member of Swiss Neurological Society, Swiss Society for Neurorehabilitation, and SW!SS REHA. Dr Michel reported receiving grants from SNSF, Swiss Heart Foundation, Faculty of Biology and Medicine of the University of Lausanne, and Porphyrogenis Foundation outside the submitted work. Dr Hemkens reported receiving grants from SNSF (179667) during the conduct of the study; working for Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), University of Basel and University Hospital Basel, which is supported by Foundation of Clinical Neuroimmunology and Neuroscience Basel; and RC2NB having a contract with Roche for Dr Hemkens' steering committee participation outside the submitted work. Dr Gensicke reported receiving grants from SNSF during the conduct of the study; grants from AbbVie, Merz, and Ipsen; and personal fees from AbbVie outside the submitted work. Dr Traenka reported receiving grants from Swiss Heart Foundation; honoraria from Reha Rheinfelden for lectures during the conduct of the study; and grants from Swiss Heart Foundation outside the submitted work. No other disclosures were reported.

Funding/Support: This study was funded by SNSF (33IC30_179667).

Role of the Funder/Sponsor: SNSF had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The ESTREL Investigators are listed in Supplement 4.

Data Sharing Statement: See Supplement 6.

Additional Information: Patients or members of the public were not involved in this study's design, conduct, or recruitment. The research question and outcome measures were based on established clinical priorities and existing scientific evidence.

REFERENCES

1. Grefkes C, Fink GR. Recovery from stroke: current concepts and future perspectives. *Neurol Res Pract*. 2020;2:17. doi:10.1186/s42466-020-00060-6

2. Winstein CJ, Stein J, Arena R, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2016;47(6):e98-e169. doi:10.1161/STR.0000000000000098

3. Cramer SC. Drugs to enhance motor recovery after stroke. *Stroke*. 2015;46(10):2998-3005. doi:10.1161/STROKEAHA.115.007433

4. Kumar A, Kitago T. Pharmacological enhancement of stroke recovery. *Curr Neurol Neurosci Rep*. 2019;19(7):43. doi:10.1007/s11910-019-0959-2

5. Keser Z, Francisco GE. Neuropharmacology of poststroke motor and speech recovery. *Phys Med Rehabil Clin N Am*. 2015;26(4):671-689. doi:10.1016/j.pmr.2015.06.009

6. Viale L, Catoira NP, Di Girolamo G, González CD. Pharmacotherapy and motor recovery after stroke. *Expert Rev Neurother*. 2018;18(1):65-82. doi:10.1080/14737175.2018.1400910

7. Berends HI, Nijlant JM, Movig KL, Van Putten MJ, Jannink MJ, Ijzerman MJ. The clinical use of drugs influencing neurotransmitters in the brain to promote motor recovery after stroke: a Cochrane systematic review. *Eur J Phys Rehabil Med*. 2009;45(4):621-630.

8. McAllister TW. Polymorphisms in genes modulating the dopamine system: do they influence outcome and response to medication after traumatic brain injury? *J Head Trauma Rehabil*. 2009;24(1):65-68. doi:10.1097/HTR.0b013e3181996e6b

9. Tritsch NX, Sabatini BL. Dopaminergic modulation of synaptic transmission in cortex and striatum. *Neuron*. 2012;76(1):33-50. doi:10.1016/j.neuron.2012.09.023

10. Abe M, Schambra H, Wassermann EM, Luckenbaugh D, Schweighofer N, Cohen LG. Reward improves long-term retention of a motor memory through induction of offline memory gains. *Curr Biol*. 2011;21(7):557-562. doi:10.1016/j.cub.2011.02.030

11. Scheidtmann K, Fries W, Müller F, Koenig E. Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: a prospective, randomised, double-blind study. *Lancet*. 2001;358(9284):787-790. doi:10.1016/S0140-6736(01)05966-9

12. Lokk J, Salman Roghani R, Delbari A. Effect of methylphenidate and/or levodopa coupled with physiotherapy on functional and motor recovery after stroke—a randomized, double-blind, placebo-controlled trial. *Acta Neurol Scand*. 2011;123(4):266-273. doi:10.1111/j.1600-0404.2010.01395.x

13. Sonde L, Lökk J. Effects of amphetamine and/or L-dopa and physiotherapy after stroke—a blinded randomized study. *Acta Neurol Scand*. 2007;115(1):55-59. doi:10.1111/j.1600-0404.2006.00728.x

14. Acler M, Fiaschi A, Manganotti P. Long-term levodopa administration in chronic stroke patients: a clinical and neurophysiologic single-blind placebo-controlled cross-over pilot study. *Restor Neurol Neurosci*. 2009;27(4):277-283. doi:10.3233/RNN-2009-0477

15. Ford GA, Bhakta BB, Cozens A, et al. Dopamine Augmented Rehabilitation in Stroke (DARS): a multicentre double-blind, randomised controlled trial of co-careldopa compared with placebo, in addition to routine NHS occupational and physical therapy, delivered early after stroke on functional recovery. *Efficacy Mech Eval*. 2019:6(5). doi:10.3310/eme06050

16. Çelik C, Uzun MK. The effect of levodopa treatment combined with rehabilitation program on functional motor recovery in stroke patients (in Turkish). *Turkish J Phys Med Rehabil*. 2004:18-20.

17. Engelter ST, Frank M, Lyrer PA, Conzelmann M. Safety of pharmacological augmentation of stroke rehabilitation. *Eur Neurol*. 2010;64(6):325-330. doi:10.1159/000322134

18. Engelter ST, Urscheler N, Baronti F, et al. Frequency and determinants of using pharmacological enhancement in the clinical practice of in-hospital stroke rehabilitation. *Eur Neurol*. 2012;68(1):28-33. doi:10.1159/000335895

19. Zietz A, Kaufmann JE, Wiesner K, et al. Enhancement of STroke REhabilitation with Levodopa (ESTREL): rationale and design of a randomized placebo-controlled, double blind superiority trial. *Eur Stroke J*. 2024;9(4):1093-1102. doi:10.1177/23969873241255867

20. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. *Lancet Neurol*. 2011;10(2):123-130. doi:10.1016/S1474-4422(10)70314-8

21. Dennis M, Forbes J, Graham C, et al. Fluoxetine to improve functional outcomes in patients after acute stroke: the FOCUS RCT. *Health Technol Assess*. 2020;24(22):1-94. doi:10.3310/hta24220

22. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human participants. *JAMA*. 2025;333(1):71-74. doi:10.1001/jama.2024.21972

23. Egelko A, Kirchoff-Torres KF, Ramaswamy S, et al. Including distal motor function within the NIHSS: correlation with motor arm function and IV rt-PA treatment response. *J Stroke Cerebrovasc Dis*. 2021;30(11):106046. doi:10.1016/j.jstrokecerebrovasdis.2021.106046

24. Leira EC, Coffey CS, Jorge RE, et al. The NIHSS supplementary motor scale: a valid tool for multidisciplinary recovery trials. *Cerebrovasc Dis*. 2013;36(1):69-73. doi:10.1159/000351514

25. Community of Interests for Physiotherapy in Rehabilitation (in German). 2021. Accessed August 19, 2025. https://igptr.ch/igptr-n/

26. Kwakkel G, Stinear C, Essers B, et al. Motor rehabilitation after stroke: European Stroke Organisation (ESO) consensus-based definition and guiding framework. *Eur Stroke J*. 2023;8(4):880-894. doi:10.1177/23969873231191304

27. Wiesner K, Schwarz A, Meya L, et al. Interrater reliability of the Fugl-Meyer motor assessment in stroke patients: a quality management project within the ESTREL study. *Front Neurol*. 2024;15:1335375. doi:10.3389/fneur.2024.1335375

28. Hernández ED, Forero SM, Galeano CP, Barbosa NE, Sunnerhagen KS, Alt Murphy M. Intra- and inter-rater reliability of Fugl-Meyer Assessment of lower extremity early after stroke. *Braz J Phys Ther*. 2021;25(6):709-718. doi:10.1016/j.bjpt.2020.12.002

29. Hochleitner I, Pellicciari L, Castagnoli C, et al. Intra- and inter-rater reliability of the Italian Fugl-Meyer Assessment of upper and lower extremity. *Disabil Rehabil*. 2023;45(18):2989-2999. doi:10.1080/09638288.2022.2114553

30. Liz L, da Silva TG, Michaelsen SM. Validity, reliability, and measurement error of the remote Fugl-Meyer Assessment by videoconferencing: tele-FMA. *Phys Ther*. 2023;103(8):pzad054. doi:10.1093/ptj/pzad054

31. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient 1: a method for evaluation of physical performance. *Scand J Rehabil Med*. 1975;7(1):13-31. doi:10.2340/1650197771331

32. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the Patient-Reported Outcomes Measurement Information System (PROMIS) global items. *Qual Life Res*. 2009;18(7):873-880. doi:10.1007/s11136-009-9496-9

33. Cella D, Choi SW, Condon DM, et al. PROMIS. *Value Health*. 2019;22(5):537-544. doi:10.1016/j.jval.2019.02.004

34. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20(7):864-870. doi:10.1161/01.STR.20.7.864

35. Broderick JP, Mistry EA. Evolution and future of stroke trials. *Stroke*. 2024;55(7):1932-1939. doi:10.1161/STROKEAHA.123.044265

36. Collen FM, Wade DT, Robb GF, Bradshaw CM. The Rivermead Mobility Index: a further development of the Rivermead Motor Assessment. *Int Disabil Stud*. 1991;13(2):50-54. doi:10.3109/03790799109166684

37. Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer scale in people with minimal to moderate impairment due to chronic stroke. *Phys Ther*. 2012;92(6):791-798. doi:10.2522/ptj.20110009

38. Pandian S, Arya KN, Kumar D. Minimal clinically important difference of the lower-extremity Fugl-Meyer Assessment in chronic-stroke. *Top*

Stroke Rehabil. 2016;23(4):233-239. doi:10.1179/1945511915Y.0000000003

39. Duncan PW, Goldstein LB, Horner RD, Landsman PB, Samsa GP, Matchar DB. Similar motor recovery of upper and lower extremities after stroke. *Stroke*. 1994;25(6):1181-1188. doi:10.1161/01.STR.25.6.1181

40. Molina-Luna K, Pekanovic A, Röhrich S, et al. Dopamine in motor cortex is necessary for skill learning and synaptic plasticity. *PLoS One*. 2009;4(9):e7082. doi:10.1371/journal.pone.0007082

41. Vitrac C, Nallet-Khosrofian L, Iijima M, Rioult-Pedotti MS, Luft A. Endogenous dopamine transmission is crucial for motor skill recovery after stroke. *IBRO Neurosci Rep*. 2022;13:15-21. doi:10.1016/j.ibneur.2022.05.008

42. Hosp JA, Pekanovic A, Rioult-Pedotti MS, Luft AR. Dopaminergic projections from midbrain to primary motor cortex mediate motor skill learning. *J Neurosci*. 2011;31(7):2481-2487. doi:10.1523/JNEUROSCI.5411-10.2011

43. Kronenberg G, Balkaya M, Prinz V, et al. Exofocal dopaminergic degeneration as antidepressant target in mouse model of poststroke depression. *Biol Psychiatry*. 2012;72(4):273-281. doi:10.1016/j.biopsych.2012.02.026

44. Momosaki S, Ito M, Yamato H, et al. Longitudinal imaging of the availability of dopamine transporter and D2 receptor in rat striatum following mild ischemia. *J Cereb Blood Flow Metab*. 2017;37(2):605-613. doi:10.1177/0271678X16635183

45. Sieber MW, Guenther M, Jaenisch N, et al. Age-specific transcriptional response to stroke. *Neurobiol Aging*. 2014;35(7):1744-1754. doi:10.1016/j.neurobiolaging.2014.01.012

46. Knecht S, Breitenstein C, Bushuven S, et al. Levodopa: faster and better word learning in normal humans. *Ann Neurol*. 2004;56(1):20-26. doi:10.1002/ana.20125

47. Mohr C, Landis T, Bracha HS, Fathi M, Brugger P. Human locomotion: levodopa keeps you straight. *Neurosci Lett*. 2003;339(2):115-118. doi:10.1016/S0304-3940(02)01480-5

48. Pearson-Fuhrhop KM, Minton B, Acevedo D, Shahbaba B, Cramer SC. Genetic variation in the human brain dopamine system influences motor learning and its modulation by L-Dopa. *PLoS One*. 2013;8(4):e61197. doi:10.1371/journal.pone.0061197

49. Stinear CM. Dopamine for motor recovery after stroke: where to from here? *Lancet Neurol*. 2019;18(6):514-515. doi:10.1016/S1474-4422(19)30162-0