



Interventions to promote work participation after ischaemic stroke: A systematic review

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ABSTRACT

Only a disappointingly low proportion of patients successfully engage in professional activities after ischaemic stroke. This systematic review maps all contemporary evidence regarding interventions aiming to promote return-to-work in survivors of ischaemic stroke. We performed a search according to Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines and searched five reference databases. Prospective trial registers and grey literature were also assessed, and we executed backwards and forward reference searching. The study protocol was registered in PROSPERO (CRD42017077796). The search yielded 444 records of which 174 were duplicates. Backward and forward reference searching resulted in 808 unique records. Eleven articles were retained for full-text analysis and two met the selection criteria. A controlled before-after study showed beneficial effects of intravenous thrombolytic treatment in patients with moderate to severe acute ischaemic stroke. A retrospective study with low methodological quality reported improved vocational outcome of an outpatient rehabilitation program in patients with mild to moderate ischaemic stroke. We conclude that there currently is insufficient evidence regarding the effectiveness of interventions to promote return-to-work in patients with ischaemic stroke, though intravenous thrombolytic therapy has shown beneficial effects and there are indications that rehabilitation programs may also be advantageous.

1. Introduction

Professional reintegration after ischaemic stroke is a major societal problem as many patients fail to return to work despite excellent functional outcome. Patients not resuming professional activities are denied the positive effects that the work environment may offer, such as a social context, promotion of well-being, and a sense of purpose and satisfaction. Moreover, they exhibit an increased risk of recurrent stroke or other cardiovascular complications. The health-economic picture is also dire as no less than 45% of stroke survivors are younger than 65 years, accounting globally for 5.2 million first strokes yearly and one-third of the \$1.75 trillion annual costs associated with stroke in the United States alone are attributable to the inability of stroke survivors

to return to work.

Especially neuropsychological factors, such as mood disorders and cognitive complaints, may negatively affect professional reintegration [1–5]. Patients not resuming professional activities are denied the positive effects that the work environment may offer, such as a social context, promotion of well-being and a sense of purpose and satisfaction [6,7]. Moreover, they are at increased risk of recurrent stroke or other cardiovascular events [8], depression and higher mortality rates [9].

The success rate of stroke survivors to return to work varies greatly (9–91%), which mainly may be attributed to variability between studies regarding the definitions of stroke and work, the differences in study populations, and dissimilar follow-up periods [10,11]. It may not

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be justified to amalgamate patients with cerebral ischaemia and those with intracranial haemorrhage when assessing professional activity because their therapeutic options and prognosis, including the probability to return-to-work, differ greatly [12–20].

Contrasting sharply with the plethora of studies evaluating prognostic variables for employment after stroke [21–25], only sparse data are available on the efficacy of interventions aiming to promote work participation in ischaemic stroke survivors. This knowledge gap has been recognized by the US Department of Education, which already in 2008 has selected the enhancement of functional and employment outcomes of stroke patients as her top research priority [26]. Along the same lines, internationally accepted guidelines on stroke management recognize the lack of good quality evidence on interventions to promote reemployment and advocate return-to-work as a quality indicator for stroke care [27,28]. Nevertheless, there is a large unmet need regarding possible strategies to assist ischaemic stroke patients with their professional reintegration.

2. Objectives

This systematic review aims to identify and evaluate the effectiveness of any intervention reported in the literature to promote return-to-work after ischaemic stroke. All interventions aiming at neurological or functional recovery are included, as are interventions focusing specifically on professional reintegration that for instance could include forms of job coaching or work place adaptations.

3. Materials and methods

3.1. Criteria for considering studies for this review

The review was conducted in accordance with the Preferred Reporting Items for Systematic Review guidelines [29]. As randomised controlled trials may not often be conducted in this context, the choice was made to also accept controlled before-after studies, prospective cohort studies, time-series, before-after comparisons without a concurrent control group, quality of care studies, and comparison with arbitrary controls. The intervention could be compared to 'no intervention', a sham intervention or to any other type of intervention aiming to support a return to professional activities. Cross-sectional studies (i.e. surveys looking at the present situation only), prognostic studies (evaluating prognostic factors only) and case reports were not accepted.

Only studies reporting on patients aged 18 years or older who were diagnosed with ischaemic stroke were eligible. Publications reporting on mixed populations containing patients diagnosed with ischaemic stroke were also taken into account provided the results of patients with ischaemic stroke could be distilled from the data or if patients with ischaemic stroke composed the large majority of the study population (i.e. $\geq 80\%$ of all patients).

Any intervention aiming to support a return to professional activities was taken into account. An intervention is defined as any kind of active manipulation of the environment, behaviour or disease with the intention to improve or promote health.

The primary outcome parameter was the proportion of participants who successfully returned to work after ischaemic stroke. Various definitions of return-to-work can be found in the literature [24]. According to international standards, returning to employment, unpaid labour, leisure, unemployment or retirement are all regarded as a vocation [30]. This complete data set was taken into account when available, with a return to competitive employment (paid work) as the key parameter [24,31,32]. Secondary outcomes could involve the time interval between stroke onset and return to professional activities, the proportion of participants who maintained professional activities over time, the time spent off work or being on sick leave, or the score on a validated and standardized workability scale.

3.2. Search methods

We searched MEDLINE (PubMed interface), EMBASE, Web of Science, Scopus and the Collaborative Review Group Register. The search for possibly relevant studies was based on the publications' titles and abstracts. To maximize the output, we used dedicated controlled vocabulary (MeSH for MEDLINE, Emtree for EMBASE) and free words, including applicable keywords, their synonyms, related terms and alternative spellings thereof. The search syntax was translated for each interface (Supplement Table 1). The search included records in English, French, German, Spanish and Dutch. There was no limitation regarding the date of publication. Papers published online ahead of print were also considered.

We also consulted all relevant prospective trial registers (www.clinicaltrials.gov; www.clinicaltrialsregister.eu; <http://www.strokecenter.org/trials/>; <http://isrctn.com>) and the grey literature (www.opengrey.eu; <https://www.ahrq.gov/>). We screened the reference lists of all relevant publications for additional papers (backward reference searching). Furthermore, related publications were screened via exploration of all citing articles of relevant studies in Web of Science and linkages via similar articles in MEDLINE (forward reference searching).

3.3. Data collection and analysis

For each search, we documented the type of database and interface, the date of the search, the implemented search strategy and its results. All results were exported to Endnote (Thomson Reuters Scientific, New York) in RIS format and deduplicated before being loaded into Rayyan software [33]. Review Manager 5.3 (Cochrane Collaboration) was used for documentation of the review, data storage and analysis of the study results.

Three investigators used the Rayyan tool to independently assess the titles and abstracts of all records identified in the searches against the inclusion and exclusion criteria. One reviewer (RB) evaluated all records and each of the other two reviewers (AVE and LG) assessed half of the records. To promote reliability among reviewers, collection of all pertinent information was guided using a form for evaluation of records. Any conflicting decisions regarding the selection of a record were resolved in discussion with a fourth reviewer (MM). Full-text papers were acquired for all records that were deemed to be relevant or where eligibility was unclear. All full-text papers were studied independently by three investigators as described above and relevant data were recorded using a data extraction and assessment form. Potential moderators and confounders of study outcomes were assessed using the Risk Of Bias In Non-randomised Studies of interventions tool [34].

4. Results

Supplement Table 1 provides a detailed overview of the results per database. The number of publications retrieved via PubMed, EMBASE, Web of Science, Scopus, the Collaborative Review Group Register, clinicaltrials.gov, clinicaltrialsregister.eu, Stroke Trials Registry, ISRCTN.com, Opengrey.eu and AHRQ.gov was 78, 117, 87, 144, 11, 1, 0, 0, 0, 3 and 3, respectively. Fig. 1 provides an overview of the literature search and recruitment process. The search was executed on October 30th 2017 and yielded 444 potentially relevant records, of which 174 duplicates were removed. Based on screening of the titles and the abstracts, 259 records were excluded because the population could not be identified as (mainly) consisting of patients diagnosed with ischaemic stroke ($n = 66$) and at least 18 years old ($n = 18$). 189 studies were excluded because they did not evaluate an intervention to promote return-to-work using an appropriate study design and in 162 records, no relevant and well-defined outcome parameter was reported. The inter-rater agreement was 96.2% and consensus was obtained through discussion for the remaining records. Eleven articles met the

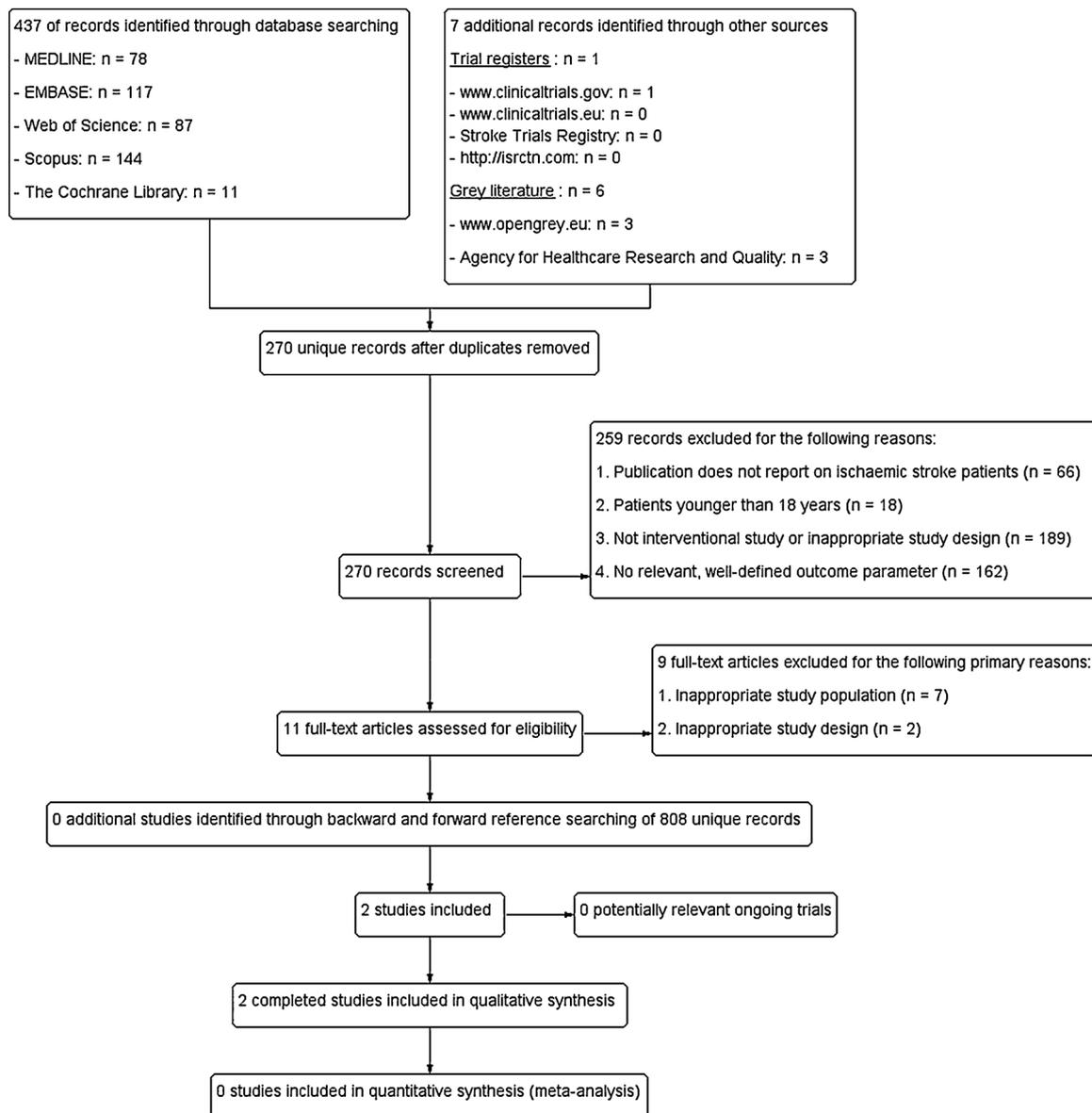


Fig. 1. PRISMA study flow diagram.

selection criteria and were retrieved for full-text evaluation. Backward and forward reference searching yielded 1123 records. After removal of 315 duplicates, 808 unique records were evaluated against the selection criteria but none were retained for full-text evaluation. Two papers met the predefined selection criteria for inclusion in this systematic review. Supplement Table 2 lists the nine full-text articles that were not retained for review and the rationale thereof.

The characteristics of the included studies are detailed in Table 1. In terms of study design, one prospective [32] and one retrospective study [31] were identified. There were no randomised controlled trials, one controlled before-after study without randomisation [32] and one before-after comparisons without concurrent control group [31]. The total number of ischaemic stroke patients within the studies ranged from 172 to 276, with a total of 315 patients receiving an intervention to promote return-to-work. Both populations are characterized by a male preponderance (> 60%) and rather advanced age (mainly patients in their fifties), yet differ substantially regarding the setting (outpatient vs. inpatient), stroke severity, stroke latency, type of the intervention, and duration of follow-up. The methodological quality of the study by Perna et al. is estimated to be low based on the retrospective design, the absence of a comparator, the short duration of follow-up and the high risk

of bias. The study reported by Stefanovic et al. may have sufficient quality, though caution is warranted given the lack of randomisation, restrictive patient selection criteria and variability of follow-up duration. The risk of bias is assessed in Table 2. The overall risk of bias is estimated to be high in the study by Perna et al. but low in the controlled before-after study reported by Stefanovic et al. We did not undertake a meta-analysis given the heterogeneity of the two identified reports regarding study design, setting, population, type of intervention, duration of follow-up and methodological quality. In the absence of data, a health economic evaluation was not executed either.

The effect size of a postacute outpatient program consisting of twice-weekly treatment for 3 months including neuropsychological services, social work, physical, occupational and speech therapy depending on the participant's needs. On a weekly basis, participants received one hour of neuropsychological support, one hour of social work services and 2 to 4 h of physical and occupational therapy, is moderate for the key outcome parameter [31]. Out of 123 participants with competitive employment before ischaemic stroke, 39 were able to return to this status (31.7%). Many others were active in modified jobs or as a homemaker, volunteer or student. The proportion of inactive patients, however, increased from 19 to 48 for those in leisure and from 7

Table 1
Characteristics of included studies.

Reference	Design	Setting	Population	Description of intervention	Outcomes	Follow-up	Methodological quality
Perma [31]	Single-centre retrospective study	Outpatient program at the Institute for Rehabilitation and Research, Houston, Texas, USA	Diagnosis: ischaemic stroke N= 172 Age: 56.8 y (12.5) * Male gender: 64.0% Stroke severity: mild to moderate Stroke latency: less than 6 months Inclusion criteria: - diagnosis - ischaemic stroke	Program consisting of twice-weekly treatment for 3 m, including 1 h of neuropsychological services per week, 1 h of social work services per week, 2 to 4 h physical therapy per week, 2 to 4 h occupational therapy per week, and speech therapy.	1. Proportion of patients returning to professional activities (before stroke/after intervention): - Competitive employment: 123/39 - Modified job: 22/7 - School: 3/6 - Homemaker: 4/11 - Volunteer: 5/18 - Leisure: 19/48 - Nonproductive: 7/25 2. MPAL-4 (before intervention/after intervention: 46.19 (15.59) / 25.16 (15.27)*)	At completion of program (3 m)	Low
Stefanovic [32]	Before-after comparison without a concurrent control group		- completion of program Diagnosis: acute ischaemic stroke				
	Single-centre controlled before-after study with measurement of outcomes in intervention and control group	Inpatient Stroke Unit at the Neurology Clinic Belgrade, Serbia	N: I= 143, C= 133 Age: I: 52 y (44-56), C: 52 y (44-56) # Male gender: I: 72.7%, C: 69.2% Stroke severity: moderate to severe Stroke latency: < 24 h Inclusion criteria: - diagnosis ischaemic stroke with onset < 24 h - pre-stroke functional independence - working in paid employment before stroke onset	I: intravenous thrombolytic therapy C: no intravenous thrombolytic therapy	1. Return to full-time paid job: I: 43/143 C: 20/133 2. Return to any kind of job: I: 56/143 C: 42/133	3 y# (range 1-7 y)	Sufficient

C, control; h, hours; I, Intervention; m, months; MPAL-4, Mayo Portland Adaptability Inventory-4; y, years. * Data given as mean (standard deviation); # Data given as median (interquartile range).

Table 2
Risk of bias in included studies.

Reference	Bias due to confounding of effect of intervention	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcome	Bias in selection of the reported result	Overall bias
Perna [31]	High: variability in the components of the intervention depending on participants' characteristics.	High: only participants who completed the program were included. Dropouts were excluded from analysis.	Low: intervention group is clearly defined. Information used to define intervention group was recorded at the start of the intervention. Classification of the intervention status was probably not affected by knowledge of the outcome.	Unclear: there is insufficient information available to assess potential bias due to deviations from intended interventions.	Low: outcome data were available for (nearly) all participants.	High: assessment of the MPAI-4 may have been influenced by knowledge of the intervention received. Outcome assessors were probably aware of the intervention received by participants.	Low: the reported effect is probably not the result of multiple outcome measurements, multiple analyses or evaluation of subgroups.	High
Stefanovic [32]	Low: no confounding effect of the thrombolytic therapy to be expected.	Low: intervention group and controls were adequately matched and selection of patients was not influenced by other characteristics than the time delay between stroke onset and possible initiation of thrombolytic therapy.	Low: both groups are clearly defined using information at the start of the intervention. Classification of the intervention status was not affected by knowledge of the outcome.	Low: there are no indications of deviations from the intended intervention. There were no important co-interventions. There are no indications that interventions were not successfully implemented for most participants.	Low: outcome data are available for all participants. No participants were excluded due to missing data on the intervention status or on other variables.	Low: outcome measures were probably not influenced by knowledge of the intervention. Methods of outcome assessment were comparable in both groups. There were no systematic errors in measurement of the outcome related to in the intervention received.	Low: the reported effect is probably not the result of multiple outcome measurements, multiple analyses or evaluation of subgroups.	Low

MPAI-4, Mayo Portland Adaptability Inventory-4.

to 25 for nonproductive persons. The mean change in the Mayo Portland Adaptive Inventory-4 from start to end of the program was 21 points, corresponding with relevant improvement of disability for most patients. Yet the standard deviation of 13 points suggests substantial variation between individuals.

Compared to controls, treatment with intravenous thrombolytics resulted in roughly a doubling of the proportion of patients with moderate to severe ischaemic stroke who were able to return to a full-time paid job (15.0% vs. 30.1%) [32]. The hazard ratio for returning to a full-time job was 2.07 (95% confidence interval, 1.21–3.51) for those treated with thrombolytics compared to patients not receiving this intervention. Using regression analysis, intravenous thrombolysis was identified as an independent predictor for returning to a full-time job. Notably, this effect was obtained without additional interventions and all patients were able to maintain their professional activities. However, both in the intervention and the control group, up to 44% of patients with excellent functional outcome failed to resume professional activities. Patients not receiving thrombolytic therapy were more likely to engage in part-time professional activities. The majority of patients returning to professional activity were able to do so 3–12 months after the stroke.

5. Discussion

This review is the first to systematically evaluate available literature covering interventions to promote return-to-work in patients suffering from an ischaemic stroke. An extensive search in five reference databases, multiple trial registers and grey literature using permissive selection criteria yielded only two relevant studies. Perna et al report on a retrospective study evaluating an outpatient program for patients with mild to moderate ischaemic stroke in the previous 6 months, providing twice-weekly treatment for 3 months consisting of neuropsychological services, social work, physical therapy and speech therapy [31]. This intervention resulted in a return to competitive employment for about thirty percent of patients after 3 months. However, these results require cautious interpretation given the low methodological quality. The study by Stefanovic et al. is a prospective controlled before-after study without randomisation evaluating the effect of intravenous thrombolytic therapy in patients with moderate to severe acute ischaemic stroke [32]. Thirty percent of patients receiving thrombolytic therapy returned to a full-time paid job, which was twice as high compared to the patients not receiving this treatment.

The strengths of this systematic review are its execution by an independent, experienced research team using the latest evidence and working on a prespecified protocol implementing a robust methodology for data abstraction and quality appraisal. Further, the search strategy did not restrict results by study design nor publication date. Non-English reports and information were also taken from additional sources, among which grey literature search and extensive forward and backward citation chasing.

Though not a weakness of the review methodology in se, only little relevant data covering this domain are currently available in the literature. The significant methodological and clinical heterogeneity of the included studies precludes quantitative analysis. The results are, therefore, limited to a qualitative description with questionable generalisability to real-life situations of ischaemic stroke survivors at vocational age. It should also be taken into account that professional integration may be influenced by many possible interventions, that in itself differ between various phases of stroke care. In the first hours after stroke onset, interventions may be directed at limiting ischaemic brain damage (e.g. by administration of recanalization treatments), whereas intensive rehabilitation care focusing on recovery of the neurological deficits generally is the mainstay in the first months after stroke. Thereafter, interventions may aim more at maximization of functional independence and social participation. In addition to the variability due to the different phases of stroke care, the relevance of

interventions also depends on the stroke severity and the residual neurological deficits.

Several studies were excluded from the analysis because they report on epidemiologic data or predictive parameters regarding return-to-work, but not on the evaluation of interventions to stimulate professional re-integration. The aggregated evaluation of heterogeneous study populations or ambiguity regarding the stroke subtype without the possibility to reliably extract data on ischaemic stroke patients was another frequent exclusion criterion. It may not be excluded that some relevant information was lost in the process. Also, it is not inconceivable that publications on the topic may be available in other languages than English, French, German, Spanish or Dutch. Yet, it is implausible that the number of studies reported in these languages would suffice to allow firm conclusion drawing. Confronted with the scarce results when using these criteria for the systematic review, one could consider changing the selection criteria and/or the goal of the review. However, we preferred to adhere to the prespecified criteria and objectives as described in the study protocol.

Except for the Psychosocial Outcomes In Stroke (POISE) cohort, the literature contains no traceable data regarding the effect of intravenous thrombolytic therapy on return-to-work after ischaemic stroke. The POISE study did not show a beneficial effect of thrombolytic therapy, which may be attributed to the very small sample size (17 patients) [35].

There is one other systematic review evaluating return-to-work after ischaemic stroke. This report, however, concentrates on epidemiologic information and predictive parameters for various vocational outcomes but contains no information regarding interventions to stimulate return-to-work [36]. Several reports evaluate return-to-work in study populations aggregating ischaemic and haemorrhagic stroke [21–25,30,37–40] or even various forms of acute brain injury [41–43]. Given the substantial differences in treatment options, secondary prevention, rehabilitation, and prognosis (including return-to-work) [12–20,44], these findings may not directly be translated to patients with ischaemic stroke. However, some reports provide valuable information to serve as a basis for future research. Workplace interventions tailored to the patient's functional ability and to specific professional challenges [38], resource facilitation [41] and dedicated occupational services [42,45] showed beneficial effects in these populations, whereas advances in conventional rehabilitation programs may not have yielded such a result [39]. Nevertheless, the variability between miscellaneous vocational interventions is high and their most effective components and optimal target population remain to be elucidated [30].

Furthermore, a very recent systematic review and meta-analysis by Duong et al. uncovers considerable variability in operational definitions of return-to-work and inconsistency regarding the follow-up intervals in stroke patients [46]. Rightly, the authors recommend the development and implementation of a broadly accepted definition of return-to-work and standardized follow-up intervals as this would improve comparability between future studies evaluating interventions promoting professional reintegration of stroke patients.

There currently is insufficient evidence to conclude that vocational rehabilitation would be superior to conventional rehabilitation to improve return-to-work [40]. Multimodal, individualized and integrative approaches yet are promising as they reckon with the person's impairments, coping and motivation, but also with job demands and adaptability, social support and the functioning of rehabilitation services [25,43].

6. Conclusions

Although return-to-work is recognized as a pivotal individual and societal objective for ischaemic stroke survivors, our main finding regrettably is the striking lack of scientific data on the matter. There currently is insufficient evidence regarding the effectiveness of

interventions to promote professional reintegration in this population. Intravenous thrombolytic therapy has shown beneficial effects and there are indications that rehabilitation programs may also be advantageous, especially when conventional and vocational techniques are integrated and tailored at the individual level.

Continued research on strategies to improve return-to-work after ischaemic stroke is needed. The inclusion of vocational outcome parameters in future studies evaluating emergency stroke treatments, secondary prevention and rehabilitation would be a major step forward.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

The authors declare that they have no conflict of interest concerning this publication.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.clineuro.2019.105458>.

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