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EFFICACY OF PHYSIOTHERAPY INTERVENTIONS LATE AFTER STROKE: A META-ANALYSIS

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ABSTRACT

Objective. Physiotherapy is usually provided only in the first few months after stroke, while its effectiveness and appropriateness in the chronic phase are uncertain. We conducted a systematic review and meta-analysis of randomized clinical trials (RCT) to evaluate the efficacy of physiotherapy interventions on motor and functional outcomes late after stroke. Methods. We searched published studies where participants were randomized to an active physiotherapy intervention, compared to placebo or no intervention, at least 6 months after stroke. Outcome was change in mobility and activities of daily living (ADL) independence. Quality of trials was evaluated using the PEDro scale. Findings were summarized across studies as effect size (ES) or, whenever possible, weighted mean difference (WMD) with 95% confidence interval (CI) in random effects models. Results. Fifteen RCT were included, enrolling 700 participants with follow-up data. The meta-analysis of primary outcomes from the original studies showed a significant effect of the intervention (ES 0.29, 95% CI 0.14–0.45). Efficacy of the intervention was particularly evident when short- and long- distance walking (SDW, LDW) were considered as separate outcomes, with WMD of 0.05 m/sec (95% CI 0.008–0.088) and 20 m (95% CI 3.6– 36.0), respectively. Also ADL improvement was greater, though non-significantly, in the intervention group. No significant heterogeneity was found. Interpretation. A variety of physiotherapy interventions improve functional outcomes even when applied late after stroke. These findings challenge the concept of a plateau in functional recovery of patients that had experienced stroke and should be valued in planning community rehabilitation services.

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INTRODUCTION

Beside being the third leading cause of death, stroke is the main cause of severe disability in the aging populations of industrialized countries.[1] The dynamics of the disabling process after stroke is complex. Although most stroke survivors show some neurological recovery in the initial post-acute phase, usually within the first three months,[2] improvement may continue well beyond this time. As many as 40% to 60% of patients will recover functional independence in the domains of mobility and ADL from three months to 10 years after a stroke[2] and at a widely variable pace.[3] Conversely, once a given level of independence is reached, it can be hardly maintained long term, as functional status generally tends to deteriorate slowly over time.[4,5]

In general, rehabilitation services are designed without fully taking into account the complexity in functional evolution of stroke survivors. Although a variety of in-hospital or out-of-hospital multidisciplinary interventions may be proposed to promote motor function recovery,[6] physiotherapy usually is deemed appropriate only within weeks or a few months after stroke.[7] Thus, it is unusual that patients with "chronic" stroke are offered any form of rehabilitation.[4] This <u>is due to</u> the limited availability of resources <u>as well as to</u> the paucity of high quality evidence <u>of</u> the efficacy of late rehabilitation. In <u>view</u> of scarce and inconclusive findings from RCT, the concept prevails that <u>there is</u> a limit to late functional recovery after a stroke and doubts are cast upon the effectiveness of late motor rehabilitation interventions. As a <u>result</u> evidence-based practice guidelines <u>generally agree</u> that stroke survivors with persistent disabilities <u>should</u> be periodically assessed for further possible interventions, whereas agreement is scarce on the strength of recommendations on late rehabilitation.[6,8-11] The present systematic review and meta-analysis of RCT was performed to evaluate the efficacy of motor rehabilitation and physiotherapy interventions conducted late after stroke.

METHODS

In accordance with the meta-analysis of randomized controlled trials (QUOROM) statement, [12] we conducted an extensive search for published RCT performed at least 6 months after stroke onset, enrolling five or more adults in each group, randomized to an active physiotherapy intervention aimed either at improving mobility and ADL independence, or at controlling treatment (placebo or no intervention). Active treatment had to be represented by conventional rehabilitation (including neuromuscular interventions, practicing functional activities, muscle strengthening and application of assistive equipments), and had to be provided or supervised by qualified physiotherapists (alone or within a multidisciplinary team). This selection focused on physiotherapy interventions that are considered standard practice in stroke rehabilitation, [13-15] excluding techniques which are highly innovative (e.g. robotic therapy) or poorly used in most community-based rehabilitation services (e.g. treadmill training with partial body weight support). Because we focused on outcomes represented by functional abilities mostly involving lower extremities, we also excluded studies where active treatment targeted upper extremities (e.g. constraint induced movement therapy).

We performed an electronic search of original papers, published in English or Italian, indexed in MEDLINE, PEDro, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINHAL, ISI Web of Science, and EMBASE, with no temporal limits up to January 2010, using the following combination of keywords: (stroke OR cerebrovascular accident OR cerebrovascular

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disorders) AND (rehabilitation OR physical therapy OR physiotherapy OR occupational therapy OR exercise OR exercise therapy OR training) AND (randomized controlled trial OR meta-analysis). To ensure retrieval of all potentially relevant RCT, we scanned reference lists of pertinent articles, and performed handsearch of major journals. Reference lists of articles retrieved were evaluated for relevant publications. Setting, duration of intervention and of follow-up were recorded, but not used as selection criteria. Full texts of all articles judged to be of possible interest on the basis of title and abstract were retrieved. Two reviewers (FF, MDB) independently evaluated the studies selected for final inclusion; disagreement was resolved by consensus.

Outcome of the study was difference between groups at the end of the treatment period in mobility and ADL independence, measured with previously validated tools. Relevant data were extracted using a standard data recording spreadsheet, including characteristics of the population involved (age, gender, time elapsed from stroke), sample size, number of participants completing the study, characteristics of the intervention (therapeutic approach, setting, duration and professionals involved), primary and secondary objectives, results related to all the outcomes assessed, and other characteristics useful for quality evaluation (see below). Where information was not available in the published material, details were requested from the authors.

The PEDro database,[16] which scores published RCT on rehabilitation, was consulted for quality evaluation. The PEDro score, developed by the Centre for Evidence-Based Physiotherapy, has been shown to be reliable[17] and particularly useful for assessing the quality of studies in stroke rehabilitation.[18] Criteria for quality assessment are represented by randomness and concealment of allocation, baseline comparability between groups, blinding of participants, therapists, and assessors, <u>adequacy</u> of follow-up assessments, intention-to-treat analysis, betweengroup comparisons, point estimates and variability. The total PEDro score ranges from 0 (poor quality) to 10 (excellent quality); a score of 6 is conventionally considered as a threshold to identify high quality studies.[16] The same criteria were applied to evaluate <u>the</u> quality of the two most recent studies,[19,20] not found in the PEDro database.

Analytic procedures

To obtain the same data format for as many outcome measures as possible, preliminary data manipulation was performed as follows. In one study[21] mean and pooled standard deviation (SD) were calculated to <u>create</u> a single intervention group from data originally <u>divided into</u> three experimental groups, which differed only <u>in</u> the specific care setting (outpatient, home, and mixed). Missing SD values for the end of treatment Functional Independence Measure (FIM) scale were substituted with baseline values in one study[22] or were calculated from reported standard error of the mean in another.[20] Finally, mean and SD data were obtained directly from the authors of a study,[23] where most outcome data had been originally reported as median and interquartile range. Original values of outcome measures which decrease with improving performance were reverted into corresponding negative values.[24,25]

Three studies, in which a cross-over design was used,[24,26,27] were analyzed as parallel group RCT, by calculating effects before the point of cross-over. In one study,[19] data pertinent to the present meta-analysis were represented only by those collected in one of three intervention arms and to controls.

A variety of different outcome measures were found, sometimes also in the same study, within the broad category of mobility and ADL independence. The primary outcome of each original study was chosen as the primary measure of interest of this meta-analysis. When a primary outcome had not been explicitly declared, the first outcome reported in the area of mobility and ADL independence was selected. Due to variability of outcome measures, standardized ES and 95% CI were calculated for this outcome, using Cohen's *d* estimator, as the difference between post-test values in the intervention and control groups, divided by the pooled SD. A second set of comparisons was performed, by separately pooling measures of ADL independence, SDW (usually 10 meters), and LDW (6 min walking). For the first of these comparisons, ES was calculated, whereas for SDW and LDW WMD and 95% CI, as clinically meaningful outcome measures, were compared between intervention and control groups. For this purpose, the original SDW measure units were converted into m/sec as a common unit; a study[21] which reported SDW speed in terms of relative velocity was excluded from this specific analysis. Results were pooled across studies with DerSimonian-Laird random effects models,[28] anticipating possible heterogeneous effects among different treatment strategies.

StatsDirect® (version 2.7.2) was used to perform statistical analysis. A p value <0.05 was assumed to represent a significant result.

RESULTS

Of 200 titles retrieved, 121 were excluded because <u>they</u> did not meet the inclusion criteria. Of the remaining 79 titles, 76 were found in full text and were evaluated by two independent investigators, who eventually included only 15 studies,[19-27,29-34] fulfilling the selection criteria. The two main causes of exclusion were <u>when</u> stroke onset <u>was</u> less than 6 months before enrollment and <u>if</u> experimental interventions <u>were</u> not coherent with our inclusion criteria (**Figure 1**).

<Insert Figure 1 here>

Participants

The sample size of selected trials ranged from 13 to 170 participants, totaling 730 randomized participants, 700 of whom were reassessed at follow-up. The proportion of participants reassessed at follow-up was similar (p=0.506) between active treatment (n=370, 96%) and controls (n=330, 95%). All studies except one[21] detailed demographic and clinical characteristics of the sample. Age was 40 years or above (weighted mean age: 70.3 years) and 59% of participants were males. The proportion of the side affected was comparable between treatment groups. Major comorbidities and, in particular, other neuromuscular and skeletal diseases or dementia were exclusion criteria in all RCT but two.[19-26,29-32,34] Eleven studies[19,21,22,25-27,29-31,33,34] did not include participants with severe cognitive or sensory deficits, and four[21,32-34] specified that participants had to be clinically stable. Stroke occurred at least 6 months before enrolment in five studies,[20,23,28-30] 9 months in one study,[26] and at least 12 months in the others[19,21-24,27, 32-34] (weighted mean: 4 years).

Baseline functional level ranged widely. Authors, with one exception,[19] specified various functional inclusion criteria: moderate to severe disability,[22-24,27] being able to walk without[34] or else with or without assistive devices,[20,21,25,26,29,30,32,33] a minimum walking capacity (15 minutes[26,32] or a given distance[25,29,30,33,34]), minimum[34] or maximum[30] walking speed, a minimum activity tolerance of 45 minutes.[26,29,31] Most studies allowed classifying participants at baseline according to Perry's Ambulation Classification:[35] 15.4% of participants were household ambulators, 60.7% were limited community ambulators, and 15.6% were full community ambulators, whereas this classification could not be obtained for the remaining 8.3%, whose functional level was of severe-to-moderate disability as an inclusion criterion.[22,27]

As reported in nine out of 15 articles, studies differed for duration and kind of off-protocol treatment delivered. Three RCT specified that all[21,22] or 13 out of 19[27] participants had received inpatient rehabilitation in the acute phase. One study reported that 50 out of 63 participants had <u>received</u> inpatient rehabilitation after the initial hospital stay, and 41 <u>had</u> outpatient rehabilitation after discharge home.[32] In two articles, participants had completed rehabilitation;[20,30] three studies required the absence of physical therapy treatments four to six months before enrollment,[22,23,27] and three others clarified that no other type of rehabilitation was delivered in the period of the study.[21,25,33]

Intervention

The duration of a single treatment session ranged between 10 and 120 minutes. The intervention lasted from 4 to 26 weeks (with a frequency from less than one up to 5 sessions per week) and was delivered at home in three cases,[19,24,27] in an outpatient setting in ten cases[20,22,25,26,29-34] (three of which were in groups of 8 to 12 participants[20,22,32]), and in a mixed out-patient and home-based setting in the remaining two[21,23] (**Table 1**).

In most studies, conventional therapeutic approaches (neuromuscular interventions, practicing functional activities, muscle strengthening and application of assistive equipments), were combined, with the aim of improving mobility or independence. As <u>illustrated</u> in studies, or specified by authors on request,[29,31,34] active intervention was practiced or supervised by physical therapists, alone, within a multidisciplinary staff (which might include occupational therapists, exercise physiologists, or instructors), or in collaboration with the family (**Table 1**).

Outcome measures

A variety of outcome measures had been used in the original studies (**Table 1**). The FIM–motor scale[22] and the Rivermead Mobility Index[23] were indicated as primary outcomes. First mobility or ADL independence outcome measures reported were the Barthel Index,[27] the Timed-Up-and-Go-Test,[25] SDW speed,[19-21,24,26,29,30,33,34] and the 6-minute walking test (6MWT).[31,32] Overall, four studies had measures of ADL independence,[22-24,27] whereas measures of walking ability, either on SDW or LDW, were reported in 13,[19-21,23-26,29-34] out of 15 studies, of which six[19,20,25,30,31,33] had both SDW and LDW measures.

| Age, y | ears* | Gen | der | Т | reatment | Main | Duration | N. of treatment | Total | Providers | Setting |
|---------|-------|------------|-------|-----|-----------|------------|----------|-----------------|-------------|---------------|----------|
| | | M / | F | | | outcome† | (weeks) | sessions | duration of | | |
| | | | | | | | | | treatment | | |
| | | | | | | | | | (hours) | | |
| Int | Ctr | Int | Ctr | Int | Ctr | | | | | | |
| 45 - 70 | | NA | | NI | Untreated | SDW | 26 | 52 | 52 | PT and family | Mixed |
| | | | | | | normalized | | | | (spouse or | (out- |
| | | | | | | by stature | | | | companion) | patient, |
| | | | | | | | | | | | home) |
| 723 | 72.0 | 27/22 | 20/25 | FA | Untreated | SDW | 13 | Mean 4 range 1- | NA | РТ | Home |

| | | | | | | | | | o j stature | | | | v ompunion) | punent, |
|-----------|----|----|---------|--------|-------|-------|----|---------------|-------------|----|------------------|------------|--------------------|----------|
| | | | | | | | | | | | | | | home) |
| Wade[24] | 48 | 41 | 72.3 | 72.0 | 27/22 | 20/25 | FA | Untreated | SDW | 13 | Mean 4, range 1- | NA | РТ | Home |
| 1992 | | | (9.7) | (10.6) | | | NI | | | | 11 | | | |
| | | | | | | | AE | | | | | | | |
| Werner | 28 | 12 | 66 (13) | 59 (9) | 14/ | 5/7 | NI | Untreated | FIM-mm | 12 | 48 | 96 | Multidisciplinary | Out- |
| [22] 1996 | | | | | 14 | | MS | | | | | | staff (PT + OT) | patient‡ |
| Teixeira | 6 | 7 | 65.8 | 69.4 | 1/5 | 6/1 | MS | Untreated | SDW | 10 | 30 | Between 30 | Multidisciplinary | Out- |
| [26]1999 | | | (10.2) | (8.8) | | | FA | | | | | and 45 | staff (PT + EP) | patient |
| Kim[29] | 10 | 10 | 60.4 | 61.9 | 7/3 | 7/3 | MS | Passive range | SDW | 6 | 18 | 13.5 | РТ | Out- |
| 2001 | | | (9.5) | (7.5) | | | | of motion | | | | | | patient |

N. of

participants

with FU

data

Int Ctr

5

15

Study,

year

Wall[21]

1987

| Green[23] | 81 | 80 | 71.5 | 73.5 | 49/36 | 46/39 | FA | Untreated | RMI | Between 3 | Median 3, range | NA. Individual | PT | Mixed |
|-----------|----|----|---------|---------|-------|-------|----|--------------|------|-----------|-------------------|----------------|-------------------|----------|
| 2002 | | | (8.7) | (8.3) | | | NI | | | and 13 | 0-22 (5 | treatment | | (out- |
| | | | | | | | | | | contacts | participants were | duration | | patient, |
| | | | | | | | | | | | evaluated, but | averaged 44 | | home) |
| | | | | | | | | | | | were not treated) | min. | | |
| Ada[30] | 13 | 14 | 66 (11) | 66 (11) | 9/4 | 10/4 | NI | Sham home | SDW | 4 | 12 | 6 | РТ | Out- |
| 2003 | | | | | | | | exercise | | | | | | patient |
| | | | | | | | | program | | | | | | |
| Lin[27] | 9 | 10 | 61.4 | 62.8 | 7/2 | 6/4 | NI | Untreated | BI | 10 | 10 | 10 | РТ | Home |
| 2004 | | | (11.2) | (9.4) | | | FA | | | | | | | |
| | | | | | | | | | | | | | | |
| Ouellette | 21 | 21 | 65.8 | 66.1 | 28/ | /14 | MS | Range of | 6MWT | 12 | 36 | NA | PT | Out- |
| [31] 2004 | | | (2.5) | (2.1) | | | | motion and | | | | | | patient |
| | | | | | | | | upper body | | | | | | |
| | | | | | | | | flexibility | | | | | | |
| | | | | | | | | exercises | | | | | | |
| Pang[32] | 32 | 31 | 65.8 | 64.7 | 19/13 | 18/13 | MS | Seated upper | 6MWT | 19 | 57 | 57 | Multidisciplinary | Out- |
| 2005 | | | (9.1) | (8.4) | | | NI | extremity | | | | | staff (PT + TO + | patient‡ |

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| | | | | | | | | exercises | | | | | EI) | |
|-----------|----|----|---------|-----------|-------|-------|----|-------------|-----|----|----|------------|-----|----------|
| Yang[33] | 24 | 24 | 56.8 | 60.0 | 16/8 | 16/8 | MS | Untreated | SDW | 4 | 12 | 6 | PT | Out- |
| 2006 | | | (10.2) | (10.4) | | | NI | | | | | | | patient |
| Yang[34] | 13 | 12 | 59.5 | 59.2 (12) | 7/6 | 7/5 | NI | Untreated | SDW | 4 | 12 | 6 | РТ | |
| 2007 | | | (11.8) | | | | | | | | | | | |
| Flasbjer | 15 | 9 | 61 (5) | 60 (5) | 9/6 | 5/4 | MS | Usual daily | TUG | 10 | 20 | NA | РТ | Out- |
| [23] 2008 | | | | | | | | activities | | | | | | patient |
| Ng[19] | 25 | 29 | 56.9 | 55.5 (8) | 20/5 | 20/9 | NI | Untreated | SDW | 4 | 20 | NA | PT | Home |
| 2009 | | | (8.6) | | | | | | | | | | | |
| Mudge[20] | 31 | 27 | 76 | 71 | 19/12 | 13/14 | NI | Social | SDW | 4 | 12 | Between 10 | PT | Out- |
| 2009 | | | (39-89) | (44-86) | | | | and | | | | and 12 | | patient‡ |
| | | | | | | | | educational | | | | | | |
| | | | | | | | | sessions | | | | | | |
| | | | | | | | | | | | | | | |

Table 1. Characteristics of the studies included

* Data are reported as mean (SD) or range

[†] Main outcome was represented by the primary outcome, when explicitly declared, or by the first mobility and ADL independence outcome reported.

‡ In groups of 8 to 12 persons.

Abbreviations. 6MWT: Six-Minute Walk Test, AE: Application Of Assistive Equipments, BI: Barthel Index, Ctr: Control group, EI: Exercise Instructor, EP: Exercise Physiologist, FA: Practicing Functional Activities, FIM-mm: Functional Independence Measures - motor measure, FU: follow-up, Int: Intervention group, MS: Muscle Strengthening, NA: Not Available, NI: Neuromuscular Interventions, OT: Occupational Therapist, PT: Physiotherapist, RMI: Rivermead Mobility Index, SDW: Short Distance Walk, TUG: Timed Up and Go Test.

Quality evaluation

Following PEDro criteria,[16] trials selected for this meta-analysis had a quality score ranging from three to eight (mean 6.3). Randomization was concealed in <u>seven</u> trials;[19,20,23,30,32-34] assessors were blinded in all studies but two,[19,20,22-25,27,29-34] whereas both participants and therapists could never be blinded to group assignment. All studies except one[26] reported baseline data by randomization group. Based on the original description, analysis was by intention-to-treat in six cases.[19-21,29,31,32] One article[22] was not accurate in reporting variability of follow-up data (**Table 2**).

| | Wall [21] | Wade [24] | Werner [22] | Teixeira [26] | Kim [29] | Green [23] | Ada [30] | Lin [27] | Ouellette [31] | Pang [32] | Yang [33] | Yang [34] | Flansbjer [25] | Ng [19] | Mudge [20] |
|--|--------------|--------------|----------------|------------------|--------------|---------------|--------------|--------------|-------------------|--------------|--------------|--------------|-------------------|--------------|---------------|
| Random allocation | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | ✓ | \checkmark | ✓ | \checkmark | \checkmark | \checkmark | ✓ | \checkmark | \checkmark |
| Concealment of allocation | | | | | | \checkmark | \checkmark | | | \checkmark | \checkmark | \checkmark | | \checkmark | \checkmark |
| Comparability of groups at baseline | √ | \checkmark | \checkmark | | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | |
| Blinding of patients | | | | | | | | | | | | | | | |
| Blinding of therapists | | | | | | | | | | | | | | | |
| Blinding of assessors | | \checkmark | \checkmark | | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark |
| Adequacy of follow-up | | \checkmark | | | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark |
| Analysis by intention to treat | | | | | \checkmark | \checkmark | | | \checkmark | \checkmark | | | | \checkmark | \checkmark |
| Between-group statistical comparisons | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark |
| Reports of point estimates and measures of variability | \checkmark | \checkmark | | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark | \checkmark |
| PEDro score (/10) | 4 | 6 | 4 | 3 | 7 | 8 | 7 | 6 | 7 | 8 | 7 | 7 | 6 | 8 | 7 |

 Table 2. PEDro quality score of the studies included.

Meta-analysis

The meta-analysis of all outcome measures showed a pooled ES of 0.29 (95% CI 0.14–0.45; p <0.001) in favour of the intervention, with no heterogeneity (**Figure 2**).

<Insert Figure 2 here>

In terms of ADL independence, a trend in favour of the intervention did not reach statistical significance, with a pooled ES of 0.08 (95% CI -0.21–0.37; p=0.583) and no heterogeneity (**Figure 3**).

<Insert Figure 3 here>

Active treatment significantly improved both SDW and LDW ability, as shown by WMD of 0.05 m/sec (95% CI 0.008–0.088; p=0.017) (**Figure 4**) and 20 m (95% CI 3.6–36.0; p=0.017) (**Figure 5**), respectively, with no significant heterogeneity. These figures represented an 8% gain over baseline values of SDW and LDW.

<Insert Figures 4 and 5 here>

DISCUSSION

This study provides evidence, drawn from systematic search and meta-analysis of RCT, that a variety of conventional motor rehabilitation and physiotherapy interventions, applied late after stroke, improve motor and functional outcomes, compared to no treatment or placebo. Specifically, SDW and LDW ability improved substantially.

Systematic reviews show that organized multidisciplinary care and rehabilitation are effective in the early phase of a stroke, improving survival and independence, and reducing length of hospital stay and need for institutionalization.[35-39] A meta-analysis of RCT demonstrates that therapy-based rehabilitation services, targeting community-dwelling patients within one year of stroke, improve ADL independence and reduce the risk of further functional deterioration.[40] Another meta-analysis of RCT[41] reports that augmented exercise therapy time of at least 16 hours within the first 6 months after stroke obtains a measurable improvement in ADL and, to a lesser degree, in instrumental ADL and gait speed. A Cochrane systematic review reports that, compared to no treatment or placebo, a mix of conventional rehabilitation approaches significantly improves the recovery of postural control and lower limb function following stroke, thus enhancing independence.[42] Finally, an RCT reports that older patients that had had a stroke benefit on a short-term basis from a higher intensity of community-based rehabilitation, especially in the domains of social participation and health-related quality of life.[43]

Solid scientific evidence supports the practice of physiotherapy early after a stroke, while evidence is more controversial for physiotherapy interventions applied after six months or more from the acute phase. A Cochrane review[44] analyzed five RCT with 487 participants that had suffered stroke, at least 75% of whom were recruited one year after the event. They were randomized to receive a therapy-based rehabilitation intervention or conventional care. Primary outcome was the proportion of participants who deteriorated or were dependent in ADL at the end of the follow up. Although no conclusive evidence was found that therapy-based rehabilitation

improves ADL independence,[44] the sensitivity to interventions of such a hard outcome is limited. Another recent Cochrane review that investigated the effectiveness of overground gait training for improving overall measures of gait function in people who had <u>suffered</u> a stroke, found limited evidence of benefits for variables such as gait speed or 6MWT.[45] Gait speed and mobility measures, such as those considered in the present meta-analysis, have robust metric properties,[46] are more sensitive to change and represent major, clinically relevant endpoints.[47] Notably, in the only included study reporting a favourable effect of active treatment on ADL, number and cumulative duration of treatment sessions were substantially greater than in other studies.[22] <u>Consequently</u>, we might speculate that, as in early stroke rehabilitation,[41] late rehabilitation effects on ADL may well be a matter of treatment intensity and duration.

Using mobility measures as an outcome, the present meta-analysis shows favourable effects of physiotherapy late after stroke, thus contributing to fill an important knowledge gap. However, we are aware of the limitations of the evidence provided, stemming from the small number of participants enrolled, as well as from differences in type, frequency, and intensity of interventions delivered and outcomes assessed. All these characteristics usually increase heterogeneity and threaten validity. Nevertheless, no statistical evidence of heterogeneity was detected. Moreover, the rehabilitation interventions applied were similar to those routinely used in clinical practice, and study outcomes were represented by simple, previously validated functional measures. Furthermore, it should be noted that almost all the outcome measures selected have been identified as core measures in stroke rehabilitation.[48] Thus, we believe that the present meta-analysis reflects stroke rehabilitation as practiced in most community services. <u>As</u> evaluated according to PEDro methodology,[16] the quality of the studies included was satisfactory: since blinding of participants and therapists cannot be obtained in this kind of trials, the mean score of 6.3 (**Table 2**) should be weighed against a maximum score of only 8, not 10, points obtainable.[49] When strengths and limitations of the RCT contributing to this metaanalysis are carefully balanced, we feel that the findings obtained are valid, clinically meaningful, and generalizable.

The clinical and public health implications of this study deserve further attention. In general, rehabilitation services for stroke survivors are available and deliver more intensive interventions in the initial phase <u>after the stroke</u>, gradually decreasing thereafter.[4] Six to 12 months after the acute phase, physical therapy is usually no longer provided, especially when patients appear to reach a plateau and fail to improve further with prolonged treatment.[50] Yet, our findings suggest that a significant functional recovery can be observed <u>after a stroke</u> later than usually believed. <u>The improvement observed was small, below what is usually considered</u> <u>clinically meaningful,[46] but it possibly challenges the concept itself of a plateau,</u> which might rather stem from the delivery of less intensive therapy.[51]

Before existing practices are definitively changed, further studies are required to corroborate our findings and <u>to clarify areas of uncertainty they cannot solve</u>. First of all, it would be interesting to make clear if delivering higher doses of physiotherapy, or targeting patients more accurately, would lead to greater improvement. Likewise, the potential economic implications of our results deserve careful consideration and further investigation. Most healthcare systems cannot afford allocation of additional resources to physiotherapy programs, extended several months to years after stroke onset. However, scientific evidence of clinical efficacy should not be overlooked in the face of pure economic constraints: cost-effectiveness analyses, as well as studies on predictors of recovery, should be performed to help clinicians and politicians make informed decisions on this issue.

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COMPETING INTEREST

The authors report no conflicts of interest.

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FIGURE LEGENDS

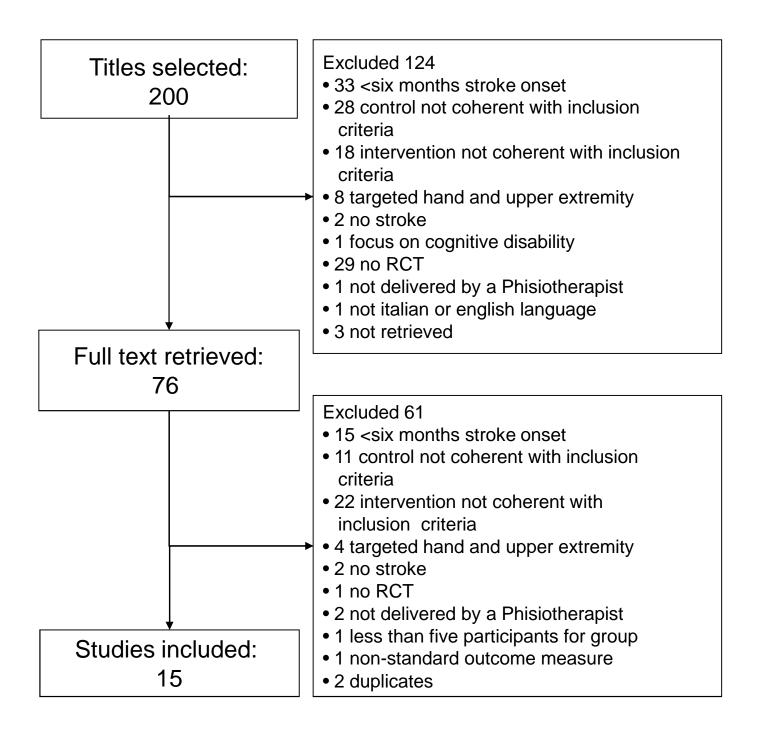
Figure 1. Literature search flow chart, and main exclusion criteria.

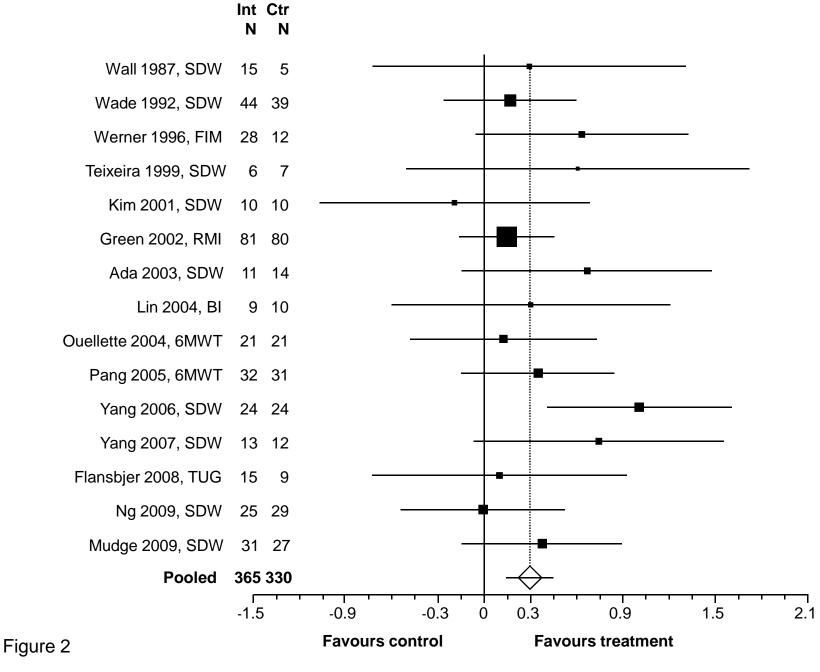
Figure 2. Plot of random effects meta-analysis of effect size for all the outcomes considered. **Abbreviations.** 6MWT: 6-minute walking test, BI: Barthel Index, Ctr N: Control group sample size, ES: effect size, FIM: Functional Independence Measure, Int N: Intervention group sample size, RMI: Rivermead Mobility Index, SDW: short distance walk, TUG: Timed Up-and-Go test.

Figure 3. Plot of random effects meta-analysis of effect size for the outcomes of ADL independence. **Abbreviations** as in Figure 2.

Figure 4. Plot of random effects meta-analysis of weighted mean differences for the outcomes of SDW. **Abbreviations** as in Figure 2.

Figure 5. Plot of random effects meta-analysis of weighted mean differences for the outcomes of LDW. **Abbreviations** as in Figure 2.





Pooled ES: 0.29 (0.14 - 0.45), p= <0.001

Cochran Q= 12.9, p= 0.535 I²= 0%

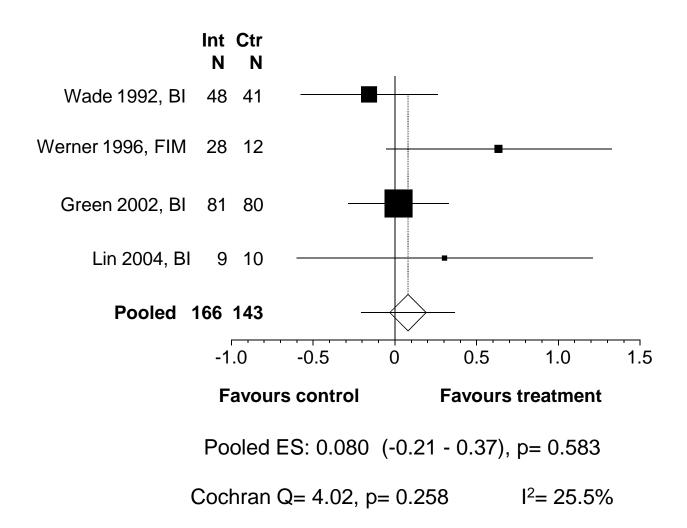


Figure 3

