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European Journal of Physical and Rehabilitation Medicine 2021 June;57(3):460-71
DOI: 10.23736/S1973-9087.21.06887-8

SYSTEMATIC REVIEW

THE ITALIAN CONSENSUS CONFERENCE CICERONE

Robotic-assisted gait rehabilitation following stroke: a systematic review of current guidelines and practical clinical recommendations

Rocco S. CALABRÒ [1] *, Gregorio SORRENTINO [2], Anna CASSIO [3], Davide MAZZOLI [4], Elisa ANDRENELLI [5], Emiliana BIZZARINI [6, 7], Isabella CAMPANINI [8], Simona M. CARMIGNANO [9], Simona CERULLI [10], Carmelo CHISARI [11], Valentina COLOMBO [12], Stefania DALISE [11], Cira FUNDARÒ [13], Valeria GAZZOTTI [14], Daniele MAZZOLENI [15], Miryam MAZZUCCHELLI [16], Corrado MELEGARI [17], Andrea MERLO [4, 8], Giulia STAMPACCHIA [17], Paolo BOLDRINI [18], Stefano MAZZOLENI [19], Federico POSTERARO [20], Paolo BENANTI [21], Enrico CASTELLI [22], Francesco DRAICCHIO [23], Vincenzo FALABELLA [24], Silvia GALERI [25], Francesca GIMIGLIANO [26], Mauro GRIGIONI [27], Stefano MAZZON [28], Franco MOLTENI [29], Giovanni MORONE [30], Maurizio PETRARCA [31], Alessandro PICELLI [32], Michele SENATORE [33], Giuseppe TURCHETTI [34], Donatella BONAIUTI [35] on behalf of Italian Consensus Conference on Robotics in Neurorehabilitation (CICERONE)

[1]IRCCS Centro Neurolesi Bonino-Pulejo, Messina, Italy; [2]Department of Medicine and Rehabilitation, Polyclinic of Monza, Monza-Brianza, Italy; [3]Spinal Cord Unit and Intensive Rehabilitation Medicine, AUSL Piacenza, Villanova sull'Arda and Castel San Giovanni, Piacenza, Italy; [4]Gait and Motion Analysis Laboratory OPA Sol et Salus, Torre Pedrera, Rimini, Italy; [5]Department of Experimental and Clinical Medicine Università Politecnica delle Marche (UNIVPM), Ancona, Italy; [6]Spinal Cord Unit, Department of Rehabilitation Medicine, Gervasutta Hospital, Udine, Italy; [7]Azienda Sanitaria Universitaria Friuli Centrale (ASU-FC), Udine, Italy; [8]Neuromotor and Rehabilitation Department, LAM-Motion Analysis Laboratory, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy; [9]Rehabilitation Therapeutic Center, Tramutola, Potenza, Italy; [10]IRCCS A. Gemelli University Polyclinic Foundation, Rome, Italy; [11]Section of Neurorehabilitation, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [12]Montecatone Rehabilitation Institute, Imola, Bologna, Italy; [13]Unit of Neurophysiopathology, ICS Maugeri, Montescano Institute, Pavia, Italy; [14]Centro Protesi Vigorso di Budrio, Istituto Nazionale Assicurazione Infortuni sul Lavoro (INAIL), Budrio, Bologna, Italy; [15]School of Physical and Rehabilitation Medicine, University of Milano-Bicocca, Milan, Italy; [16]Elias Neuroriabilitazione, Parma, Italy; [17]Unit of Spinal Cord, University Hospital of Pisa, Pisa, Italy; [18]Italian Society of Physical and Rehabilitation Medicine (SIMFER), Rome, Italy; [19]Department of Electrical and Information Engineering, Polytechnic of Bari, Bari, Italy; [20] Department of Rehabilitation, ASL12, Viareggio, Lucca, Italy; [21]Pontifical Gregorian University, Rome, Italy; [22]Pediatric Neurorehabilitation, Bambino Gesù Children's Hospital, Rome, Italy; [23]Department of Occupational and Environmental Medicine, Epidemiology and Hygiene, INAIL, Monte Porzio Catone, Rome, Italy; [24]Italian Federation of Persons with Spinal Cord Injuries (FAIP Onlus), Rome, Italy; [25]Fondazione Don Carlo Gnocchi Onlus, Milan, Italy; [26]Department of Mental and Physical Health and Preventive Medicine, Luigi Vanvitelli University of Campania, Naples, Italy; [27]National Center for Innovative Technologies in Public Health, Italian National Institute of Health, Rome, Italy; [28]Unit of Rehabilitation, ULSS (Local Health Authority) Euganea, Camposampiero Hospital, Padua, Italy; [29]Villa Beretta Rehabilitation Center, Valduce Hospital, Costa Masnaga, Lecco, Italy; [30]Santa Lucia Foundation IRCCS, Rome, Italy; [31]The Movement Analysis and Robotics Laboratory, Bambino Gesù Children's Hospital, Rome, Italy; [32]Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy; [33]Associazione Italiana Terapisti Occupazionali (AITO), Rome, Italy; [34]Sant'Anna High School, Institute of Management, Pisa, Italy; [35]Piero Redaelli Geriatric Institute, Milan, Italy

*Corresponding author: Rocco S. Calabrò, IRCCS Centro Neurolesi Bonino-Pulejo, S.S. 113 Contrada Casazza, 98124 Messina, Italy.
E-mail: salbro77@tiscali.it

ABSTRACT

INTRODUCTION: Stroke is the third leading cause of adult disability worldwide, and lower extremity motor impairment is one of the major determinants of long-term disability. Although robotic therapy is becoming more and more utilized in research protocols for lower limb stroke rehabilitation, the gap between research evidence and its use in clinical practice is still significant. The aim of this study was to determine the scope, quality, and consistency of guidelines for robotic lower limb rehabilitation after stroke, in order to provide clinical recommendations.

EVIDENCE ACQUISITION: We systematically reviewed stroke rehabilitation guideline recommendations between January 1, 2010 and October 31, 2020. We explored electronic databases (N.=4), guideline repositories and professional rehabilitation networks (N.=12). Two independent reviewers used the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, and brief syntheses were used to evaluate and compare the different recommendations, considering only the most recent version.

EVIDENCE SYNTHESIS: From the 1219 papers screened, ten eligible guidelines were identified from seven different regions/countries. Four of the included guidelines focused on stroke management, the other six on stroke rehabilitation. Robotic rehabilitation is generally recommended to improve lower limb motor function, including gait and strength. Unfortunately, there is still no consensus about the timing, frequency, training session duration and the exact characteristics of subjects who could benefit from robotics.

CONCLUSIONS: Our systematic review shows that the introduction of robotic rehabilitation in standard treatment protocols seems to be the future of stroke rehabilitation. However, robot assisted gait training (RAGT) for stroke needs to be improved with new solutions and in clinical practice guidelines, especially in terms of applicability.

(*Cite this article as:* Calabrò RS, Sorrentino G, Cassio A, Mazzoli D, Andrenelli E, Bizzarini E, *et al.*; Italian Consensus Conference on Robotics in Neurorehabilitation (CICERONE). Robotic-assisted gait rehabilitation following stroke: a systematic review of current guidelines and practical clinical recommendations. Eur J Phys Rehabil Med 2021;57:460-71. DOI: 10.23736/S1973-9087.21.06887-8)

KEY WORDS: Stroke; Lower extremity; Gait; Systematic review.

Introduction

Stroke represents the leading cause of disability and the second cause of death world-wide.[1] The main neurological impairment after stroke is hemiparesis that frequently affects the subject’s ability to perform activities of daily living (ADL), including walking.[2] As people age, the incidence of age-related diseases, such as stroke, increases and therefore, considering the lower mortality rate of acute stroke, prevalence rate and burden of such disease is growing worldwide.[3] About one-third of stroke survivors do not regain independent walking ability and in those who succeed, gait is mainly characterized by an asymmetrical pattern, with a decreased walking speed and increased stride width and double support phase.[4, 5]

Robot-assisted gait rehabilitation (RAGT) is the technology that has shown the greatest advances in the rehab field in the last decades.[6] The robot-assisted rehabilitation devices focus on motor learning (resulting from intensive, repetitive, and task-oriented motor activities) that requires the subject’s effort, attention and involvement.[6, 7] Moreover, robotic devices can help understand individual needs by adapting rehabilitation to the patients’ impairment and providing the therapist with more objective measures of their performance.[6] With these perspectives, robotic devices could be integrated into clinical practice for stroke survivors.[8]

Nowadays several robotic devices for stroke rehabilitation are available. Generally speaking, a robot is “a reprogrammable, multifunctional manipulator designed to move material, parts, or specialized devices through variable programmed motions to accomplish a task.”[9] There is a significant gap between engineers that create devices for rehabilitation and the underlying neuroscience related to motor deficits and rehabilitation after stroke. Indeed, there are different schools of thought aimed at investigating/creating the desired goal and type of interaction, the physical implementation of the method, and the neural mechanisms that are intended to be targeted or evoked. Each device may be designed using different strategy to analyze and rehabilitate gait disorders following stroke, *i.e.* 1) targeted sensorimotor pathways (using inter-limb coordination mechanisms, cutaneous and haptic perception, equilibrioception, audition and vision); 2) physical implementation (by goal directed and task oriented training, electrical and magnetic stimulation, exoskeletons and powered orthoses, body weight support, treadmill training and foot plates); and 3) interaction goal and type (through error augmentation *via* physical interaction and error correction *via* physical interaction).[10]

Robots used in rehabilitation are generally categorized into end-effector (EE) and exoskeleton (Exo) types according to their mechanical structures.[11, 12] It is noteworthy that exoskeletons are more commonly used in patients with more severe deficits, including those with complete hemiplegia, whilst those with mild to moderate deficit may better benefit from the functional challenges offered by end-effectors.[6] For example, Lokomat,[13] BLEEX,[14] HAL[15] and LOPES[16] are typical exoskeleton robots, while Gait-Trainer,[17] G-EO System[18] and Haptic Walker[19] are end-ef-

TABLE I.—*Characteristic of the different robots' subcategories.*

Types	Use	Characteristic	Models
Treadmill-based exoskeleton robots	RS	Usually composed of a weight support system and runs on a treadmill through the lower-limb exoskeleton frame	Lokomat, lokohelp, and active leg exoskeleton (ALEX).
Leg orthoses and exoskeletons	RS/FD	To assist subjects with lower-limb motor dysfunction to complete the routine activities such as walking, standing, sitting, and going up- and downstairs	Active ankle-foot orthosis (AAFO), knee-ankle-foot orthosis (KAFO), and hybrid assistive limb (HAL).
Foot plate-based end-effector devices	RS	Suspension weight loss gait rehabilitation robot, it was based on the movement of the lower limb to stimulate the muscles of the lower limb orderly and assist the subjects to complete gait training	The foot plate-based end-effector devices consist of the gait trainer GTI, haptic walker, and the G-EO Systems. Gait trainer (GTI).
Platform-Based end-effector robots	RS	The subject is included in the control loop by continuously monitoring his/her state, extracting objective biomechanical and electromyographic indicators and, consequently, adapting the level of assistance provided by the robotic platform	Ruegst ankle, ARBOT, and parallel ankle robots.

RS: rehabilitation session; FD: functional design.

fector robots. According to their rehabilitation principles, exoskeleton robots can also be further divided into two other sub-categories (*i.e.* treadmill-based and leg outhouses to train over ground), while the end-effector robots have footplate-based and platform-based types[17, 19-22] (Table I).

Exoskeleton robots are usually fixed in various parts of the human limb, while producing different forces/torques that could allow the interaction with the limb redundant degrees of freedom. End effector robots are instead easier to adapt to the patient, as there is no restriction on the movement.[23] Indeed, previous works[24, 25] demonstrated the efficacy of end effectors (with regard to the gait trainer) only in people affected by postacute stroke, whereas exoskeletons had controversial results both in the acute and subacute phases.

Rationale and objectives

There are still gaps between research evidence and robotic device use in clinical practice.[26] Guidelines may allow clinicians using the current evidence by supporting effective interventions and advising against treatments that are not evidence-based.[27] Many countries have their own guidelines, with different content and scope, level of evidence and detail, more or less updated, making it difficult to implement them in the clinical practice.[28]

It is not always easy to evaluate the quality of published guidelines. To this end, the Appraisal of Guidelines for Research and Evaluation II (AGREE II) could be considered a valid tool,[29] given that in recent years it has been widely used in the rehabilitation field.[30-32]

The present review seeks to investigate the indications, methodological quality and the conformity of stroke guidelines dealing with lower limb robot-assisted rehabilitation using the AGREE II tool. Moreover, it aims at identifying gaps and limits of the current evidence-based practice providing recommendations for potential improvements.

Evidence acquisition

We followed the Equator Network reporting recommendations outlined in the Appraisal of Guidelines, Research and Evaluation (AGREE) II instrument[32] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[33] Our systematic search used popular search databases, guidelines repertories, and professional rehabilitation networks in line with SPIDER tool strategy.[34] PubMed, ISI Web of Knowledge, Embase and SciELO Citation Index databases were searched independently and synchronously by two authors (RSC, AC) up to October 31, 2020. Guideline repositories included Australian National Health and Medical Research Council clinical practice guidelines, Canadian Medical Association Infobase of Clinical Practice Guidelines, National Library for Health Guidelines Database (UK), US National Guideline Clearinghouse, Guidelines International Network, New Zealand Guidelines Group, e-Guidelines, NICE, Scottish Intercollegiate Guidelines Network (SIGN), Guidelines International Network, National Guideline Clearinghouse, National Collaborating Centre for Chronic Conditions. Search terms included words related to brain stroke, rehabilitation, guidelines, robotic therapy, and lower limb.

Search strategy

The following search strategy was used: ("stroke" [MeSH Terms]) AND ("rehabilitation" [MeSH Terms]) AND ("practice guideline" [publication type]) OR "recommendation" OR "guideline" (publication type) OR "consensus development conference" (publication type) AND ("2010/01/01" [date - publication]: "2020/10/31" [date - publication]).

Guideline inclusion criteria

We included all guideline recommendations for Robot-Assisted Gait Training (RAGT) in adults with stroke published between January 1, 2010 and October 31, 2020. A guideline was considered as a set of the latest recommendations based on evidence appraisal and consensus from a single writing group, even if such recommendations were published separately. Only English written guidelines were considered for eligibility. Our search was focused on guidelines referring to stroke rehabilitation and, in particular, those considering the use of robotic devices for lower limb rehabilitation.

Guideline analysis

Titles and abstracts were screened, and full-text papers reviewed independently by two reviewers (RSC and AC) using predetermined criteria, as in the previous paragraph. In case of disagreement, an independent reviewer (DB) mediated to achieve consensus. Reviewers identified information, treatment recommendations and their level of evidence/grade of recommendations (when available). Moreover, each guideline was checked for the year, edition, country, national/international recommendations contained. Textual descriptive synthesis of recommendations was used to analyze the scope, context and consistency of the founded guidelines. Then, the AGREE-II instrument[32] was used to appraise the methodological quality of the included guidelines. It consists of 23 key items organized within 6 domains followed by 2 global rating items ("overall assessment" or general evaluation). Each domain captures a unique dimension of guideline quality: scope and purpose (items 1-3), stakeholder involvement (items 4-6), rigor of development (items 7-14), clarity and presentation (items 15-17), applicability (items 18-21) and editorial independence (items 22-23). The tool uses a 7-point agreement scale from 1 (strongly disagree) to 7 (strongly agree) for each item. Each guideline was independently rated by four raters. Domain scores were calculated by summing up all the scores of the individual items and by scaling the total as a percentage of the maximum possible score for that domain as follow:

$$\frac{\text{Obtained\_score} - \text{Minimum\_possible\_score}}{\text{Maximum\_possible\_score} - \text{Minimum\_possible\_score}} \times 100$$

When minimum/maximal possible score is calculated respectively:

$$\frac{\text{Strongly\_disagree}}{\text{Strongly\_agree}} \times \text{N(items)} \times \text{N(appraisers)}$$

As suggested by the AGREE II,[32] we decided to give precedence two domains (applicability and overall assessment), taking into account a quality threshold of >70% for the main domains.

Finally, recommendations from the guidelines were synthesized to provide a unified version.

Evidence synthesis

The flow diagram in Figure 1 shows our search results. A total of 1219 records were found. After having screened the title and abstract, 1094 were excluded because they did not meet the research purpose. Finally, only 10 guidelines matched the inclusion criteria. The detailed information about the guidelines is available in Table II.[7, 35-43] They cover seven different regions/countries all over the world; three out of the ten guidelines do not report the funding. Moreover, four of the included guidelines focused on stroke management, the other six on stroke rehabilitation.

Synthesis of recommendations for RAGT use

Rehabilitation assisted by robotic devices is generally recommended to improve lower limb motor function and strength,[44] although the exact characteristics of people

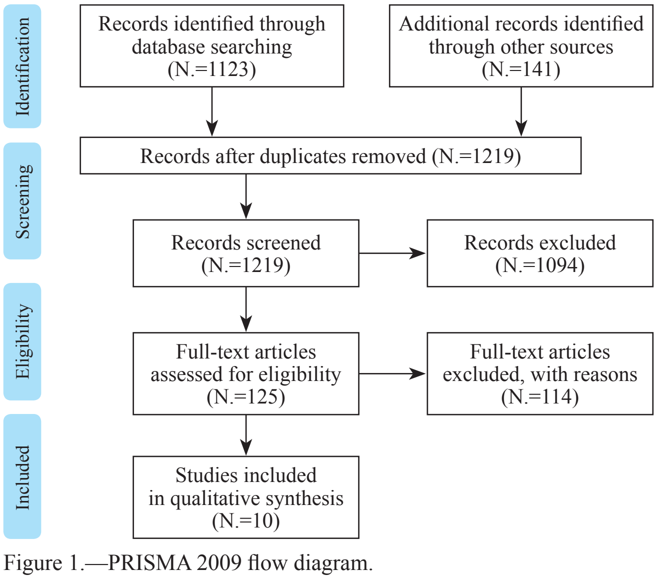

Figure 1.—PRISMA 2009 flow diagram.

TABLE II.—*Characteristics of included clinical practice guidelines.*

Study	Year	Edition	Country	Funding	Focus	Evidence source
American Heart Association/American Stroke Association[7]	2016	2	USA	R	SR	Css, RCT, MA/SRL
Stroke Foundation of New Zealand[35]	2010	1	New Zealand	R	SM	RCT, MA/SRL
Department of Veterans Affairs, Department of Defense[36]	2019	4	USA	NR	SM	Css, RCT, MA/SRL
Royal College of Physicians[37]	2017	5	UK	R	SM	Css,RCT, MA/SRL
Stroke Foundation[38]	2017	5	Australia	R	SM	Css, MA/SRL
Canadian stroke best practice recommendations 2020[39]	2020	6	Canada	R	SR	Css, RCT, MA/SRL
Scottish Intercollegiate Guidelines Network[40]	2010	2	Scotland	NR	SR	RCT, MA/SRL
Royal Dutch Society for Physical Therapy[41]	2014	2	Netherland	NR	SR	RCT, MA/SRL
Evidence-Based Review of Stroke Rehabilitation[42]	2016	1	Canada	R	SR	RCT, MA/SRL
National Clinical Guideline for stroke NICE[43]	2013		UK	R	SR	RCT, MA/SRL

NR: not reported; R: reported; SM: stroke management; SR: stroke rehabilitation; Css: Cochrane search strategies; RCTs: randomized controlled trials; MA/SRL: meta-analysis systematic review of the literature.

with stroke who may benefit from robotic devices as well as the right timing to use the robotic devices are still unknown. Generally, guidelines suggest that electro-mechanical assisted training can be proposed to a selected group of people affected by stroke, when the necessary equipment is already available and healthcare professionals are proficient in the use of the equipment. All guidelines agree that RAGT should not be used in place of conventional gait rehabilitation. Robot-assisted training for people with stroke who are unable to walk autonomously has shown to improve their walking speed, the distance walked, heart rate, sitting and standing balance, walking ability and the performance in the activities of daily life (Table III).[7, 35-43]

Only, two guidelines[7, 35] specified the disease phase for recommendations. The American Heart Association/American Stroke Association[7] states that the use of electro mechanically assisted, and weight-relieving gait training (including RAGT) seems to be indicated in non-ambulatory people or in those with poor walking ability in subacute stroke. According to the Stroke Foundation of New Zealand[35] electro mechanically assisted gait rehabilitation should be built to provide as much practice as possible within the first six months after stroke.

At least three guidelines[37, 41, 43] advice for the use of RAGT in patients who are more severely impaired. On the contrary, other guidelines[36, 40] affirm that there is insufficient evidence to recommend the use of robotic devices following stroke. None of the guidelines provides clear indications about the protocols (*i.e.* frequency, intensity, time and type of robotic device) to use at different stages of the disease. Poor details are also provided about the type of recommended robotic device (*i.e.* end effector *vs.* exoskeleton), interaction and controllers.

Nonetheless, the evidence-based review of stroke rehabilitation[42] states that data on the superiority of the Lokomat over conventional or treadmill therapy are conflicting, whereas end-effectors robots lead to better walking-related outcomes than conventional treatments.

Quality and methodology of the guidelines

According to the AGREE II, Table IV[7, 35-43] shows the methodological quality of the included guidelines across six domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability and editorial independence.

All of the guidelines included in this work have a sufficient general evaluation (GE); some of them[36, 37, 39-41, 43] have an excellent GE. Applicability was higher than our threshold in half of the guidelines.[35, 37-40]

No domain was considered highly inadequate, but stakeholder involvement, with a scoring of 43 given to the American Heart Association/American Stroke Association guidelines[7] (which also got the lowest score in applicability). With regard to the scope and purpose, nearly all of the guidelines, but N. 8 and 40, clearly described their overall objectives, health questions and target populations perform well.

The clarity of presentation and rigor of development domains were considered adequate in all of the guidelines, with excellent results in 8 out of 10 of them. Most guidelines did not describe the facilitators and barriers of their applications and did not sufficiently consider the costs of applying their recommendations. No inadequacies are reported in the Editorial Independence domain, with excellent results for some guidelines[37, 38, 41, 43] The underperforming guidelines essentially did not clearly provide financial support and conflict of interest statement information.

TABLE III.—*Main findings of the Recommendation about the use of robotic lower limb rehabilitation after stroke.*

Development organization	Findings	Grading system	Level of evidence*/ Grade of recommendation°
American Heart Association/ American Stroke Association[7]	Adjuvant therapy with electro-medical devices is more effective than traditional therapy alone in people with acute / subacute strokes (within the first 3 months) and unable to walk. Walking training with robots (always in association with standard rehabilitation therapy) can be taken into consideration in the rehabilitation treatment of people with stroke. Immediately after the onset of a stroke, the use of mechanically assisted and weight-relieving gait training (treadmill with weight relief, gait trainer, robotic devices) is indicated in non-ambulatory people with stroke or with poor walking ability. If fixed exoskeletons (such as the Lokomat) and end-effectors (such as GT3) seem to give good results, there is still no evidence for wearable devices such as Ekso-GT and Indego.	AHA concerning classes and levels of evidence	Class IIa; Level A
Stroke Foundation of New Zealand[35]	One or more of the following robotic assisted rehabilitation techniques can be used in addition to conventional ground walking therapy: Cueing of cadence Mechanically assisted gait (via treadmill or robotic device) Training with virtual reality Rehabilitation should be structured to provide as much practice as possible within the first six months after stroke.	Guidelines International Network (G-I-N) and SIGN systems	Grade B Grade B Grade C Grade A
Department of Veterans Affairs, Department of Defense[36]	There is insufficient evidence to recommend for or against the use of robotic devices during gait training There is weak evidence to propose virtual reality to enhance gait recovery.	Self-making system	GRADE I
Royal College of Physicians[37]	Those who are able to walk independently should be rehabilitated with a treadmill with or without weight relief or with other tools capable of enhancing the walk (no specific reference is made to robotics, but some devices may fall within the recommendation). Those unable to walk independently should be treated with electro-medical devices (including robots). Robot-assisted movement therapy should only be used as an adjunct to conventional therapy when the goal is to reduce arm impairment or in the context of a clinical trial.	Not applicable	Not available
Stroke Foundation[38]	Strong recommendation: It is useful to undertake, as much as possible, a repetitive and tailored exercise aimed at making the gait (or its components) more functional. Weak recommendation: In people with stroke with walking difficulties, one or more of the following interventions can be used – virtual reality Electromechanically assisted gait training (by treadmill or automated/robotic mechanical devices). Biofeedback Cueing of cadence Electrical stimulation	Not applicable	Not available
Canadian stroke best practice recommendations 2020[39]	Electromechanical (robotic) gait training devices could be considered for subjects who would not otherwise exercise gait (i.e. more impaired patients). They should not be used in place of conventional walking therapy.	Self-assessed	Early-Level A; Late-Level A
Scottish Intercollegiate Guidelines Network[40]	Robotic rehabilitation could be used to increase the possibilities to regain the ability to walk independently in people with more severe stroke, although the time taken to achieve the goal may be longer than that of subjects receiving conventional gait training. There are not enough prompts to determine if the effect of this intervention occurs as a result of the electro-mechanical device or as a result of the additional time spent in rehabilitation. Electro-mechanical assisted training can be proposed to a selected group of people with stroke, when the necessary equipment is already available and healthcare professionals are proficient in the use of the equipment.	SIGN system	Level A
Royal Dutch Society for Physical Therapy[41]	Robot-assisted training for people with stroke who are unable to walk autonomously has been shown to improve their walking speed, the distance walked, the heart rate, the sitting and standing balance, the walking ability and the performance in the basic activities of daily life (BADL), compared to conventional therapy (including walking on ground). The combination of robot-assisted gait training with functional electrostimulation of the paretic leg has been shown to improve sitting and standing balance and walking ability of people with stroke, compared to conventional therapy. Poor evidence on the use of VR	Self-making system	Level 1 Grade E
Evidence-Based Review of Stroke Rehabilitation[42]	Data on the superiority of the Lokomat over conventional or treadmill therapy are conflicting. End-effectors robots perform better on walking-related outcomes than conventional treatments.	Self-assessed	Level 1
National Clinical Guideline for stroke NICE[43]	People who are unable to walk independently at the start of treatment do not seem to benefit from training with a treadmill but may benefit from electromechanical assisted gait training.	Self-assessed	Level 3-4

Level of evidence: level 1 (systematic review and metanalysis); level 2 (RCT); level 3 (comparative, case-control studies); level 4 (case series, case studies). Grade of the recommendation: A (body of evidence can be trusted to guide practice, as in level 1-2); B (body of evidence can be trusted in most situations, as in level 2 studies with moderate bias); C (body of evidence provides some support for recommendations; level 3); D (recommendations must be applied with cautions; levels 4, or 2-3 with high bias); grade I (insufficient information to formulate recommendations; grade E (Nil grade system used, alternative approach based on evidence and consensus).

TABLE IV.—*AGREE-II scores for each domain (Dom.) and general evaluation (GE).*

Development organization	Dom 1	Dom 2	Dom 3	Dom 4	Dom 5	Dom 6	GE
	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applica-bility	Editorial independence	
American Heart Association/American Stroke Association[7]	58	44	64	77	53	62	65
Stroke Foundation of New Zealand[35]	75	79	80	72	71*	64	67
Department of Veterans Affairs, Department of Defense[36]	85	76	88	80	57	79	83*
Royal College of Physicians[37]	86	84	95	88	78*	83	88*
Stroke Foundation[38]	81	84	88	90	71*	86	75*
Canadian stroke best practice recommendations 2020[39]	84	86	88	82	84*	75	87*
Scottish Intercollegiate Guidelines Network[40]	82	90	82	83	76	63	80*
Royal Dutch Society for Physical Therapy[41]	86	84	95	91	61	80	81*
Evidence-Based Review of Stroke Rehabilitation[42]	58	83	63	77	61	70	63
National Clinical Guideline for stroke NICE[43]	84	79	91	88	65	82	80*

A cut off of >70 has been used to assess the quality of the guidelines.
*Recommended guidelines.

Discussion

As far as we know, this is the first systematic review on current guidelines and practical clinical recommendations on RAGT following a stroke. The main goal of a medical guideline is to provide an evidence-based and easily accessible tool to guide clinicians in choosing the treatment strategy, summarizing the available published literature. We found only 10 international guidelines published from 2010 to 2020 dealing with this topic.

Which guidelines to recommend? Quality issues

To evaluate the quality and methodological issues of the included guidelines we used the AGREE II. The tool is used for different purposes in different contexts and the relative importance of the six domains is expected to vary depending on the user's needs. We have considered a threshold of 70% and our domain of particular interest was applicability (beyond overall assessment), which was higher than our threshold in half of guidelines.[35, 37-40] Thus, the Canadian Stroke Recommendations,[39] having the highest overall assessment and applicability, could be indicated as the best guidelines to follow concerning RAGT in stroke.

Nonetheless, the quality of the reviewed guidelines was heterogeneous, and the domain that generally got the lower scores was "applicability." The main factor which reduced applicability was that only about two-thirds of the guidelines have been developed specifically for stroke rehabilitation, while the others are dedicated to stroke management, resulting in little space for robot-assisted rehabilitation with poor indications to properly address RAGT, *i.e.* patients who may benefit from a specific robotic device, the optimal time window and dose (number of repetitions, duration of each session), frequency and duration of the treatment.

The highest-rated domains were instead "rigor of development" and "clarity of presentation," as most guidelines described the criteria for selecting the evidence, the methods for formulating the recommendations with easily identifiable key recommendations.

The different methods used by each guideline developmental group may explain some of the differences observed between guidelines. Other explanations may be related to the year of guideline development, date of search, and eligibility criteria.[31]

Evidence-based recommendations and gaps

This systematic review on stroke guidelines further supports that, in more severely impaired people with stroke, RAGT increases the possibility to regain an independent gait, and this should be considered as either "add on" treatment[35-39] or even in substitution of the traditional rehabilitation.[40-43] The improvement in gait recovery with electromechanically assisted gait could be explained by the fact that the intervention provides the opportunity to perform a more intensive, repetitive, and task-oriented training than would be possible with the conventional over-ground walking alone.

Several guidelines suggested the combination of RAGT with other non-standard rehabilitation therapies, such as functional electrical stimulation (FES)[35, 41] and virtual reality (VR),[7, 35, 36, 38, 41] to further improve lower limb motor outcomes.

Only three guidelines[35, 38, 41] give indication for the use of VR in patients with stroke, but no mention exists on whether VR should be applied alone or during RAGT (*e.g.* Lokomat-Pro), as RAGT plus VR leads to better functional outcomes.[45] With the exception of the American Heart/Stroke Association,[7] no clear indications emerge from current guidelines concerning people suffering from chronic stroke, although there is no significant evidence that the robot-assisted treatment may provide better effects than the conventional therapy in this phase.[16, 24] The emerging lack of interest in the guidelines for this phase does not mean that the chronic phase has not been investigated in the literature. Different studies,[46, 47] in fact, demonstrate an "add on" positive effects of RAGT on conventional rehabilitation therapy in chronic individuals with stroke.

Even though it is widely recognized that most spontaneous behavioral recovery tends to occur within the first 3 months after stroke onset, different patterns of recovery may then emerge depending on many complex factors, and therefore, neuroplasticity phenomena with functional recovery may also be present in the chronic phase. Such processes and related outcomes should be taken into consideration to better understand when to expect recovery, managing the most appropriate treatment, and determine the timing of rehabilitation, including the robotic assisted one. Nonetheless, most of the evidence on chronic stroke comes from pilot or observational studies, and every conclusion on the utility of RAGT in this patient population is controversial.[48] Future guidelines should focus on the different phases of stroke, indicating the features of the patients that may better benefit from a specific robotic device. In fact, patients that are more impaired seem to benefit more from RAGT, although the optimal time window has not been yet clarified.

Unfortunately, guidelines are poor in details about the type of recommended robotic device (*i.e.* end effector *vs.* exoskeleton), although the guidelines by the American Heart/Stroke Association state that both fixed exoskeletons (such as the Lokomat) and end-effectors (such as GT3) seem to lead to good outcomes, whereas there is still no evidence for wearable devices such as Ekso-GT and Indego.[7] Moreover, there is some evidence that people with stroke undergoing end-effector training had better outcomes than those submitted to exoskeleton devices.[7, 24, 42] The different features of the devices are fundamental for their "real" applicability in clinical practice, although their use also depends on the patient's impairment and disability. Because locomotion is the result of complex dynamic interactions between feedback mechanisms and a central controller in the brain, the rehabilitation methods that work best use a fundamental understanding of this coordination of human gait. It is well-known that in order to be effective, therapy should begin as soon as possible and provide an intensive training that incorporates multiple sensory mechanisms in a structured way.[10]

RAGT for rehabilitation purposes are designed with the intent of evoking the muscle activation synergies and neural plasticity through specific repetitive motor coordination exercises. To this end, it has been shown that RAGT interact with a multilevel autonomic neural circuitry, *i.e.* inter-limb coordination[49] composed by locomotion patterns from spinal circuits and descending pathways, that modulate real-time gait corrections[10] in both hemiplegic and in healthy subjects.[50] Furthermore, end-effectors and exoskeleton devices drive the gait kinetic during all the gait cycle or only during limited specific gait phase, dealing with internal and external body force. However, it is still far from being established and recommended when and how and for whom a specific device could be used.[44]

A main problem when dealing with rehabilitation guidelines is the lack of consensus around standardized outcome measures to assess the effects of RAGT.[51] None of the included Guidelines deals with any specific assessment tool, and this is one of the gaps that should be covered in the near future. Several scales assess different aspects of the gait recovery following stroke: 1) the 10-Meter Walk Test (10MWT) widely used to evaluate the speed of walking; 2) the 6-Minute Walk Test (6MinWT) to evaluate endurance of walking; 3) the Rivermead Mobility Index (RMI) to assess mobility; and 4) the Berg Balance Scale (BBS) to evaluate balance. Another widely used tool is the Functional Ambulation Category (FAC), 6-point scale assesses ambulation ability by determining how much human assistance the stroke patient needs during the gait regardless of whether or not they use a personal assistive device. Geroin *et al.*[51] suggested a customizable set of outcome measures to adapt to the different hypotheses. For instance, the Motricity Index (MI), Modified Ashworth Scale (MAS), FAC, 10MWT and 6MinWT could be chosen for discriminative measurements of subjects' features with reference to body function and structure, and activity domain, respectively. In contrast, if an assessor desires to predict a specific ability that people with stroke may be able to perform after treatment, the RMI and PASS (postural assessment scale for stroke) or TIS (trunk impairment scale) may be used.[52] In literature, few studies utilized standardized multifactorial tools, like gait analysis, to study the RAGT's attitude in modifying the gait pattern in a cohort of people with stroke.

Finally, current guidelines lack the optimal dose (number of repetition and time of therapy), frequency and duration of the robot-assisted rehabilitation treatment. To this end, the Advanced Robotic Therapy Integrated Centers (ARTIC) network was created in order to collect data from people with stroke using RAGT in a wide variety of clinical settings, as well as to develop guidelines concerning the use of RAGT, with regard to Lokomat.[53]

The strength of our review was the broad search conducted based on the Equator Network reporting recommendations outlined in the Appraisal of Guidelines, Research and Evaluation (AGREE) II instrument[32] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[33] Moreover, this is the first review to summarize the available international guidelines for individual RAGT intervention in patients with stroke, to provide clinicians with evidence based information in their rehab practice.

Guidelines are formulated to provide clinicians with practical indications to improve patient's care and cure in clinical settings. However, the reviewed international guidelines to date have only partially addressed RAGT in patients with stroke, with poor indications for clinicians. As the use and diffusion of robots and electromechanically assisted devices is growing in the rehabilitation field, an international guideline aimed at indicating the specific device to use as well the timing of treatment, frequency and dosage (*i.e.* number and duration of training sessions, exercises and period of training) is needed. We believe that different training with different approaches and kinds of devices should be used in the different stages of the disease. Indeed, according to principles of neurosciences, walking training should be provided in the most physiological possible way and this is not always possible, as the device should fit with the patient's disability and comorbidities. The more severe the disability of the subject affected by stroke, the higher the assistance and the constraint level provided by the robot/device. In contrast, in presence of an improved subject's ability, machine constraint should be reduced, allowing an adequate level of training intensity and increasing training variability and training sensorimotor stimuli with "lighter" devices. Finally, when subjects are able to walk in an autonomous manner they might have a reduced or no indication for the walking training assisted by a grounded robot. This theoretical schema will allow adequate training with the proper intensity and repetition, preventing physical deconditioning and learning non-use. To this end, the level of walking ability measured by the FAC could be a good marker for device use in subjects affected by stroke as proposed in a previous work.[44]

This systematic review supports the use of robot-assisted therapy, coupled with conventional physical therapy, to improve gait in people with stroke (Table V). The reviewed international guidelines altogether suggest that the earlier the training starts, the better the gait recovery will be. Moreover, people with stroke that are more impaired seem to benefit more from RAGT. Despite the increasing evidence of robotic device effectiveness on lower limb strength and motor function in gait rehabilitation after stroke, the quality of the reviewed guidelines was heterogeneous, and the lack of consensus around standardized outcome measures further complicates the comparison between different studies. Some of the reviewed guidelines are of good/excellent quality and, for example, indications by the Canadian Stroke Guidelines[39] may be followed in clinical practice because of their high AGREE scores. Current guidelines need to be improved, especially in the field of applicability, given that this was the domain with the lower scores. Guidelines with higher applicability scores are fundamental, because such domain affect more than the other the use of the devices in clinical practice. Indeed, facilitators and barriers will impact the application of guideline recommendations, requiring additional resources in order to apply them. Guidelines should clarify the selected subgroups with stroke that could benefit from robotic devices, as well as the optimal time window and

TABLE V.—*The main recommendations and gaps of the available guidelines for robotic rehabilitation following stroke.*

Main recommendations	Gaps
Electromechanical devices, including robots for gait training, could be considered for subjects who would not otherwise exercise gait (i.e. more impaired patients). RAGT should not be used in place of conventional gait training. Better outcomes are obtained within the first 3-6 months after stroke.	No indication on the specific device to use either in the different phases of stroke or on a specific aim. Integration of Robotic therapy in the individual rehabilitation plan. Poor information on the timing and dosage as well as frequency of the rehabilitative training, according to patient's characteristics (treatment protocol). Absence of specific assessment tools to evaluate RAGT after effects. Improvement of the learning transfer from robotic to daily activities.

RAGT: robotic assisted gait training.

dose, frequency and duration of the robot-assisted rehabilitation treatment. Moreover, guidelines are also poor in details about the type of recommended robotic device, although there is some evidence that end-effectors may lead to better outcomes.[24] People with stroke and caregivers' perspective and usability of RAGT should also be taken into consideration in order to improve compliance and involvement in the rehabilitation path, as demonstrated in other neurological disorders.[54]

Limitations of the study

The present study has some limitations. Firstly, it was based only on English language guidelines, so we could have missed some national guidelines, *e.g.* the Italian SPREAD guidelines on stroke.[55] Secondly, the AGREE II instrument did not involve the judgment of the recommendation opinions decided with a high variability among guidelines. The AGREE system is a useful tool for the qualitative assessment of the methodological rigor in the guidelines drafting. Nevertheless, it does not deal with the specific (*i.e.* substantial) issues of the topic since it does not involve an assessment of the cost-benefit of the robot-assisted rehabilitation on people with stroke. Indeed, effectiveness is probably considered by the authors more important than economic sustainability, also given that the former is less difficult to prove than economic efficiency and sustainability. Nonetheless, from a healthcare system perspective, to fully understand the cost-effectiveness ratio of robot-assisted rehabilitation is fundamental to provide people with stroke with the best treatment options. A recent study has indicated that robot-assisted therapy had a better economic outcome than conventional therapy.[56] Moreover, we have not preregistered the work in a dedicated database, including PROSPERO and INPLACY.

Finally, guidelines development groups have used different methods to create recommendations, leading to variability in both quality and scope. International guidelines are needed to overcome this issue.

Conclusions

In conclusion, although evidence may support the use of RAGT in clinical practice to train people with stroke, future research is needed for introducing new rehabilitation approaches overcoming the limitations of the current technology and indicating the "more appropriate prescription" of robotic devices as a potentially effective rehabilitation tool.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Rocco S. Calabrò, Gregorio Sorrentino, Anna Cassio and Donatella Bonaiuti have given substantial contributions to manuscript conceptualization and supervision, Davide Mazzoli, Elisa Anderenelli, Emiliana Bizzarrini, Isabella Campanini, Simona M. Carmignano, Simona Cerulli, Carmelo Chisari, Valentina Ccolombo, Stefania Dalise, Daniele Mazzoleni, Miryam Mazzucchelli, Corrado Melegari, Andrea Merlo, Cira Fundarò and Giulia Stampacchia to quality assessment of the RCT review, Paolo Boldrini, Stefano Mazzoleni, Federico Posteraro, Paolo Benanti, Enrico Castelli, Francesco Draicchio, Vincenzo Falabella, Silvia Galeri, Frabcesca Gimigliano, Mauro Grigioni, Stefano Mazzon, Franco Molteni, Giovanni Morone, Maurizio Petrarca, Alessandro Picelli, Michele Senatore and Giuseppe Turchetti to organization committee supervision and scientific technical committee of the CICERONE consensus conference supervision, manuscript editing and revision, Rocco S. Calabrò, Gregorio Sorrentino, Anna Cassio, Giovanni Morone and Donatella Bonaiuti to manuscript supervision. All authors read and approved the final version of the manuscript.

Acknowledgements.—The present study has been carried out within the framework of the Italian Consensus Conference on "Rehabilitation assisted by robotic and electromechanical devices for persons with disability of neurological origin" (CICERONE), promoted by the Italian Society of Physical and Rehabilitation Medicine (SIMFER, Società Italiana di Medicina Fisica e Riabilitativa) and Italian Society of Neurological Rehabilitation (SIRN, Società Italiana di Riabilitazione Neurologica) (2019-2021)." The authors wish to acknowledge Dr. Antonina Donato for English editing.

History.—Article first published online: May 5, 2021. - Manuscript accepted: May 4, 2021. - Manuscript revised: April 27, 2021. - Manuscript received: February 15, 2021.