

## Chapter 5

# **Constraint Induced Movement Therapy for the paretic upper limb in acute or subacute stroke: a systematic review**

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## ABSTRACT

**Background:** Constraint-induced movement therapy (CIMT) is a commonly used intervention to improve upper limb function after stroke. The effectiveness of CIMT and its optimal dosage during acute or subacute stroke is still under debate, however.

**Objective:** To examine the literature on the effects of CIMT in acute or subacute stroke.

**Methods:** A literature search was performed to identify randomized, controlled trials (RCTs). Studies with the same outcome measure were pooled by calculating the Mean Difference (MD). Separate quantitative analyses for High Intensity (HI) and Low Intensity (LO) CIMT were applied when possible.

**Results:** Five RCTs were included, comprising 106 participants. The meta-analysis demonstrated significant MDs in favor of CIMT for the Fugl-Meyer arm, the Action Research Arm Test, the Motor Activity Log, Quality of Movement and the Grooved Pegboard Test. Non-significant MDs in favor of CIMT were found for the Motor Activity Log, Amount of Use. Separate analyses for HI and LO CIMT resulted in significant favorable MDs for LO CIMT for all outcome measures, in contrast to HI CIMT.

**Conclusions:** This meta-analysis demonstrates a trend towards positive effects of HI and LO CIMT in acute or subacute stroke, but also suggests that LO CIMT may be more beneficial during this period than HI CIMT. However, these results were based on a small number of studies. Therefore, more trials are needed applying different doses of therapy early after stroke and a better understanding is needed about the different time windows in which underlying mechanisms of recovery operate.

## INTRODUCTION

Stroke is one of the main causes of disability in the Western world.<sup>1</sup> Although most patients show significant gains in motor function early after stroke onset,<sup>2</sup> a large proportion still shows significant long-term impairments of upper limb function, limitations of activities and restrictions in social participation after stroke.<sup>2-4</sup>

Constraint Induced Movement therapy (CIMT) is a neurorehabilitation approach developed to improve the use of the more affected upper limb after stroke. The original therapy involves inducing the use of the more affected limb by constraining the less affected limb for up to 90 percent of waking hours over a 2-week period, including 2 weekends. During this period, repetitive training of the more affected limb using shaping principles is applied for 6 hours on each weekday, as well as a transfer package of adherence-enhancing behavioural strategies.<sup>5</sup>

On the basis of a systematic review involving 19 RCTs (N=619), Sirtori and colleagues<sup>6</sup> concluded that CIMT is an effective therapy for improving upper limb function and ADLs outcomes. However, the application of CIMT is heterogeneous and several modified forms of CIMT (mCIMT) have been advocated in the literature. These modified forms are generally characterized by less time dedicated to shaping procedures, shorter constraining time of the less affected limb as well as the lack of applying behavioral strategies.

One aspect that is particularly debated in the literature is the optimal dosage of (m)CIMT that is started in the first days and weeks post stroke.<sup>7-10</sup> For example, several animal studies<sup>7,9,10</sup> have shown that early exclusive use of the impaired forelimb within the first 7 to 15 days post ischemic stroke may increase the lesion volume,<sup>9,10</sup> may have detrimental effects on sensorimotor function<sup>7</sup> and may result in chronic behavioral deficits.<sup>7,9,10</sup> In line with this finding, the VECTORS study<sup>8</sup> found a negative dose-response relationship for early (m)CIMT therapy in stroke patients starting 10 days post stroke. Their results showed that a CIMT application involving 3 hours of shaping on every workday in combination with constraining the less affected limb for 90% of the waking hours for every day, including weekends for a period of 2 weeks led to significantly less upper extremity motor improvement at 90 days than 2 hours of shaping therapy and 6 hours of restraining per day. On the other hand, some studies also suggest that there may be a critical time window of heightened reactive neuroplasticity by upregulation of growth promoting factors during the process of spontaneous neurological recovery in the first few weeks post stroke.<sup>11,12</sup>

The purpose of the present review was to systematically review the literature on the effects of (m)CIMT on the paretic upper limb in patients with acute or subacute stroke. Sensitivity analysis was used to investigate the impact of the (m)CIMT dosage in acute or subacute stroke.

Although we hypothesized that the use of (m)CIMT would have a positive effect on upper limb recovery, we also expected that a lower dose of (m)CIMT would be more beneficial than the traditional form of CIMT during the acute or subacute phase after stroke.

## MATERIALS AND METHODS

### Definitions

Stroke has been defined by the World Health Organization as ‘a clinical syndrome typified by rapidly developing signs of focal or global disturbance of cerebral functions, lasting more than 24 hours or leading to death, with no apparent causes other than of vascular origin.’<sup>13</sup>

In the present review, the acute or subacute phase was defined as the time window in which time-dependent spontaneous neurological recovery still occurs, which is typically within the first 10 weeks after stroke onset.<sup>12</sup>

To investigate the impact of the (m)CIMT dosage during acute or subacute stroke, the interventions that were included in this review were categorized as “high intensity” (HI CIMT) or “low intensity” (LO CIMT). In line with the VECTORS study,<sup>8</sup> HI CIMT was defined as 3 hours or more of repetitive training per day in combination with restraining of the less affected limb for 90% of waking hours, whereas LO CIMT was defined as less than 3 hours of repetitive training per day and constraining of the less affected limb for less than 90% of waking hours.

## 5

### Study identification

Potentially relevant literature was identified through computerized and manual searches. The following electronic databases were systematically searched through December 2010: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, Physiotherapy Evidence Database (PEDro), WHO ICTRP trial register and EBSCO/SportDiscus. The following MeSH headings and keywords were used: stroke, cerebrovascular accident, constraint induced movement therapy, forced use and randomized controlled trial. Additional relevant studies were identified by examining bibliographies of review articles as well as references from retrieved articles. Studies published up to December 2010 were included if they met the following inclusion criteria: (1) the study was a Randomized Controlled Trial (RCT); (2) CIMT was applied focusing on the upper limb; (3) participants were patients with stroke who were at least 18 years of age; (4) Participants were recruited and observed within the acute or subacute phase after stroke onset; (5) the study was published in English, German or Dutch. Two authors (J.B.

and R.N.) independently reviewed the titles of the identified references, selected the relevant studies on the basis of title and abstract and subsequently checked independently if the selected studies satisfied the inclusion criteria. If a study that did not provide conclusive information in the abstract, the full text was retrieved and reviewed. Disagreements were resolved by consensus, and a third review author (G.K.) was consulted if disagreements persisted.

## Methodological quality

Two independent reviewers (J.B., R.N.) assessed the methodological quality of each RCT using the PEDro scale.<sup>14</sup> PEDro is a reliable and valid scale consisting of 11 items, in which the first item relates to external validity and the other 10 items assess the internal validity of a clinical trial. One point was given for each criterion that was satisfied (except for the first item, which was allocated a YES or NO), yielding a maximum score of 10. The higher the score, the better the quality of the study. PEDro scores  $\geq 4$  points were classified as “high quality,” whereas studies with  $\leq 3$  points were classified as “low quality.”<sup>15</sup> Low quality studies were excluded from the current review. Reviewers were not blinded to authors, journals, or outcomes. Agreement regarding each item was evaluated by calculating a Kappa statistic. In case of disagreement, consensus was sought, but if disagreement persisted, a third independent review author (G.K.) made the final decision.

## Quantitative analysis

The extracted data (i.e. the numbers of patients in the experimental and control groups and the mean and standard deviation (SD) of post-intervention scores for each intervention group) were checked independently by 2 reviewers. For each outcome variable, the results were pooled by calculating the mean difference (MD) and 95% CIs when outcomes were reported on the same scale. When outcomes were reported on different scales the standardized mean difference (SMD) was calculated. MDs or SMDs and the corresponding SDs were calculated using the difference in post-intervention means between the experimental and the control groups. The chi-squared test was used to test for homogeneity, set at a significance level of 10%. Because the chi-squared test tends to underestimate heterogeneity in meta-analyses,  $I^2$  was calculated as well to provide an estimate of the percentage of variability due to heterogeneity rather than chance alone.<sup>16</sup> If significant heterogeneity was found ( $I^2$  values  $\geq 50\%$ ) a random effects model was applied.<sup>16</sup> In case of statistical heterogeneity, a sensitivity analysis was considered for methodological quality with respect to randomization, allocation concealment, blinding of final outcome assessment, and use of intention-to-treat analysis. For all outcome variables, the

critical value for rejecting  $H_0$  was two-tailed and set at a level of 0.05. The Review Manager 5 software package was used to calculate the MDs or SMDs and to visualize the results by using forest plots.

### Subgroup analysis

Because the optimal dose of (m)CIMT when started in the first weeks post stroke is still under debate, separate quantitative analyses for HI CIMT and LO CIMT were applied if possible. MDs or SMDs could not be defined on outcome measures when only one study had applied HI or LO CIMT. However, in order to explore the differential effects of HI and LO CIMT, the data of such a single study is also presented in forest plots, while the difference between the experimental and the control groups within the study of interest is reported only as “difference”.

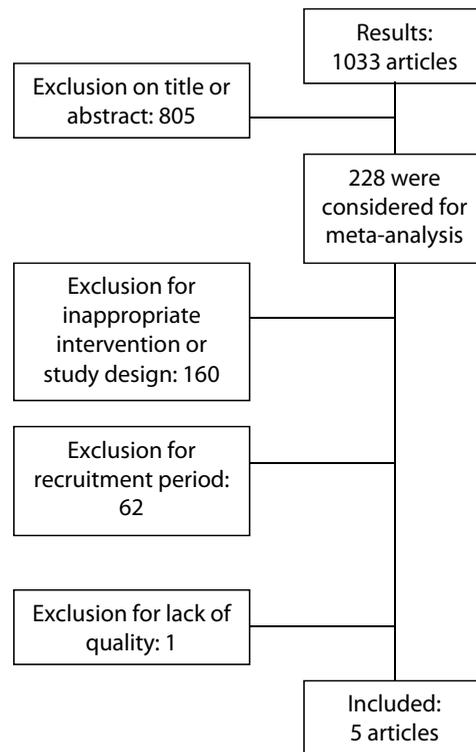
## RESULTS

### Study identification

The search strategy yielded 1033 citations. The results of the electronic search strategy in different data bases are available by the corresponding author. After selection based on title and abstract, 805 studies were excluded. Figure 5.1 shows the flow chart of identified studies that were considered for inclusion. Reasons for exclusion were that the interventions did not fit in with the definitions given above, or that studies had been conducted in a different patient population. Of the remaining 228 full-text articles, 160 were excluded because of inappropriate intervention or study design. Sixty-two studies were excluded because of recruitment outside the acute or subacute phase, and finally one study was excluded because of lack of quality.<sup>17</sup> Screening of references did not yield any further studies. A total of 5 studies were included in this systematic review,<sup>8, 18-21</sup> comprising 106 participants. In two studies HI CIMT was compared with usual care,<sup>18, 21</sup> two studies compared LO CIMT with usual care<sup>19, 20</sup> and one study compared HI CIMT with LO CIMT and usual care.<sup>8</sup> The timing to start the intervention varied between studies from a mean of 4.4 days in the study by Page et al.<sup>20</sup> to a median of 11 days in the study by Boake et al.<sup>18</sup> The main characteristics of the included studies are shown in Table 5.1.

### Methodological quality

Table 5.2 shows the methodological quality scores of the included studies, according to the PEDro scale. The PEDro scores ranged from 1 to 8 points, with a median score of 6.5 points.



**Figure 5.1** Flowchart of study identification.

The assessment of the methodological quality using the 10-item PEDro scale resulted in a Cohen's  $\kappa$  of 0.75 between the two independent review authors. All studies, except that by Grotta et al.<sup>17</sup> scored at least 6 points on the PEDro scale. The study by Grotta et al.<sup>17</sup> was excluded from further analysis.

### Quantitative analysis

Since results for all outcome variables were reported on the same scale, MDs were calculated. Pooling of outcomes was possible for (1) upper limb impairment, measured with the Fugl-Meyer motor assessment of the arm (FMA), (2) upper limb capacity, measured with the Action Research Arm Test (ARAT), (3) dexterity, measured with the Grooved Pegboard Test (GPT) and (4) perceived upper limb capacity, measured with the Motor Activity Log (MAL) for amount of use (AOU) and quality of movement (QOM).

**Table 5.1** Characteristics of the studies included in this review

Study (year)	N (E/C)	Mean (SD) age of the patients	Recruitment period (days after stroke)	Length of therapy (weeks)	Times of assessment	Upper limb function requirements	Outcomes	Intervention groups and intensity of therapy	Conclusion
Boake (2007)	16 (9/7)	HI CIMT: 63.1 (14.3) Control: 58.9 (14.0)	Median: 11 Range 5–19	2	Day 0, 14 and 90	1–3 on the motor arm item of the NIHSS; At least 10° of active movement in the thumb and 2 or more fingers.	FMA, GPT, MAL	<ul style="list-style-type: none"> <li>• HI CIMT (3hrs/d, 6d/w. Mitten: 90% of waking hrs)</li> <li>• Control therapy (3hrs/d, 6d/w)</li> </ul>	Long-term improvement in motor function of the affected UE did not differ significantly between patients who received CIMT and those who received traditional therapy at the same frequency and duration.
Dromerick (2000)	20 (11/9)	LO CIMT: 61.5 (13.7) Control: 71.4 (5.3)	Mean: 6 SD: 2.6 Range: 4–14	2	Day 0 and 14	1–2 on the motor arm item of the NIHSS; ≥3 on the upper-arm item of the MAS	ARAT, BI, FIM	<ul style="list-style-type: none"> <li>• LO CIMT (2hrs/d, 5d/w. Mitten: 6hrs/d)</li> <li>• Control therapy (2hrs/d, 5d/w)</li> </ul>	CIMT was associated with less arm impairment at the end of treatment, compared to traditional therapy.

Dromerick (2009)	52 (35/17)	LO CIMT: 62.8 (12.8)	Mean: 9.7 SD: 4.6	2	Day 0, 14 and 90	1-3 on the motor arm item of the NIHSS; $\geq 3$ on the upper-arm item of the MAS	ARAT, FIM, SIS, WBFS, GDS	<ul style="list-style-type: none"> <li>• LO CIMT (2hrs/d, 5d/w. Mitten: 6hrs/d)</li> <li>• HI CIMT (3 hrs/d, 5d/w. Mitten: 90% of waking hours)</li> <li>• Control treatment (2hrs/d, 5d/w)</li> </ul>	<p>CIMT was equally as effective but not superior to an equal dose of traditional therapy. Higher intensity CIMT resulted in less motor improvement at 90 days, indicating an inverse dose-response relationship.</p> <p>CIMT may accelerate motor recovery when started within the first 2 weeks after stroke</p>
Ro (2006)	8 (4/4)	HI CIMT: 58.8 (14.5)	Mean E: 8.5 Mean C: 10 Range: 6-12	2	Day 0, 14 and 90	1-3 on the motor arm item of the NIHSS; At least 10° of movement of the fingers	GPT, FMA, MAL	<ul style="list-style-type: none"> <li>• HI CIMT (3hrs/d, 6d/w. Mitten: 90% of waking hours)</li> <li>• Control therapy (3hrs/d, 6d/w)</li> </ul>	
Page (2005)	10 (5/5)	LO CIMT: 58.6 (6.3)	Mean: 4.4 SD: 2.32 Range: 2-9	10	Day 0 and 70	At least 10° active movement in the fingers and 20° at the wrist	FMA, ARAT, MAL	<ul style="list-style-type: none"> <li>• LO CIMT (1/2 hrs/d, 3d/w. Mitten: 5hrs/d, 5d/w)</li> <li>• Control therapy (1/2 hrs/d, 3d/w)</li> </ul>	<p>CIMT is a promising regime for improving more affected limb use and function in acute cerebrovascular accident.</p>

E/C, experimental/control group; NIHSS, National Institutes of Health Stroke Scale; MAS, Motor Assessment Scale; HI CIMT, High Intensity Constraint Induced Movement Therapy; LO CIMT, Low Intensity Constraint Induced Movement Therapy; FMA, Fugl Meyer motor assessment Arm; GPT, Grooved Pegboard Test; MAL, Motor Activity Log; ARAT, Action Research Arm Test; BI, Barthel index; FIM, Functional Independence Measure; SIS, Stroke Impact Scale; WBFS, Wong-Baker Faces Scale; GDS, Geriatric Depression-15 Scale.

\* N=19 for the HI CIMT group, N=16 for LO CIMT. Total intervention group: N=35.

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**Table 5.2** Methodological quality of the included trials, assessed with the 10-item PEDro scale

	1	2:	3:	4:	5:	6:	7:	8:	9:	10:	PEDro
Eligibility criteria specified (Yes/No)	Random allocation	Concealed allocation	Comparable at baseline	Blinded subjects	Blinded therapists	Blinded assessors	Adequate follow-up	Intention to treat analysis	Between group comparisons	Point estimates and variability	total score (0–10)
Boake 2007	Yes	1	0	0	0	1	0	1	1	1	6
Dromerick 2000	Yes	1	0	0	0	1	1	0	1	1	6
Dromerick 2009	Yes	1	0	0	0	1	1	1	1	1	7
Grotta 2004	Yes	1	0	0	0	0	0	0	0	0	1
Ro 2006	Yes	1	0	0	0	1	1	1	1	1	7
Page 2005	Yes	1	1	0	0	1	1	1	1	1	8

Item 1–10: 1, criterion was satisfied; 0, criterion was not satisfied.

### Fugl-Meyer motor assessment of the arm

Figure 5.2a shows a significant heterogeneous MD for the three studies that assessed the FMA<sup>18, 20, 21</sup> (MD [random], 11.00; 95% CI: 2.50–19.49; Z=2.54; P=0.01; I<sup>2</sup>=51%).

The two studies that used HI CIMT yielded a non-significant MD (MD: 9.36; 95% CI: -7.12–25.84). The study that used LO CIMT yielded a significant difference in favor of the experimental group (difference: 13.20; 95% CI: 6.52–19.88).

### Action Research Arm Test

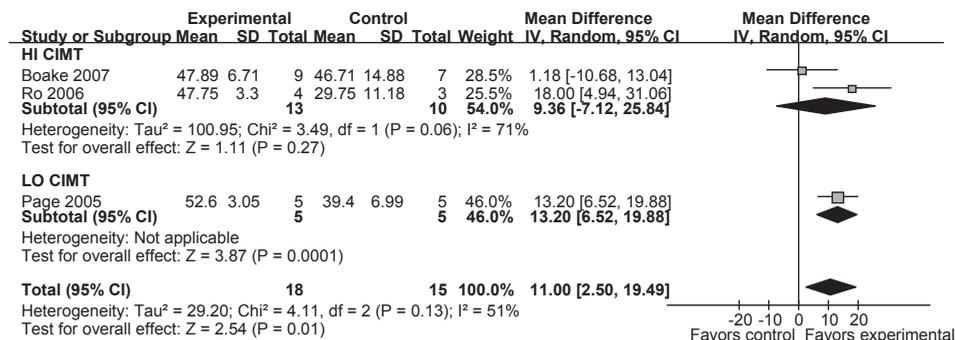
Three studies evaluated the effect of CIMT on the ARAT.<sup>8, 19, 20</sup> The VECTORS study<sup>8</sup> included two separate trials, one in which HI CIMT was compared with a lower dose of traditional Upper Extremity (UE) therapy and one in which LO CIMT was compared with dose-matched traditional UE therapy.

Figure 5.2b shows a significant heterogeneous total MD on the ARAT (MD [random], 7.88; 95% CI: 1.09–14.66; Z=2.28; P=0.02; I<sup>2</sup>=64%).

The study that used HI CIMT yielded a non-significant difference in favor of the control group (difference: -2.27; 95% CI: -13.65–9.11). The three studies that used LO CIMT yielded a significant MD in favor of the experimental group (MD: 11.25; 95% CI: 6.49–16.01).

### AOU and QOM of the Motor Activity Log

Figure 5.2c shows that pooling the results of the three studies that assessed the MAL<sup>18, 20, 21</sup> yielded a non-significant heterogeneous MD for the AOU (MD [random], 1.15; 95% CI: -0.33–2.62; Z=1.52; P=0.13; I<sup>2</sup>=81%).



**Figure 5.2a** Meta-analysis of CIMT in the acute phase after stroke: Fugl-Meyer motor assessment – Arm.

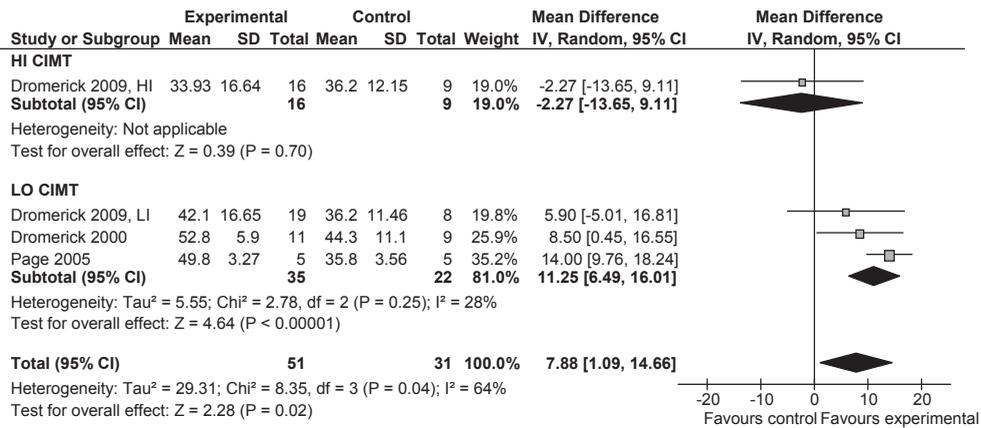


Figure 5.2b Meta-analysis of CIMT in the acute phase after stroke: Action Research Arm Test.

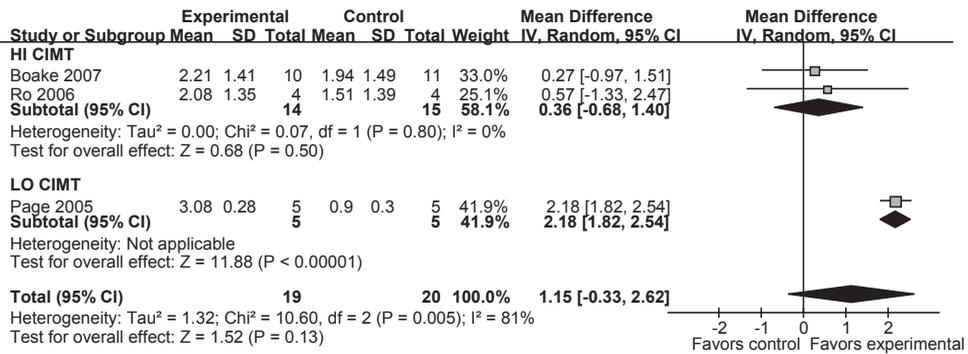


Figure 5.2c.1 Meta-analysis of CIMT in the acute phase after stroke: Motor Activity Log – Amount of Use.

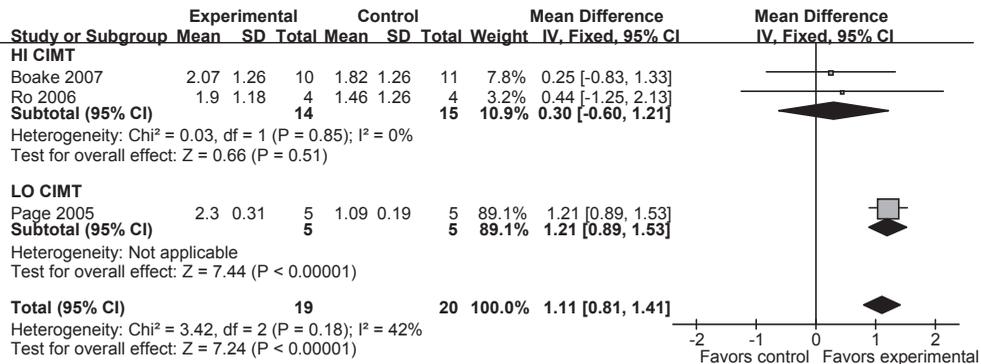
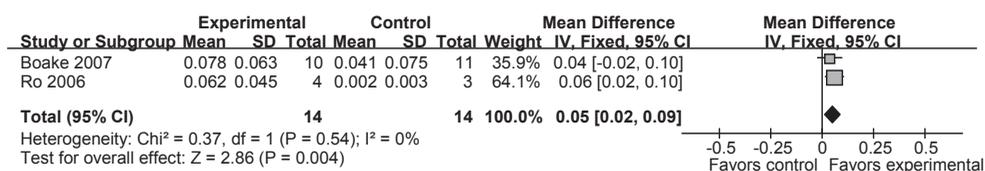


Figure 5.2c.2 Meta-analysis of CIMT in the acute phase after stroke: Motor Activity Log – Quality of Movement.



**Figure 5.2d** Meta-analysis of CIMT in the acute phase after stroke: Grooved Pegboard Test.

The two studies that used HI CIMT yielded a non-significant MD (MD: 0.36; 95% CI: -0.68–1.40). The study that used LO CIMT yielded a significant difference in favor of the experimental group (difference: 2.18; 95% CI: 1.82–2.54)

Figure 5.2c shows a significant homogeneous MD for the QOM (MD [fixed], 1.11; 95% CI 0.81–1.41; Z=7.24; P<0.001; I<sup>2</sup>=42%).

Pooling the two studies assessing QOM with a HI CIMT application resulted in a non-significant MD (MD: 0.30; 95% CI: -0.60–1.21). The study that used LO CIMT yielded a significant difference in favor of the experimental group (difference: 1.21; 95% CI: 0.89–1.53).

### ***Grooved Pegboard Test***

Figure 5.2d shows a significant homogeneous MD for the two studies<sup>18, 21</sup> that evaluated the GPT for dexterity (MD [fixed], 0.05; 95% CI: 0.02–0.09; Z=2.86; P=0.004; I<sup>2</sup>=0%). Both studies used HI CIMT.

## **DISCUSSION**

This systematic review, including 5 RCTs with a total of 106 participants, suggests an overall trend towards positive effects of LO and HI CIMT during the acute or subacute phase after stroke. Although MDs were not significant for all outcome measures, all total MDs (HI and LO CIMT combined) were in favor of the experimental group. Subgroup analyses for HI CIMT and LO CIMT resulted in positive and significant MDs for LO CIMT for all outcome measures, in contrast to HI CIMT. In line with the VECTORS study,<sup>8</sup> in which the patients in the HI CIMT group showed even lower gains compared to those in the control group and to the LO CIMT group, the current meta-analysis suggests that LO CIMT may be more beneficial during the acute or subacute phase than HI CIMT. However, the sizes and number of included studies that evaluated the effects of CIMT during the acute or subacute phase were rather

small. As a consequence, our drawn conclusions should be interpreted with caution, since the summarized findings can easily be overturned by one small neutral or negative study. In addition, the relatively small number of patients recruited for the included trials illustrates the difficulty of performing studies of this nature.<sup>22</sup> For the VECTORS study,<sup>8</sup> for instance more than 35 patients had to be screened for each enrollee (3%), while in the study by Ro et al.,<sup>21</sup> 8 (4%) out of the 187 screened patients enrolled in the trial, which also emphasizes the difficulty of generalizing the results.<sup>22</sup> However, all participants enrolled in one of the studies completed the entire intervention period and most studies<sup>18-20</sup> emphasized that implementation of the applied form of CIMT, which varied between 1.5 hours and 3 hours of therapy each day, is feasible in acute stroke rehabilitation.

Positive effects of CIMT were found at the activity level (ARAT, MAL, GPT) as well as at the impairment level (FM-arm) of the International Classification of Functioning, Disability and Health (ICF). However, scores at the activity level may also improve as a result of increased use of compensation strategies.<sup>23</sup> Future studies should therefore investigate what exactly patients learn when they improve. On the other hand, although improvement on the FM-arm purportedly reflects improvement at the impairment level, the FM-arm score includes 4 subsections: shoulder-arm, wrist, hand and coordination,<sup>24</sup> so it remains unclear what exactly changes when FM-arm scores improve. For instance, evidence for favorable effects of (m)CIMT on hand function is still weak, so more differentiated research is required.

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Between the included studies heterogeneity was found. One of the reasons for heterogeneity is the variation in the inclusion criteria concerning upper limb motor function, which differed between studies. Most studies required some proximal and distal voluntary activity,<sup>18, 20, 21</sup> whereas both of the studies by Dromerick only required proximal activity.<sup>8, 19</sup> Since the presence of finger extension may reflect the intactness of some fibers of the corticospinal tract system in the affected hemisphere, finger extension is an important prognostic determinant for upper limb outcome.<sup>25</sup> Therefore, such differences in inclusion criteria might also have a substantial influence on the overall intervention effects. Since the functional outcome of the upper limb is mainly determined by the skills of the hand and not by the transport function of the arm itself,<sup>26, 27</sup> the presence of some distal hand function in terms of visible control of some finger (and/or thumb) extension at onset may be conditional for a positive effect of CIMT. Another reason for heterogeneity might be the variation in the duration of therapy and constraining. For instance, the study by Page et al.<sup>20</sup> differed substantially from the others in terms of the length of therapy (i.e. 10 vs 2 weeks). Additionally, the original CIMT protocol consists of three main elements: (1) repetitive, task oriented training, (2) constraining use of the more affected upper limb and (3) a transfer package of adherence-enhancing behavioural methods to transfer

gains made in the laboratory or clinical setting to the patient's real-world environment.<sup>28</sup> The first two elements are well described in all articles, but it is unclear how the studies have applied the transfer package. Finally, although all studies recruited patients within 2 weeks after stroke onset, the time since stroke onset varied between studies, from a mean of 4.4 days in the study by Page et al.<sup>20</sup> to a median of 11 days in the study by Boake et al.<sup>18</sup> Since recovery mechanisms such as resolution of diaschisis and restitution of non-infarcted penumbral areas may play an important role in spontaneous neurological recovery during the first days post stroke,<sup>29</sup> small differences in the timing of the start of the study may not only have affected the rate of recruitment but also the probability of the sample to regain dexterity after stroke.<sup>25</sup> The observed heterogeneity between the studies are probably not due to the methodological quality of the studies, since PEDro scores were more or less comparable. However, because of the heterogeneity and the variety in patient populations, caution is required when comparing studies and combining results.

The suggestion that a lower dose of CIMT may be more beneficial than a potentially harmful higher dose during the acute phase after stroke, is largely based on the results of the VECTORS study.<sup>8</sup> These findings are, however, supported by several animal studies<sup>9, 10, 30, 31</sup> which have found that intensive practice of the affected limb in rats is detrimental if it occurs too soon after the infarction, when cells in the penumbral tissue are presumably still vulnerable.<sup>32</sup> For example, Kozłowski et al.<sup>10</sup> found a disrupted recovery of function after immobilization of the nonimpaired forelimb during the first 15 days.<sup>22</sup> Additionally, Shallert et al.<sup>31</sup> showed that when rats with unilateral lesions of the forelimb area in the motor cortex were forced to use the affected limb for the first 7 days post injury, the injury size increased in terms of a significantly greater loss of brain tissue compared with rats that were forced to use the affected limb from days 8 to 15. These results suggest that the region surrounding an infarct is vulnerable “to behavioural pressure” in the early days to weeks post stroke. Additionally, Bland et al.<sup>33</sup> suggested that the effects of forced use of the affected arm during the first 10 days may differ depending on cortical or subcortical involvement. They found that overuse of the affected limb in rats with a distal middle cerebral artery occlusion, resulting in an exclusively cortical infarction, worsened the outcome. In contrast, in rats with a proximal middle cerebral artery occlusion, damaging striatal neurons, not overuse but disuse of the affected limb during the first 10 days worsened the outcome, whereas overuse of the affected limb had no effect. These results suggest that neurons in the cortex may respond differently to early demands than neurons in the striatum.<sup>33</sup> It remains speculative which mechanisms are responsible for these differences.<sup>33</sup> On the other hand, Murphy and Corbett<sup>11</sup> emphasized in their review that several animal studies indicate that a critical period of heightened neuroplasticity may exist after stroke. Many of the genes

and proteins that are important for neuronal growth, synaptogenesis and the proliferation of dendritic spines are expressed at their highest levels during the first days to weeks after stroke.<sup>11</sup> A better understanding of the mechanisms responsible for upper limb recovery, as well as the optimal time windows in which these mechanisms function is a prerequisite to improve our knowledge about intervention effects on upper limb recovery and the optimal timing for intervention during the acute or subacute phase after stroke.<sup>34</sup> Therefore, future RCTs on (m) CIMT should not only investigate clinical effects but should also simultaneously explore the time-dependent macroscopic changes observed by using non-invasive techniques such as Transcranial Magnetic Stimulation (TMS) and functional Magnetic Resonance Imaging (fMRI) as a reflection of neuroplasticity.<sup>35</sup>

The present systematic review has some limitations. First, the number of studies was small, preventing a thorough sensitivity analysis to investigate the impact of (m)CIMT dosage on functional outcome. For now, we were only able to explore the differential effects by making a distinction between HI CIMT and LO CIMT, using forest plots. Second, we cannot rule out publication bias. In particular, small RCTs with negative, non-significant or inconclusive results are less likely to be submitted or accepted for publication in the literature.

In summary, the current review suggests that LO CIMT may be more beneficial during the acute or subacute phase than HI CIMT. However, because of the relatively small number of heterogeneous studies caution is required in the interpretation of the results. More research is needed, focusing on the mechanisms responsible for upper limb recovery and the optimal time windows for intervention. Currently, a single-blinded, randomized multicentre trial is being conducted in The Netherlands.<sup>34</sup> One of the main aims of this multicenter trial, under the acronym “EXPLICIT-stroke” (EXplaining PLasticITY after stroke) is to determine the effectiveness of a form of early applied mCIMT on stroke recovery mechanisms i.e. neuroplasticity, compensatory movements and upper limb neuromechanics.

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5