# Efficacy and Dose of Rehabilitation Approaches for Severe Upper Limb Impairments and Disability During Early Acute and Subacute Stroke: A Systematic Review

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## Abstract

**Objective.** The purpose of this study was to examine the evidence regarding the efficacy of rehabilitation approaches for improving severe upper limb impairments and activity during acute and early subacute stroke, taking into consideration the dosage of therapy.

**Methods.** Randomized controlled trials from PubMed, Web of Science, and Scopus databases were searched by 2 independent researchers. Studies were selected if they involved active rehabilitation interventions that were conducted in the acute stage (<7 days after stroke) or the early subacute stage (>7 days–3 months after stroke), with the aim of improving severe upper limb motor impairments and disability. Data were extracted on the basis of the type and effect of rehabilitation interventions, and on the dosage (duration, frequency, session length, episode difficulty, and intensity). Study quality was assessed using the Physiotherapy Evidence Database Scale.

**Results.** Twenty-three studies (1271 participants) with fair to good methodological quality were included. Only 3 studies were performed in the acute stage. Regardless of the type of intervention, upper limb rehabilitation was found to be beneficial for severe upper limb impairments and disability. Robotic therapy and functional electrical stimulation were identified as the most popular upper limb interventions; however, only a limited number of studies showed their superiority over a dose-matched control intervention for severe upper limb impairments in the subacute stage. A longer rehabilitation session length (<60 minutes) did not seem to have a larger impact on the magnitude of improved upper limb impairments.

**Conclusion.** Different rehabilitation approaches seem to improve severe upper limb impairments and disability in the subacute stage after stroke; however, they are not distinctly superior to standard care or other interventions provided at the same dosage.

**Impact.** Robotic therapy and functional electrical stimulation add variety to rehabilitation programs, but their benefit has not been shown to exceed that of standard care. Further research is necessary to identify the impact of dose (eg, intensity) on upper limb motor impairments and function, especially in the acute stage.

## Introduction

Stroke is known as a disabling condition.[1] The number of people living with stroke is estimated to increase by 27% between 2017 and 2047, mainly because of the ageing population and improved survival rates.[2] Immediately after stroke, reduced function of the upper limb is reported in 48% to 77% of stroke survivors.[3,4] One-third of the stroke survivors present with severe upper limb impairments; only 20% will experience a return of arm function, and only 5% will experience a full return of arm function.[5,6]

At 3 days after stroke, most patients with severe upper limb impairments have a poor prediction of recovery at 3 months after stroke.[7-9] As a result, patients with severe stroke often feel that insufficient attention was paid to promoting upper limb recovery.[10,11] In fact, the current advice for rehabilitation focus for severe upper limb impairment is to prevent secondary complications and to teach the patient to complete activities of daily living with the stronger hand.[12] One issue with severe upper limb impairment is that, even if a minimally clinically important difference is found following an intervention, patients will still not be able to use their upper limb in activities in daily living. We now need to aim for decreasing the impairment at a higher magnitude that will have an impact on activities. One approach is to implement all the ingredients for neuroplasticity, especially in the first 3 months after stroke.

After brain injury, there is spontaneous changes involving waves of growth-promoting genes,[13,14] growth of synapses and dendrites[15] and axonal remodeling,[16] enhancing structural neuroplasticity.[13] More specifically, in the acute (within 7 days after stroke) and early subacute stages (7 days to 3 months after stroke), endogenous neuroplasticity occurs resulting in the largest improvement in impairments.[17,18] However, neuroplastic changes do not always result in functional recovery.[19] Upper limb rehabilitative interventions in the acute and early subacute stage after stroke could therefore promote further therapy-induced mechanisms of plasticity and

exploit this critical narrow window of recovery and potentially result in reduction of severe impairment.[20-22]

A review of Wattchow et al investigated the type of therapeutic interventions and their effectiveness in improving upper limb function in the first 4 weeks after stroke.[23] They supported the use of constraint-induced movement therapy (CIMT) and task-specific training within the acute phase after stroke. However, their review was not restricted to severe upper limb impairments probably due to interventions such as CIMT cannot be performed by such population. Only 1 recent review, by McGlinchey et al, aimed to evaluate the effectiveness of rehabilitation interventions such as robotic therapy on physical function and immobility-related complications in severe stroke.[24] They stated there was a lack of high-quality evidence to promote the use of specific rehabilitation interventions or dosage to improve motor function and reduce immobility-related complications. This review included also patients with chronic stroke so, did not limit the inclusion of participants to the acute and early subacute stage after stroke in which enhanced neuroplasticity is occurring. Very recently, Hayward et al also conducted a systematic review exploring the timing and dose of upper limb motor rehabilitation in the first 6 months after stroke.[25] They identified that small dosages of rehabilitation were being provided early after stroke that do not result in clinically important effects. However, this review did not focus on the level of severity of upper limb impairment.

Together with the content of therapy, the dosage of upper limb rehabilitation is of clear importance to explore the interventions' efficacy. Dosage could include specific information about frequency, duration including number of days of the program, and sessions including session length, difficulty and intensity.[26,27] Overall, in a recent Cochrane review a positive effect in favor of more time in upper rehabilitation has been identified on motor impairment.[28] However, low amount of active time on upper limb rehabilitation in the acute and subacute stages after stroke has been reported.[29,30] On average, 4 minutes focused on physical therapy

and 17 minutes on occupational therapy per session. On the contrary, in people with chronic stroke, Ward et al and Daly et al identified that a high dose upper limb program resulted in clinically meaningful short- and long-term effect on impairment and activity.[31,32] Apart from lack of staff time; hypoarousal, fatigue, delirium or insomnia could possibly be patient-specific barriers or even adverse effects for implementing sufficient intensity and time spent in upper limb therapy in the acute and early subacute stage.[33]

The primary aim of this review was to systematically review studies involving upper limb rehabilitation programs for severe upper limb impairments in the first 3 months from stroke. The research question was: "Taking into account the dosage, what is clinical efficacy of rehabilitation approaches in improving severe upper limb impairments in the acute and early subacute stage after stroke?". The effect of dose parameters on upper limb motor impairment, fatigue and disability were also explored. The findings will help identify the current evidence for content, dosage and effect of upper limb rehabilitation to improve severe impairment in the early stage after stroke.

## [H1]Methods

### [H2]Data Sources and Searches

The present review was registered on Prospero (ID: CRD42021243519). The search process was conducted by 2 independent researchers (S.D. and L.S.) in February 2021. PubMed, Web of Science (index Medline), and Scopus were searched for randomized controlled trials (RCTs) with no date as a limitation and written in the English language .The detailed combination of search terms provided for each of the 3 databases is presented in Supplementary Appendix 1.

### [H2]Study Selection

Studies had to include the following components: interventions with a focus on active with the aim of improving upper limb motor impairment or disability, and a control group that used same dose rehabilitation or a dose different from the intervention group, or a nonintervention/conventional control group. Participants were included if they were in the acute stage (after day 1 and ending at day 7) or early subacute stage (beginning after day 7 and ending at 3 months) after stroke[17] and diagnosed with a stroke with severe upper limb impairments (≤22/66 on the Fugl-Meyer Assessment (FMA) for the Upper Extremity [FMA-UE]) or disability ( ≤10/57 on the Action Research Arm Test [ARAT]).[34,35] Studies were excluded if the focus was on nonmotor or on secondary upper limb impairments (eg, pain, shoulder subluxation, spasticity); no outcome measure of upper limb motor impairment; the intervention did not involve any type of active upper limb therapy (eg, mental practice, motor imagery alone); or interventions such as pharmacological or complementary therapy (eg, acupuncture, nonactive electrical stimulation), noninvasive brain stimulation, or transcranial magnetic stimulation. Participants were excluded if: the baseline severity of upper limb impairments based on a measurement of the FMA-UE or ARAT was not reported; they were <18 years of age and they had multiple strokes or other neurological pathologies.

As primary outcome measures, the FMA-UE or the ARAT was used to assess motor impairment and disability.[36,37] Level of fatigue and upper limb activity were chosen as secondary outcome measures.

After the search was conducted, duplicates were removed, followed by the first screening process based on the title and abstract of the searched articles. The second screening involved reading the full texts of the remaining scientific articles using Rayyan software.[38]

## [H2]Data Extraction and Quality Assessment

The Physiotherapy Evidence Database Scale was used to check for risk of bias.[39] For each of the included articles, masked quality ratings were performed by 2 independent researchers to establish agreement. In case of any disagreement, a third independent researcher was involved to solve the disagreement. Total scores of 0 to 3 were considered poor, 4 or 5 were considered fair, 6 to 8 were considered good, and 9 or 10 were considered excellent.[40]

The following data were extracted and collated in tables: the number of participants; the time since stroke (acute or early subacute stage after stroke); baseline stroke severity based on the FMA-UE or ARAT; age range; biological sex; type of stroke; location of stroke lesion; side of stroke lesion; description and dosage of intervention(s) and control intervention(s) using the dose articulation framework[41]; outcome measures; and relevant results in relation to significance and/or minimal clinically important difference on the FMA-UE of 12.4 points determined for moderate to severe upper limb hemiparesis in the subacute stage after stroke.[42] The latter focused on improvements over time: baseline and outcome measurements and between-group differences.

### [H2]Data Synthesis and Analysis

The range of mean ages and time since stroke was established using the TI-83 Plus Calculator.[43] Also, the range of mean baseline upper limb impairment severity scores, based on the FMA-UE or the ARAT, was established. To identify these ranges, the minimum and maximum of mean ages, mean time since stroke, and mean FMA-UE or ARAT score of each article were used. To determine the minimum and maximum time since stroke, the time had to be expressed in the same unit of time. Of the 23 articles, 7 used the number of days, 5 used the number of weeks, and 1 used the number of months since stroke. The number of days was used in order to have a uniform unit of time. To convert every outcome into the number of days since stroke, the total number of weeks was multiplied by 7 and the total number of months was multiplied

by 30. The impact of dose dimensions on FMA-UE was plotted in scatter dot plots with the JMP Pro 14 Statistical Program (SAS Institute, INC; Cary, North Carolina).

## [H1]Results

After duplicates were eliminated, 947 titles and abstracts were screened for the inclusion and exclusion criteria, and 178 studies remained. Subsequently, the second screening of full texts led to the inclusion of 23 studies in the review (Fig. 1). There were no studies that used patient-reported fatigue or other fatigue-related measures as a primary or secondary outcome measure.

The mean score of risk of bias of all included trials was 6.7 of 10. Overall, fair to good quality was established for the 23 included articles (Suppl. Appendix 2). The optimal score of 8 of 10 was achieved for 7 studies. Thirteen studies achieved a good quality rating, with a score of 6 or 7 of 10. Three studies had only a fair quality rating, with a score of 4 or 5 of 10, based on lack of masking, lack of adequate follow-up, and lack of intention-to-treat analysis. No studies had a poor quality rating, with a score of 3 or lower.

### [H2]Demographics of Population

From all of the studies, 1271 participants with stroke were included (Tab. 1). More than half of the population, 57% (n = 730), were male participants. The participants mean age ranged from 56 to 75 years old (Tab. 1). Only 3 RCTs involved participants in the acute stage after stroke (on average, time since stroke of the 3 studies ranged from 5 to 6.4 days).[44-46] Across all studies, time from stroke ranged from 5 to 48 days. The range of mean FMA-UE scores at baseline was 5.96 to 19.63, and the range of mean ARAT scores at baseline was 0 to 7.85.

### [H2]Efficacy of Robotic Therapy for Upper Limb Impairment and Disability

Eight interventions with either a robotic device for the upper limb or a mechanical arm trainer were found (Tab. 2). All studies apart from one[47] showed significant improvements over time

from robotic therapy. Two studies[48,49] showed between-group differences in upper limb impairment in comparison to other interventions at the same dosage (duration and frequency) immediately after the intervention, and one did so at 3-month follow-up.[50] The Bi-Manu-Track arm trainer resulted in short-term and long-term significant minimal clinically important difference improvements in upper limb impairments in comparison to electromyography-initiated electrical stimulation (control group).[49] Significant improvements in the FMA-UE at 6-month follow-up were reported for robot-assisted therapy: the Rheo Therapy System combined with hand functional electrical stimulation (FES) in comparison to dose-matched standard care.[48] The robotic Reha-Slide group also improved significantly more than the FES control group at the 3-month follow-up only.[50] However, significant improvements in upper limb disability at post-intervention were noted using the Box and Block Test in comparison to the results for the FES group. On the other hand, the Neurorehabilitation Robot (NeReBot) in additional to conventional therapy resulted in significant improvements in the shoulder-elbow subscore of the FMA-UE in comparison to the control group receiving only conventional therapy.[46]

### [H2]Efficacy of FES Therapy for Upper limb Impairment and Disability

Nine studies included active-assisted FES as an intervention (Suppl. Tab. 1). Four of 9 interventions resulted in significantly greater improvements on the FMA-UE postintervention in comparison to the results for conventional and dose-matched control groups[44,51-53] (Suppl. Tab. 2). The electromyography-triggered FES group improved significantly more than the conventional control group.[51] When cyclic neuromuscular electrical stimulation (NMES) was coupled with electromyography-triggered FES, significantly greater improvements in the FMA-UE score were observed in comparison to the results for the dose-matched conventional control group.[44] Shimodozono et al compared NMES simultaneously with repetitive facilitative exercise with a dose-matched conventional control.[51] The group receiving NMES showed

significant clinically meaningful improvements on FMA-UE in comparison to the conventional control group. In the study of Zheng et al.[52], the group receivingcontralaterally controlled FES group improved significantly more than the passive NMES group

## [H2]Efficacy of Mirror Therapy and Other Therapies for Upper Limb Impairment and Disability

Two of 3 studies involving mirror therapy as an intervention showed significant improvements over time but no differences between the intervention group and an active control group in upper limb impairment and activity[54,55] (Suppl. Tab. 2). Only the study of Dohle et al[54] showed a trend in favor of mirror therapy in comparison to dose-matched sham mirror therapy for the FMA finger subscore. Jung and Choi (2019) used an innovative sling suspension system to strengthen muscles around the shoulder joint.[55] The intervention group exhibited significantly greater improvements in FMA-UE scores postintervention than the dose-matched conventional bilateral exercise control group.[56] Furthermore, Laffont et al observed that the use of playing video games with the affected upper limb in comparison to dose-matched conventional therapy led to improved significant changes in the FMA wrist-hand subscore and the Box and Block Test at postintervention.[57] The rocking chair therapy conducted by Feys et al did not result in significant between-group differences immediately after the intervention.[57] However, at 6-month and 1- and 5-year follow-up assessments, the rocking chair therapy group presented significantly and clinically relevant higher scores on the FMA-UE than the sham dose-matched control group.[58]

## [H2]Impact of Dose on the Efficacy of the Intervention

To investigate the impact of dose, all RCTs that provided the actual or the change in scores at baseline and postintervention for the FMA-UE were selected; 16 of 23 studies reported these data[31,33–35,37–42,44,45,47–50] (Tab. 2; Suppl. Tabs. 1 and 2).

Most studies applied the intervention 5 d/wk, apart from 2 studies in which the intervention was applied either once or twice per week.[59,60] The impact of the duration of the treatment on changes in the FMA-UE score was analyzed in 14 studies.[44,46-50,52,54,59-63] When program duration was plotted with the FMA score, the smoothing line taken as a reference showed a larger change when the intervention duration was from 4 to 4.7 weeks (Fig. 2A). However, session length (<60 minutes) did not seem to have an impact on changes in the FMA-UE score (Fig. 2B).

A different intensity range was reported as repetitions per minute depending on the type of intervention. For example, participants using an arm cycle (MOTOmed Viva2) performed 2.5 cycles per minute,[63] whereas others using the Bi-Manu-Track arm trainer performed approximately 40 repetitions per minute.[49] Fewer repetitions were performed with FES, ranging from 2 to 6 per minute. There was a lack of coherent terminology for episode difficulty, with half of the studies reporting it as active-assisted.

**[H1]Discussion**

Evidence of therapy approaches for improving severe upper limb impairments in the acute stage after stroke is lacking. In about half of the studies, both robotic therapy and FES programs led to significant improvements in upper limb impairments in comparison to dose-matched control programs. The impact of dose dimensions such as session length on outcomes of upper limb motor impairments in our population with severe upper limb impairments in the acute and early subacute stages after stroke is questionable.

Overall, participants with severe impairments showed an improvement in upper limb motor impairment over time from any type of upper limb rehabilitation program. Although this is as expected due to spontaneous and therapy-induced mechanisms of recovery in the early stage after stroke.[13,22] Major changes in severe upper limb impairments are not regularly observed in

patients with stroke. As a result, such patients have a poor prognosis in their upper limb recovery.[9,12] Whether certain techniques should be chosen over others in early upper limb rehabilitation is currently unclear. Based on our review and published Cochrane Review,[64] robotic therapy can be considered as an effective adjunct to conventional therapy and at least equally as effective on upper limb impairments and disability as conventional upper limb therapy. Electromyography-triggered FES in addition with conventional therapy can also be as effective or superior as conventional therapy.[61] Furthermore, the use of a partial weight-bearing sling suspension system[56] and video games[57] provided significantly greater improvements than dose-matched conventional therapy. Rocking chair therapy originating from Johnstone also provided long-term clinically relevant improvements in upper limb motor impairments in comparison to the results for a sham control group.[58] Although different techniques have been shown to be beneficial, it seems that robotic therapy and FES are the preferred choice of intervention for upper limb impairments in research studies in the early stage of stroke.[30] What is routinely seen in clinical practice is a different matter due to the limited evidence of such interventions showing a superior effect to standard care at the same dosage. Current higher dose parameters implanted in research settings could be challenging to implement in current practice models. Technological equipment is relatively expensive and requires increased staff time to operate the devices during rehabilitation programs. Therefore, considerable thought and attention are needed prior to selecting technological interventions instead of conventional therapy as highly skilled therapists are needed.

Dose dimensions were overall fairly reported.[25] Our results indicate that in the early subacute stage patients with severe impairment could benefit most from upper limb programs lasting from 4 to 5 weeks. Therefore, this duration seems sufficient to last the period of the critical window of neuroplasticity after stroke.[17] However, a longer session length of less than 60 minutes does not seem to impact the level of improvement. A recent review of Hayward et al[25]

also suggested that short session lengths of less than 1 hour could lead to the inability of a too-short duration to detect clinically important effects. However, people in the very early stages of stroke experience excessive fatigue.[33] Dose-limiting factors such as severe fatigue and fatigability are experienced at a lower level in the chronic stage of stroke than in the acute stage of stroke.[65] Ward et al[31] and Meyer et al[66] reported that a higher dose of upper limb programs—using a program duration of 3 and 4 weeks of 5 sessions per week—resulted in clinically meaningful significant improvements in impairment outcomes. The Queen Square program of Ward et al delivered a higher dose of upper limb neurorehabilitation—90 hours (6 h/d) for 3 weeks—in people with chronic stroke.[31] The chosen session length in the latter study was much higher than low applied dosages of interventions included in our review. Very recently, Dromerick et al[67] conducted an RCT in which 20 extra hours of upper limb self-selected, task-specific motor therapy was most effective in the subacute stage of stroke in comparison to the acute and chronic stages of stroke. However, one must keep in mind that the previously presented studies of Ward et al,[31] Meyer et al,[64] and Dromerick et al[66] did not include a control group. In this context, the dose-response relationship in the acute and early subacute stages after stroke in stroke survivors with severe upper limb impairments is questionable.

For future research, assessing the optimal dosage including session length, difficulty and intensity of upper limb rehabilitation in the early stage of stroke should be considered. The use of unanimous definitions of dosage principals, more importantly, the description of reproducible doses such as difficulty level of the intervention is also critical. The application of the dose articulation framework of Hayward et al could help to standardize of such the descriptions of dosage in future interventions.[41]

## [H2]Strengths and Limitations of the Review

The strength of our review is that it focuses on a specific category of stroke patients in the early stage of stroke with moderate to severe upper limb impairments. Also, assesses the impact of dosage of upper limb interventions is also innovative in itself. A limitation of our review is that some studies were excluded if they did not provide a baseline mean score of the FMA-UE or the ARAT. Additionally, studies using minimal clinically important difference thresholds for the FMA-UE or ARAT to evaluate whether changes were clinically meaningful provide important information. One must also note that improvements in a severely impaired upper limb may not lead to functional use in activities of daily living. Also, we did not search the gray literature and non-English studies; however, the addition of 23 RCTs led to enough results to address our research question. Finally, meta-analyses could not be conducted since most of the studies included dose-matched control groups.

## [H2]Conclusion

Robotic therapy, FES, and other active upper limb therapy approaches (sling suspension system, video games, rocking chair therapy) are effective in improving severe upper limb impairments in the early subacute stage after stroke. However, evidence that such interventions are superior to standard care at the same dosage is limited. Evidence in the acute stage is also lacking. The corresponding dose-response relationship for impairments is also uncertain. Programs lasting 4 to 5 weeks seem to have a larger effect on severe upper limb impairments; however, the session length of less than 60 minutes does not make any difference. Future research should further explore the impact of different dose dimensions on upper limb impairments and disability, especially in the acute stage.

## Author Contributions

Concept/idea/research design: D. Steff, S. Luca, P. Feys, L. Tedesco Triccas

Writing: D. Steff, S. Luca, P. Feys, L. Tedesco Triccas

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Project management: D. Steff, P. Feys, L. Tedesco Triccas


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The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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## Tables

### Table 1.

Demographic Characteristics of All Participants[a]

| Characteristic | Value[b] | Limitation |
|---|---|---|
| Total no. of participants | 1271 | |
| Range of mean age (y) | 56.45–74.50 | |
| Sex | | |
| No. of men | 730 | |
| No. of women | 541 | |
| Range of mean time since stroke (d) | 5–48 | 1 article did not mention time since stroke |
| No. of articles considering | | |
| Acute stage (1–7 days after stroke) | 3 | |
| Early subacute stage (7 d–3 mo after stroke) | 19 | |
| Type of stroke | | |
| Ischemic | 1116 | |
| Hemorrhagic | 155 | |
| Location of stroke lesion | | Defined in 4 studies |
| Cortical/subcortical | 118 | |
| Subcortical only | 176 | |
| Side of stroke lesion | | 5 articles did not state side of stroke lesion |
| Right | 603 | |
| Left | 539 | |
| Range of mean of severity of upper limb impairments | | Based on both ARAT and FMA-UE: 2 articles |
| FMA-UE score (/66) | 5.96–19.63 | Based on FMA-UE: 16 articles[c] |
| ARAT score (/57) | 0–7.85 | Based on ARAT: 5 articles |

[a]ARAT = Action Research Arm Test; FMA-UE = Fugl-Meyer Assessment of the Upper Extremity.
[b]Values are numbers of participants unless otherwise indicated.
[c]One article did not define the baseline FMA-UE score but defined it as ≤21.

**Table 2.**

Dosage Dimensions of Robotic and Control Interventions and Effect on Upper Limb Impairment and Activity[a]

| RCT | Patients' Characteristics | Intervention(s) | Dose[b] of Intervention(s) | Control Intervention(s) | Dose[b] of Control Intervention(s) | Effects on ICF Level of Motor Function After Intervention for FMA-UE |
|---|---|---|---|---|---|---|
| Aisen et al[58] (1997) | N = 20 (11 M, 9 F); 38–72 y old; 16 R, 4 L; early subacute stage: 2–4 wk | MIT-Manus RAT: rotational movements, flexion-extension of elbow and shoulder + standard care | Duration: mean = 6.4 wk<br>Days: 5 d/wk<br>Session length: 4–5 h/wk (50–60 min/d) | MIT-Manus RAT + standard care | Duration: mean = 6.4 wk<br>Days: 1 or 2 d/wk | Robot group increased from 17.10 to 31.2[c] (Δ = 14.1)<br>Control group increased from 13.8 to 10.1[c] (Δ = 10.1)<br>Both groups improved significantly over time<br>Between-group differences: NS |
| Hesse et al[48] (2005) | N = 44 (20 M, 24 F); 33–80 y old; 40 I, 4 H; 19 R, 25 L; early subacute stage: 4–8 wk | Bi-Manu-Track AT: forearm pronation-supination, wrist flexion-extension + standard care | Duration: 6 wk<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 20 min<br>Episodes: 1 (intensity: 40 reps/min [20 elbow, 20 wrist] + 25–50 reps in total) | EMG-initiated ES; maximum wrist extension + standard care | Duration: 6 wk<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 20 min<br>Episodes: 1 (difficulty: passive-passive, active-passive, active-active if possible[2]; intensity: 3 or 4 reps/min) | AT group mean increased from 7.9 to 24.6[c] (Δ = 16.7)<br>ES group mean increased from 7.3 to 10.4[c] (Δ = 3.1)<br>All improvements over time were significant.<br>Between-group differences: significantly higher outcomes in the AT group |
| Hesse et al[49] (2008) | N = 54 (37 M, 17 F); 37–79 y old; 23 I, 31 H; 25 R, 29 L; early subacute stage: 4–8 wk | Reha-Slide AT: shoulder abduction-adduction, elbow flexion-extension, wrist flexion-extension + standard care | Duration: 6 wk<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 20–30 min net/session<br>Episodes: 1 (difficulty: active assisted; intensity: 20–30 reps/min) | EMG-initiated ES; maximum wrist extension + standard care | Duration: 6 wk<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 20–30 min net/session<br>Episodes: 1 (difficulty: active assisted; intensity: 2–4 reps/min) | AT group increased from 8.8 to 19.2[c] (Δ = 10.4)<br>ES group increased from 8.6 to 13.6[c] (Δ = 5)<br>All improvements over time were significant<br>Between-group differences: NS |
| Hesse et al[61] (2014) | N = 50 (28 M, 22 F); 18–90 y old; 41 I, 9 H; 27 R, 23 L; early subacute stage: <8 wk | Group RAT in arm studio: Bi-Manu-Track, Reha-Digit, Reha-Slide, Reha-Duo, and 2 mechanical arm trainers + standard care | Duration: 4 wk<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 30 min<br>Episodes: 2 (length: 15 min; difficulty: passive-passive, active-passive, active-active; intensity: 13–27 reps/min) | Additional individual upper limb therapy: task-oriented motor relearning program supplemented by impairment-oriented ability training + standard care | Duration: 4 wk<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 30 min<br>Episodes: 1 (difficulty: passive-passive, active-passive, active-active; intensity: 13–27 reps/min) | Robot group increased from 14.6 to 25.7[c] (Δ = 11.1)<br>Control group increased from 16.5 to 31.1[c] (Δ = 14.6)<br>Both groups improved significantly over time<br>Between-group differences: NS |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| Rabadi et al[46] (2008) | N = 30 (19 M, 11 F); 45–90 y old; 27 I, 3 H; early subacute stage: ≤4 wk | Monark bidirectional arm ergometer | Duration: 12 d<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 45 min<br>Session density: 40 min active<br>Episodes: 2 (length: 20 min; intensity: 55–60 movements/min) | Additional standard occupational and physical therapy | Duration: 12 d<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 40 min<br>Episodes: 1 (intensity: 16–18 movements/min) | Ergometer group mean increased from 9.1 to 11.62 (Δ = 2.52)<br>Robot group mean increased from 8.6 to 11.05 (Δ = 3.05)<br>Standard occupational and physical therapy group mean increased from 7.7 to 12.94 (Δ = 5.24)<br>All improvements over time: NS<br>Between-group differences: NS | |
| | | MIT-Manus: rotational movements, flexion-extension of elbow and shoulder + standard care | Duration: 12 d<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 45 min<br>Session density: 40 min active<br>Episodes: 2 (length: 20 min; intensity: 25–26 movements/min) | | | | |
| Renner et al[62] (2020) | N = 69 (32 M, 37 F); 18–85 y old; 69 I; 28 R, 41 L; 24 C, 45 SC; early subacute stage: 4–8 wk | Bilateral group: bilateral AT on arm cycle (MOTOmed Viva2) followed by synchronized bilateral HT, including elbow flexion-extension, wrist flexion-extension, and fist opening and closing + standard care | Duration: 6 wk<br>Days: 5 d/wk<br>Sessions: 2 sessions/d<br>Session length: 40 min (20 min of arm cycling + 20 min of HT)<br>Episodes: 1 (intensity: HT: 2.5 reps/min) | Unilateral group: unilateral AT on arm cycle (MOTOmed Viva2) followed by unilateral HT + standard care | Duration: 6 wk<br>Days: 5 d/wk<br>Sessions: 2 sessions/d<br>Session length: 40 min (20 min of arm cycling + 20 min of HT)<br>Episodes: 1 (difficulty with arm cycling: passive, motor assisted, or active-resistive; intensity of HT: 2.5 reps/min) | Bilateral group increased from 6.63 to 13.16[c] (Δ = 6.53)<br>Unilateral group increased from 5.29 to 9.25[c] (Δ = 3.96)<br>Both groups improved significantly over time<br>Between-group differences: NS; however, a trend in favor of the bilateral group ($P$ = .067) was found for the FMA wrist-hand subscore | |
| Rosati et al[45] (2007) | N = 24 (13 M, 11 F); 48–79 y old; 24 I; 9 R, 15 L; acute stage: means of 5.1 and 5.5 d | NeReBot group: shoulder abduction-adduction, elbow flexion-extension and pronation-supination + standard care | Duration: 4 wk<br>Days: 5 d/wk<br>Sessions: 2 sessions/d<br>Session length: 30 min<br>Episodes: 5–7 (length: 3 min, 1 min of rest; intensity: 6 or 7 | Control group: NeReBot twice/wk for 30 min (but exercises were performed with unimpaired upper limb) + standard | Duration: 4 wk<br>Days: 5 d/wk | Robot group increased from 11.6 to 34.3[c] (Δ = 22.7)<br>Control group increased from 13.6 to 26.2[c] (Δ = 12.6) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | reps/min) | care | | All improvements over time were significant<br>Between-group differences: robot group only scored significantly higher in FMA shoulder-elbow subscore | |
| Straudi et al[47] (2020) | N = 13 (8 M, 5 F); 18–80 y old; 13 I; 9 L, 4 R; 5 C, 6 SC, 2 brain stem; early subacute: <8 wk | RAT focused on multidirectional reaching: Rheo Therapy System combined with hand FES (this intervention was in addition to standard care) | Duration: 6 wk<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 100 min net/session (60 min of robot, 40 min of hand FES)<br>Episodes: 1 (difficulty: active assisted; intensity: 7.94 reps/min [robot: 10.51 reps/min; hand FES: 4.11 reps/min]) | Additional conventional therapy, dose matched with intervention group, + standard care | Duration: 6 wk<br>Days: 5 d/wk<br>Sessions: 1 session/d<br>Session length: 100 min net/session<br>Episodes: 1 (difficulty: active assisted, active; intensity: 3.76 reps/min) | RAT + FES group increased from 28.8 to 38.6[c] (Δ = 9.8)<br>Control group increased from 31.4 to 44.2[c] (Δ = 12.8)<br>Both groups improved significantly over time<br>Between-group differences: NS; however, there was a trend in favor of the RAT + FES group | |

[a]ARAT = Action Research Arm Test; AT = arm training; BBT = Box and Block Test; BI = Barthel Index; C = cortical involvement in stroke; Δ = difference between baseline and postintervention/follow-up scores of the relative outcome measure; EMG = electromyography; ES = electrical stimulation; F = female; FES = functional ES; FIM = Functional Independence Measure; FMA = Fugl-Meyer Assessment; FMA-UE = FMA of the Upper Extremity; H = hemorrhagic stroke; HT = hand training; I = ischemic stroke; ICF = International Classification of Functioning, Disability and Health; L = left stroke lesion; M = male; NS = not significant; R = right stroke lesion; RAT = robot-assisted therapy; RCT = randomized controlled trial; reps = repetitions: SC = subcortical stroke only.

[b]Dose is described according to the definitions of Hayward et al.[25]

[c]Significant difference according to the *P* value of the RCT.

## Figure Legends

Figure 1

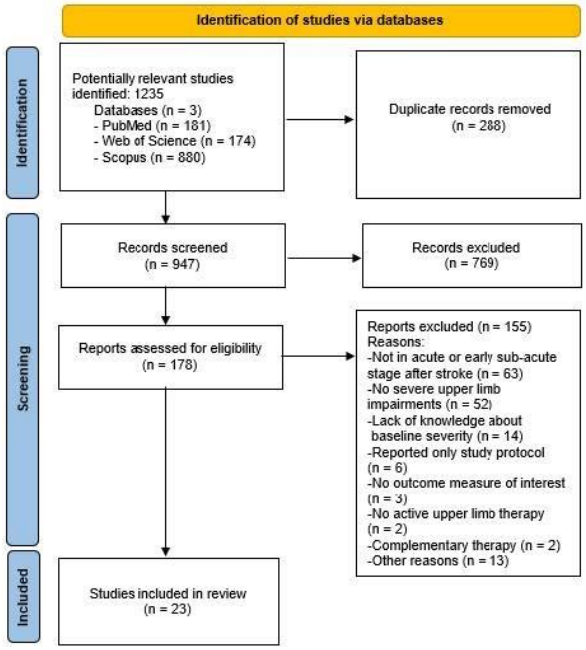

**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of screenings and the definitively included studies. “Other reasons” refers to full text in a language other than English, not involving the upper limb, no randomized controlled trial, nonmotor impairments, a population having neurological pathologies other than stroke, and a population <18 years old

Figure 2

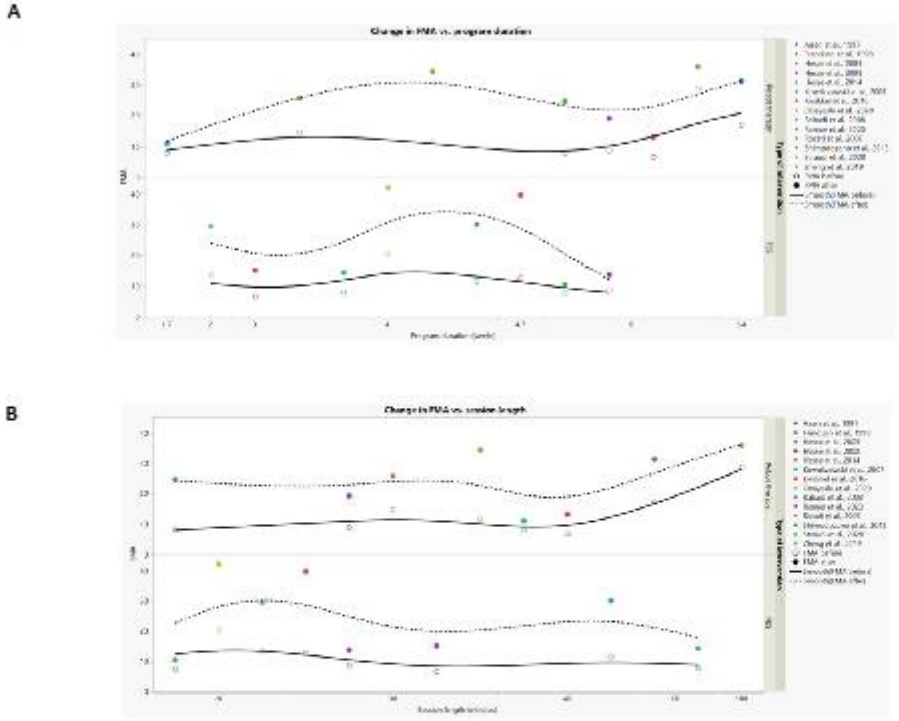


**Figure 2.** (A) Effect of program duration (x-axis) on changes in both Fugl-Myer Assessment (FMA) (left y-axis) and type of intervention (right y-axis). (B) Effect of session length and therapy sessions per day (x-axis) on changes in both FMA (left y-axis) and type of intervention (right y-axis). FES = functional electrical stimulation.