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REVIEW ARTICLE

Therapeutic strategies in vascular cognitive impairment: A systematic review of population, intervention, comparators, and outcomes

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Abstract

Introduction: Vascular cognitive impairment (VCI) is a common and heterogeneous condition, clinically and pathophysiologically, that still lacks approved treatment.

Methods: We reviewed evidence from randomized and non-randomized clinical trials in VCI to explore whether any therapeutic option warrants further investigation and to assess possible flaws in previous studies.

Results: We identified 118 studies after searching PubMed and Embase, including 19,223 participants and 5 different VCI subtypes. We found 63 different types of intervention (51 pharmacologic, 5 employing physical agent application, 7 rehabilitation approaches) compared with either placebo, best medical treatment, or other interventions. Treatment efficacy was assessed through 125 outcome measures (with a clearly pre-specified primary outcome in 50.8% of studies).

Discussion: Therapeutic trials in VCI have been heterogeneous in terms of populations, types of interventions, and outcomes. Overall, a lack of clear pathophysiological rationale for tested interventions seems to emerge, together with the need to homogenize trial study design

KEYWORDS
cerebrovascular disease, clinical trial, cognitive impairment, outcomes, study design, therapy, vascular cognitive impairment

1 | INTRODUCTION

Vascular cognitive impairment (VCI) is considered the second most common form of dementia after Alzheimer's disease (AD).[1] However, the concept of VCI is quite broad and, at least in one of the most commonly used definitions,[2] it encompasses a wide spectrum of different severity degrees of cognitive dysfunctions, from mild cognitive decline to dementia, variously associated with diverse pathological and clinical substrates (e.g., multi-infarct dementia, post-stroke dementia, subcortical ischemic vascular dementia, and small vessel disease).

Over the years, several different therapeutic approaches have been tested in patients affected by VCI, but no approved disease-modifying or symptomatic treatment has been registered yet. In fact, the many trials performed have reported negative or non-conclusive results. Various reasons have been put forward to explain this lack of efficacy.[3] First, besides a lack of intervention efficacy, heterogeneity

of the included populations, both in terms of patient inclusion criteria and cognitive decline severity, has often been blamed. Second, the use of outcome measures not primarily designed for VCI (e.g., because originally conceived for and derived from the AD field) could have underestimated the possible therapeutic efficacy of treatments. Finally, the short duration of many of the trials and often the limited study size may have hindered the detection of treatment efficacy.

The dearth of therapeutic options for patients with VCI is a major issue considering the epidemiological proportions of this condition, and its overall impact on patient's functional independence and hence overall quality of life.[4] Moreover, it is well known that there is a vascular contribution to dementia of other origins (e.g., dementia due to AD, the co-occurrence of which was once referred to as "mixed dementia")[5] and beneficial approaches to the vascular component could be useful also for these patients.

Therefore, we decided to perform a systematic review to explore which therapeutic options have been tested to date in patients with VCI, and whether a meta-analysis of these data could provide new evidence. Furthermore, this systematic review has the additional aim of providing suggestions on how to better define population, outcome, and approaches for future trials. In this article, we present a systematic review of data that concerns definition of patients included in VCI trials, types of interventions, comparators, and outcome variables used in these trials.

2 | METHODS

This work was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines for Systematic Reviews[6] and was registered on PROSPERO (CRD: 4202127093).

We performed a systematic review to identify all randomized and non-randomized clinical trials testing therapeutic interventions for VCI. We searched for any interventional study that: (1) enrolled patients with any degree of cognitive impairment due to any kind of vascular substrate; (2) tested any intervention either versus placebo or versus any other treatment, evaluated according to any type of outcome. We excluded prevention studies (i.e., studies enrolling subjects with a cerebrovascular condition but who were not cognitively impaired at baseline), studies not including human subjects, studies that also included patients with other types of dementia (e.g., AD) and did not report results for VCI patients separately. Moreover, we excluded studies not published in English.

2.1 | Search strategy

We searched two databases, Medline (PubMed) (available at www.pubmed.ncbi.nlm.nih.gov) and Embase (Embase.com), from their respective dates of inception until December 31, 2021, using combinations of the following keywords, structured in a complex research string (complete research string reported in Supplementary Materials): "vascular", "small vessel", "small vessel disease", "post-stroke", "multi-infarct", "subcortical vascular", "subcortical ischemic", "subcortical ischemic vascular", "cognitive impairment", "mild cognitive impairment", "dementia", "VAD", "therapy", "management", "prevent", "clinical trial", "meta-analysis", "randomized controlled trial".

Search results were then uploaded to Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia (available at www.covidence.org). Duplicated entries were automatically reviewed and eliminated before screening.

2.2 | Screening process

Abstracts of all retrieved records were reviewed for adherence to inclusion/exclusion criteria independently by two reviewers, randomly chosen by the reviewing software from a pool of three (C.G., G.B., and F.M.). Full texts of included abstracts were then sought. Search entries for which the full text was not available (online or printed, or after direct contact with the corresponding author) were excluded. Retrieved full-text reports were finally assessed for adherence independently by reviewers in randomized pairs, similarly as above. Included reports were finally extracted by the two reviewers and data were collected in an electronic database. Discrepancies between raters at any step were resolved by consensus with a fourth expert investigator (L.P.). All logs relative to every search step were recorded.

RESEARCH IN CONTEXT

1. **Systematic review**: We identified 118 clinical trials that investigated therapeutic intervention for vascular cognitive impairment (VCI). We found great heterogeneity in terms of evaluated VCI subtypes, degree of cognitive impairment, types of intervention, and outcomes. Most of the studies tested intervention for a short period and only a few had a follow-up period.

2. **Interpretation**: Heterogeneity in study designs, both in tested interventions and outcomes used to evaluate therapeutic efficacy, has possibly hindered identification of effect. Further complication stems from the intrinsic complexity of VCI that features different pathophysiological entities within the VCI construct. A lack of clear pathophysiological rationale for tested interventions seems also to emerge in several studies.

3. **Future directions**: Design of more standardized trials featuring tailored and homogeneous outcomes, appropriately timed according to the natural history of disease, and testing interventions with a rationale clearly rooted in the multifaceted pathophysiology of VCI are needed.

2.3 | Data collection and analysis

The following data were extracted: study details (title, lead author, country in which the study was conducted, publication year, study aim, study design, start year and end year of the trial), participants' details (degree of cognitive impairment, VCI subtype, the inclusion criteria, relevant exclusion criteria, inclusion of other dementing condition other than VCI, the total number of patients), intervention classes (pharmacological, requiring application of a physical agent, and rehabilitation strategies) and single intervention(s); dosage or any relevant specifier, intervention duration, and employed comparator (placebo or other intervention); baseline population characteristic, overall and for each trial arm (total number of patients, age, gender distribution, education level); and outcomes assessed, together with their relative data collected at the different study time points.

Possible degrees of cognitive impairment considered were "dementia," "mild cognitive impairment," and "cognitive impairment"; this latter category was assigned when the degree of cognitive impairment was not specified in the report. The possible subtypes of vascular etiology ("labels") considered were "multi-infarct," "post-stroke," "acute/subacute stroke," "subcortical vascular," "small vessel disease," and "vascular"; this latter label was attributed when the etiology was defined as vascular without specifying the subtype.

For each study, we extracted a maximum of seven outcomes; if the study had more than seven outcomes, we included all primary outcomes and outcomes selected among the remaining ones, favoring the cognitive ones. To improve the homogeneity of the results, cognitive outcomes were extracted as a single outcome in the case of global cognitive assessment (e.g., Mini-Mental Status Examination [MMSE], Montreal Cognitive Assessment [MoCA]) and as an aggregated outcome in the case of multiple tests measuring the same cognitive domain (e.g., memory).

The quality of each included study was assessed by three reviewers independently, working in randomized pairs for each report, using the National Institute of Health Quality Assessment Tool of Controlled Intervention Studies (available at www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools; last update July 2021); any conflict was resolved together with a fourth expert reviewer.

Data synthesis and quantitative analysis of extracted data were performed; descriptive analyses for reported variables were then run with IBM SPSS Statistics software (v. 28.0).

3 | RESULTS

According to the research strategy, we recovered 2382 entries and obtained 1756 unique entries after automated duplication removal. After reviewing titles and abstracts, we finally included 316 reports. Of these, 80 were excluded because they were systematic reviews or meta-analysis, 19 because the included population did not fit the inclusion criteria (mostly because subjects with mixed dementia or AD were included without distinction from patients with VCI), 19 because they were not interventional studies, and three because they did not include any cognitive-related variable. A complete report of the systematic search steps according to PRISMA Guidelines for Systematic Reviews is depicted in Figure 1.

Data from 118 studies published between December 1984 and December 2021 were extracted, cumulatively including 19,223 patients; of these, 109 were randomized controlled trials, including 18,201 patients, and 9 were non-randomized studies, including 1022 patients. The nine non-randomized studies were: seven non-randomized experimental studies, in which the pharmacological intervention was compared with other drugs ($n = 6$) or in which outcomes were evaluated in a single interventional group ($n = 1$); two non-randomized control studies, in which patients allocated in control group received placebo. A table summary of included studies together with their more relevant characteristics and a table reporting their quality assessment are available in the Supplementary Materials (Table S1 and Table S2). The mean number of patients per study was 163 (SD 230, median 87.5, range 7–1787). The distribution of study size and study size over time is depicted in Figure S1 and Figure 2 respectively.

3.1 | Characteristics of included population(s) according to major nosological entities

Included patients differed both in terms of nosological entity (i.e., the vascular "substrate" underlying cognitive decline) and degree of cognitive impairment (mild cognitive impairment or dementia). Most studies included only patients with one VCI subtype ($n = 108$), whereas few studies included patients with two ($n = 10$). The "vascular" general label was employed 62 times, "multi-infarct" label 28 times, "small vessel disease" label 15 times, "post-stroke" label 12 times, and acute/subacute stroke 7 times. Nineteen studies included other dementing nosological entities (AD or mixed dementia) but data regarding patients with VCI could be analyzed separately.

The frequency of label use evolved progressively through time to include pathophysiologically nuanced labels that replaced older, more generic, ones (e.g., from multi-infarct dementia or vascular dementia in general toward post-stroke cognitive impairment, small vessel disease–related cognitive impairment, etc.); the frequency of use through time of different nosological labels is reported in Figure 3.

Concerning the degree of cognitive impairment, most studies ($n = 109$) included only one category of cognitive impairment patients. Eighty-seven studies included patients with dementia and 29 included patients with mild cognitive impairment (MCI), whereas the degree of cognitive impairment was not specified in 2 studies. Table 1 shows the distribution of the patients according to both etiological labels and degree of cognitive impairment.

3.2 | Patient enrollment criteria

Diagnostic criteria for each of the above-reported labels varied over the years. Inclusion criteria ranged from sets of criteria such as the
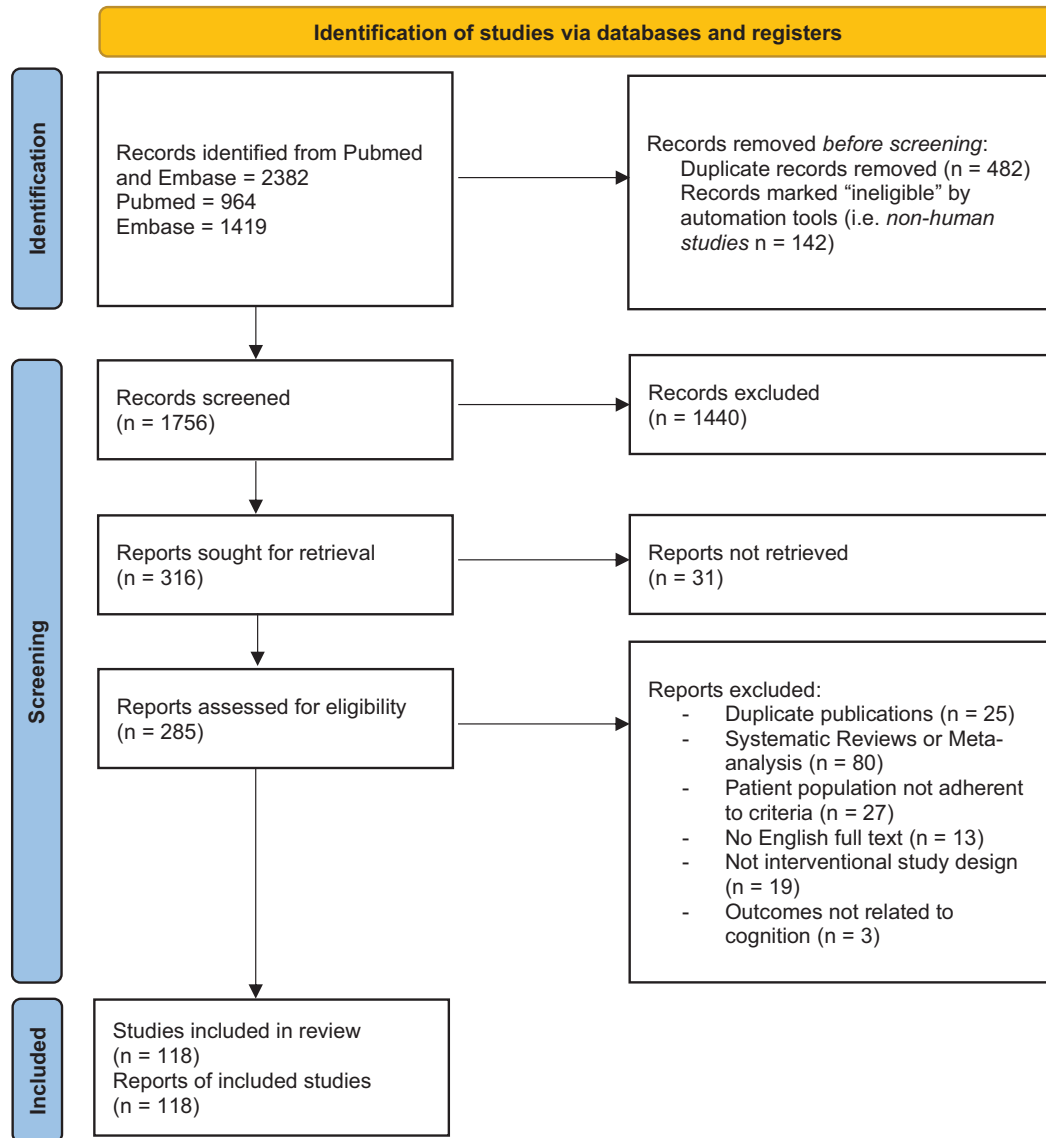
Identification of studies via databases and registers

Identification

| Records identified from Pubmed and Embase = 2382
Pubmed = 964
Embase = 1419 | → | Records removed *before screening*:
Duplicate records removed (n = 482)
Records marked "ineligible" by automation tools (i.e. *non-human studies* n = 142) |

Screening

| Records screened
(n = 1756) | → | Records excluded
(n = 1440) |

| Reports sought for retrieval
(n = 316) | → | Reports not retrieved
(n = 31) |

| Reports assessed for eligibility
(n = 285) | → | Reports excluded:
- Duplicate publications (n = 25)
- Systematic Reviews or Meta-analysis (n = 80)
- Patient population not adherent to criteria (n = 27)
- No English full text (n = 13)
- Not interventional study design (n = 19)
- Outcomes not related to cognition (n = 3) |

Included

| Studies included in review
(n = 118)
Reports of included studies
(n = 118) |

FIGURE 1 PRISMA flowchart. Flowchart of systematic review research and screening process according to 2020 PRISMA Guidelines for Systematic Reviews.

TABLE 1 Etiological labels reported in included studies stratified by degree of cognitive impairment.

	Post-stroke	Multi-infarct	Acute/subacute stroke	Vascular	Subcortical vascular	Total
Dementia	6	28	2	53	10	99
MCI*	11	0	5	11	7	34
Not reported in inclusion criteria	0	0	2	0	0	2
Total	17	28	9	64	17	135

Abbreviation: MCI, mild cognitive impairment.

National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria[7] or Diagnostic and Statistical Manual of Mental Disorders (DSM) (in its various versions), to clinical scales such as the Hachinski Ischemic Score[8] or various combination of measurements of cognitive decline (MMSE,[9] MoCA,[10] Alzheimer's Disease

Assessmeng Scale- Cognitive subscale, i.e., ADAS-Cog[11], etc.) and neuroimaging features, and combination of all the above. The most frequently reported criteria for classification and diagnosis of vascular cognitive decline were the Hachinski Ischemic Score (n = 50, 43%), the NINDS-AIREN criteria (n = 37, 31%), and the DSM-based criteria (III, III-R, IV, and 5; n = 37, 31%). These criteria were variously
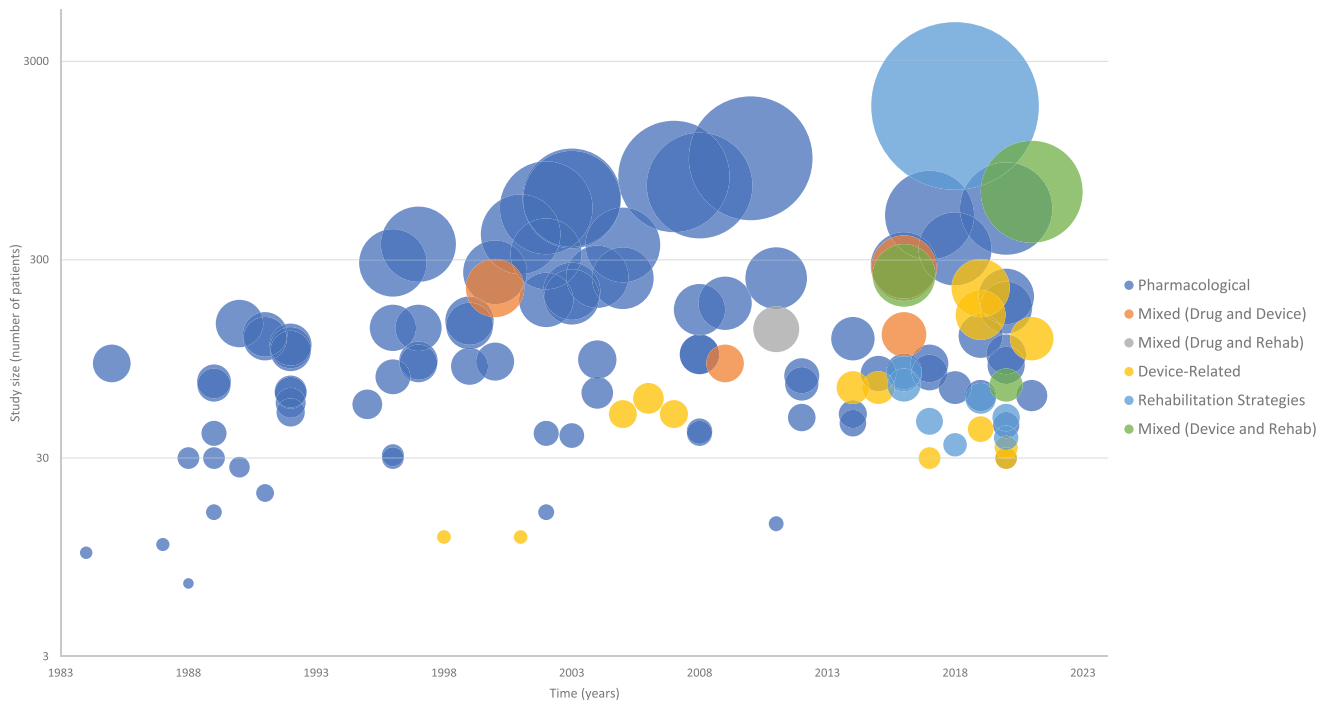
FIGURE 2 Distribution of studies according to size, year of study publication, and class of intervention tested. Bubble plot depicting distribution of studies according to their size (patient number, bubble dimension, and Y position is proportional to study size), year of publication, and class of tested intervention tested (coded according to color, as outlined in the legend below). The Y axis units are represented in a logarithmic scale.
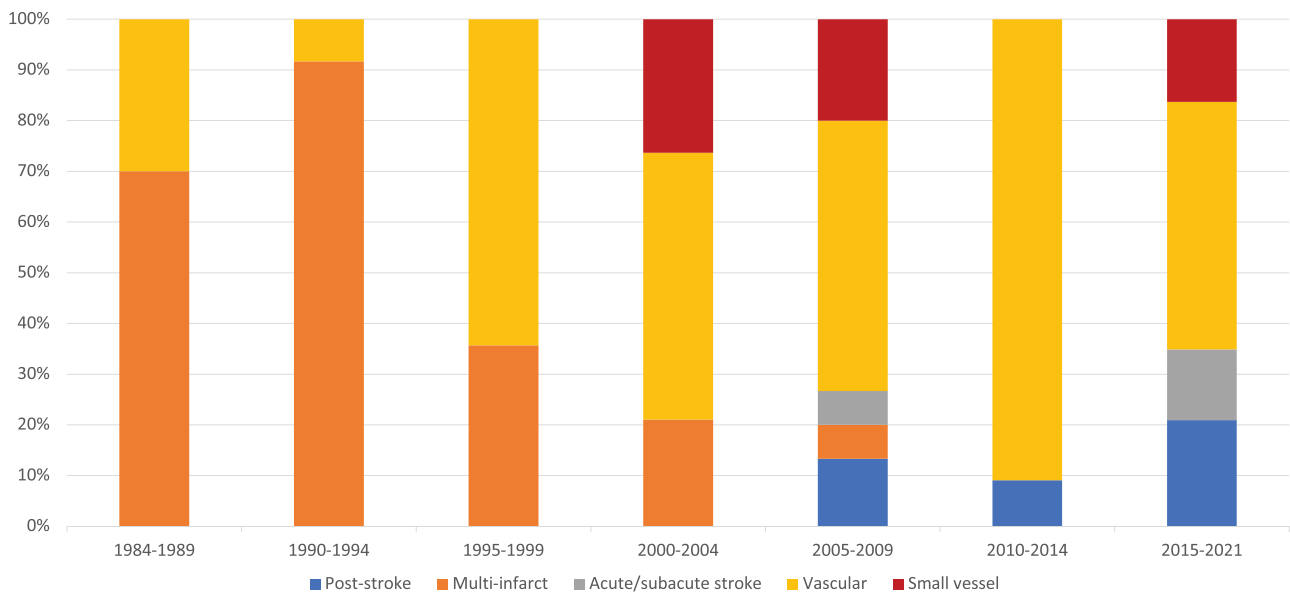

FIGURE 3 Diagnostic label use over time. Diagnostic label use over time according to study year of publication.

combined with pre-specified score intervals on short cognitive tests, mainly MMSE ($n = 51$, 43%) and MoCA ($n = 12$, 10%), or with ad hoc formulated clinical and radiological criteria ($n = 17$, 14%).

Inclusion criteria categories, their combination, and evolution of their use through time are shown in Figure S2.

3.3 | Investigated interventions

Figure 4 reports the types of interventions investigated and their combination, together with their comparators. Overall, 63 different types of intervention were outlined in this systematic review: 51
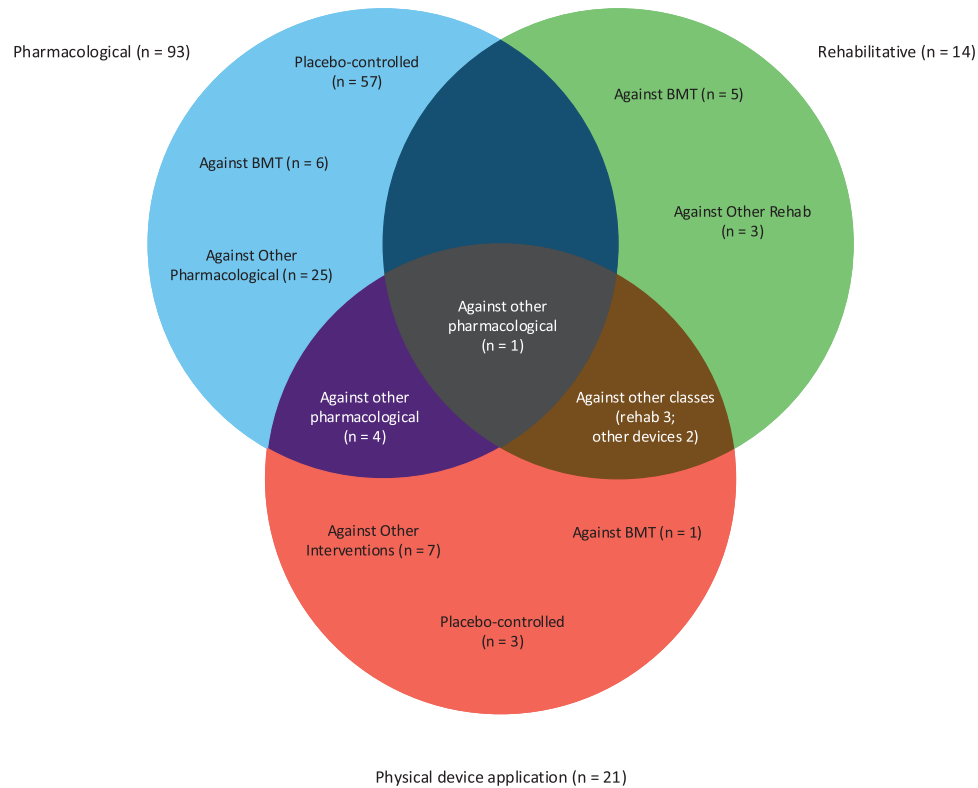
FIGURE 4 Number of studies evaluating each class of intervention along with their comparator. Venn diagram depicting the number of studies evaluating the different classes of intervention (pharmacological, requiring device application or rehabilitative), alone or in combination, stratified by comparator. BMT, Best Medical Treatment.

pharmacological, 5 employing physical devices, and 7 different rehabilitative strategies (a detail of every intervention reported by each study is reported in Table S1). A bar chart depicting the time trend in investigation of different intervention classes is reported in Figure S3.

Most studies investigated one intervention ($n = 90$), some studies investigated two interventions ($n = 24$), whereas few studies investigated three interventions, but always in a head-to-head comparison.

The most-commonly investigated pharmacological, device-related, and rehabilitative strategies are reported in Figure 5.

3.3.1 | Intervention duration and follow-up time

Overall, the mean duration of intervention was 21.60 weeks (SD 23.89), with a minimum of 1 day (single-shot interventions) and a maximum of 156 weeks (Figure S4).

Twenty-two studies (18.6%) reported a period of follow-up after the end of intervention, respectively, 11% of pharmacological studies, 75% of rehabilitative, and 50% of studies employing devices. On average, follow-up time was 10.64 weeks (SD 9.36, max 32 weeks), with device-related studies having a shorter time of investigation (mean 12.68 weeks, SD 14.32, max 52 weeks) compared to rehabilitation and pharmacological intervention (respectively: mean 21.49 weeks, SD 28.90; and mean 25.61 weeks, SD 25.8).

3.3.2 | Comparators

Placebo was reported as the only comparator in 61 studies (59%), best medical treatment was reported in 11 (10%), and other interventions were employed as comparators in 52 studies configured as head-to-head. In the latter, the three most frequently reported comparators were nimodipine ($n = 7$), citicoline ($n = 6$), and acetylsalicylic acid ($n = 6$).

3.4 | Outcomes

A total of 127 different outcomes were used. Reported outcomes included three classes of variables: cognitive measures (67.6% of the total), instrumental parameters (11.9%), and functional outcomes (20.5%). A detailed list of the most frequently employed outcomes for each of three categories along with their absolute and relative frequency is reported in Figure 6. Trends in use through time of the most employed cognitive outcomes are reported in Figure S5.

Sixty studies (50.8%) clearly identified one or more primary outcomes (27 identified one, 24 identified two, 3 identified three, and 2 identified four or more). Primary outcomes belonged to the class of cognitive measures in 80.8% of cases, to the functional outcome class in 19.2% of cases, and to the instrumental class in 1.0% of cases.
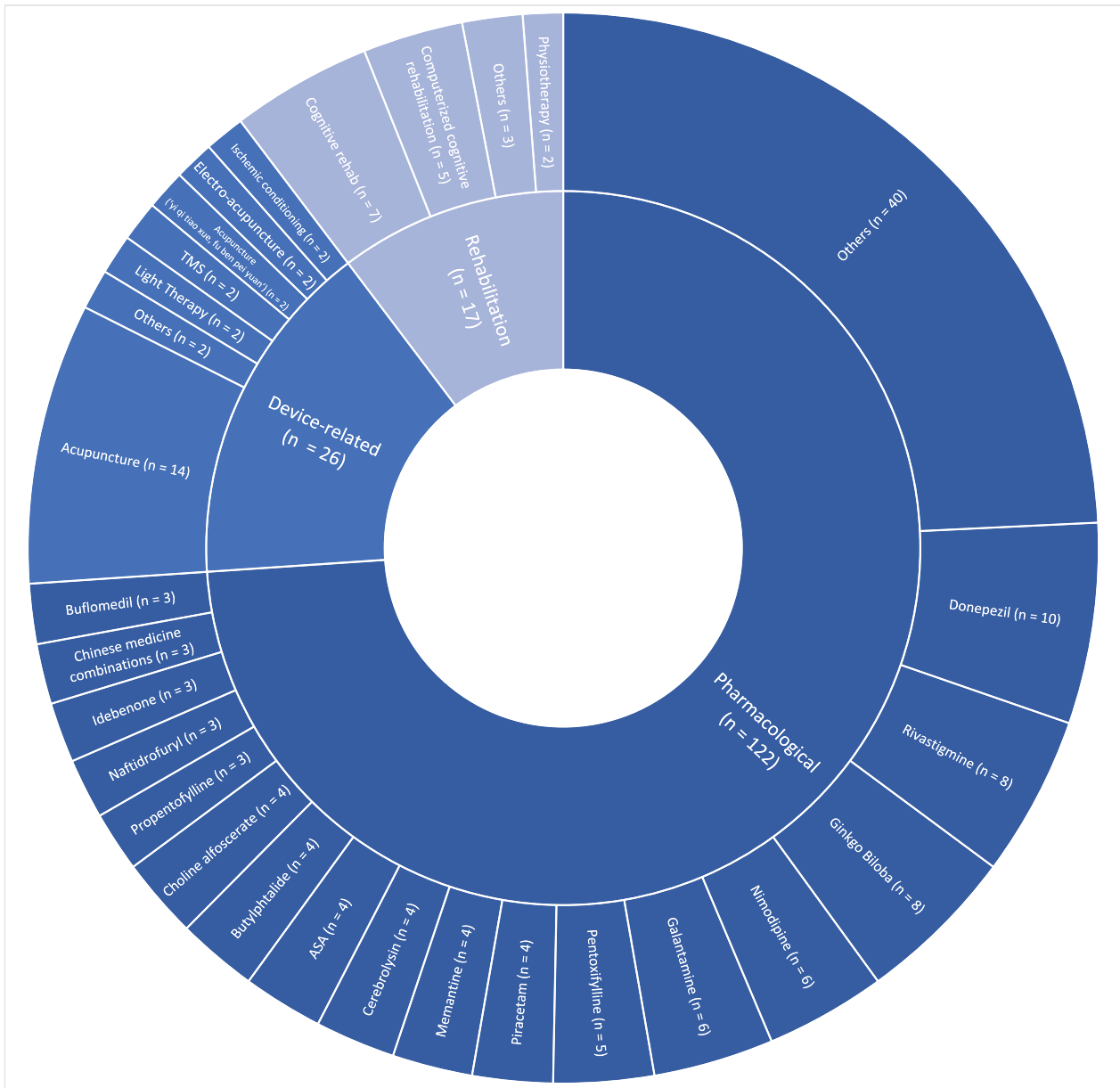
FIGURE 5 Intervention and intervention classes reported most frequently depicted according to their relative proportion. ASA, acetylsalicylic acid; TMS, transcranial magnetic stimulation.

3.5 | Study quality assessment

The quality of the studies included is reported in Table S2. Overall, 62/118 (52%) were of good, 41 (35%) were of fair, and 15 (13%) were of poor quality. A depiction of time trend in study quality is reported in Figure S6.

4 | DISCUSSION

Our systematic review of therapeutic interventions in VCI outlines a great heterogeneity among the included studies. First and foremost,

the primary source of heterogeneity stems from the VCI label itself which encompasses, by definition, different etiological subtypes of cognitive decline related to cerebrovascular disease. In addition, even in studies recruiting patients under the same diagnostic category (e.g., post-stroke cognitive decline), the operative definition of the inclusion criteria often varies from one study to another. Second, a wide range of types of intervention is reported, which tackle, often inconsistently, the different pathophysiological mechanisms of VCI. The third aspect of heterogeneity concerns the large variability in employed outcomes, ranging from cognitive to functional scales to instrumental/laboratory tools. Finally, we recorded a somewhat short duration of tested therapeutic approaches.

FIGURE 6 Outcome and outcome classes reported most frequently depicted according to their relative proportion. ADAS, Alzheimer's Disease Assessment Scale; ADCG-CGIC, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; ADL, activity of daily living; BDNF, brain-derived neurotrophic factor; BGP, Beurteilungsskala für Geriatrische Patienten; BI, Barthel index; CDR-s, Clinical Dementia Rating Scale; CDT, Clock Drawing Test; CIBIC-plus, Clinician's Interview-Based Impression of Change Plus caregiver input; CIRS, Cumulative Illness Rating Scale; DADs, Disability Assessment for Dementia; EEG, electroencephalography; FDG-PET SUVr, fluorodeoxyglucose–positron emission tomography standardized uptake value ratio; fMRI, functional magnetic resonance imaging; GBS, Gottfries-Bråne-Steen Scale; HCT, hematocrit; IADL, instrumental activity of daily living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NOSGER, Nurses Observation Scale for Geriatric Patients; NPI, Neuropsychiatric Inventory; NPS, neuropsychological testing; pIL-7, plasma interleukin 7; pSOD, plasma superoxide dismutase; rCBF, regional cerebral blood flow; SCAG, Sandoz Clinical Assessment Geriatric scale; sTNF-alpha, serum tumor necrosis factor alpha; TC, transcranial ultrasound; WMH, white matter hyperintensity.

One can also observe that many of the tested therapeutic approaches (mainly the pharmacological ones) have been repurposed from approved treatments regularly employed (or tested) in other dementing conditions, primarily AD. The same observation applies to outcome selection, with the most striking example being the use of the

MMSE and ADAS-Cog as measures of primary outcome, in most studies reporting this scale among registered outcomes variables. In fact, the ADAS-Cog is less sensitive to the cognitive changes of VCI because it targets typical AD cognitive deficits and lacks measures of processing speed and executive functions, whose decline is more commonly

associated with typical vascular changes found in VCI patients.[12] Similar considerations can be made for the use of MMSE, a measure of global cognition, which is less commonly associated than other global cognitive measures with cerebral changes seen in patients with VCI.[13] Of note, the use of these scales, in comparison with the use of other possibly more suited ones (e.g., the MoCA or the Vascular Dementia Assessment Scale [VaDAS]) has remained consistent over time (as depicted in Figure S5).

A relevant amount of study assessed the role of complementary and alternative medicine approaches, spanning from herbalistic combinations to the use of acupuncture (in its different techniques) in the attempt of ameliorating VCI symptoms.

Overall, this review points out the lack of a strong pathophysiological background of the interventions tested so far, and even more so in the oldest studies and in some studies investigating complementary and alternative medicine approaches. This suggests that future studies should be designed to target specific VCI subtypes in which the pathophysiological substrate (and thus consequently also patient definition) is more homogeneous. In this regard, VCI caused by small vessel disease might be a proper target.[12] Recently, an international consensus (the Framework for Clinical Trials in Cerebral Small Vessel Disease [FINESSE]) was released and suggested various recommendations about possible future approaches in terms of study population (including neuroimaging definition), optimal clinical endpoints (including imaging and circulating biomarkers surrogates), and cognitive tests.[14] The 2023 revision of the Standards for Reporting Vascular Changes on Neuroimaging 1 (STRIVE-1) for research into small vessel disease[15] may serve in this field as a guide for the use of neuroimaging surrogates and markers of small vessel disease.

Another relevant contribution in the field is the MarkVCID (Mark Vascular Contributions to Cognitive Impairment and Dementia) consortium paper that reported a consensus on fluid- and imaging-based biomarkers for VCI associated with cerebral small vessels.[16,17] MarkVCID consortium has identified a group of fluid- and imaging-based biomarkers, as well as procedures and protocols for participant enrollment, clinical and cognitive evaluation, collection and handling of fluid samples, acquisition of neuroimaging studies, and biomarker validation. The aim is to collect rigorous validating data for selecting and applying biomarkers to future multicenter trials in VCI.[16,17]

Our review is in line with the findings of a previous review performed some years ago on the same topic.[18] The same heterogeneity of outcomes and of investigated interventions shown then is now confirmed by our updated findings (that includes the results of 31 new trials). A similar trend of improvement of study quality in recent years, with larger study populations enrolled, and a more solid statistical design was also confirmed. In our review, however, we explored more in-depth each methodological aspect of VCI study designs, thus uncovering some other new trends. For example, in the last 10 years, and importantly in the last five , we have shown a significant increase in the number of trials performed to test non-pharmacological interventions (namely rehabilitation strategies and therapies requiring physical

agent application), which should be further analyzed and evaluated. Moreover, by the analysis of comparator use through time, for example, it has clearly emerged an increasing number of trials designed as head-to-head despite the lack of any approved treatment for VCI; findings deriving from such trials are a priori difficult to interpret because effects of both the tested intervention and the comparator are not established.

The most striking difference with the review by Smith et al.[18] is that we did not consider mixed dementia, both for inclusion in our review and for future trial enrollment, for the reasons outlined below.

Finally, and in agreement with the work by Smith and colleagues, we suggest that future trials for VCI treatments should be designed targeting specific VCI subtypes, using harmonized criteria, and employing cognitive outcomes suitable for VCI and of other subtype-specific biomarkers of disease. The choice of interventions should be based on a solid biological rationale, which must be reflected also in the choice of surrogate outcomes of treatment efficacy.

Our review has some limitations. The first one is that we relied only on two medical literature databases (Medline and Embase) and, therefore, we cannot exclude that some studies were not retrieved and included in our systematic search. Second, we only considered studies published in English: for this reason, many studies published in Chinese were excluded. In addition, the fact that we did not restrict the review to one single type of VCI subtype is a possible limitation as this, by definition, increases the heterogeneity of results. However, we intentionally planned to review the entire field of VCI treatment rather than focusing on more specific entities, to reach and produce an overview that could be as broad as the field itself. Finally, as already mentioned, in our review we did not consider patients with VCI together with a neurodegenerative pathology (also termed mixed dementia) unless data on "pure" VCI were extractable from these studies. This limitation is consequent to the decision to focus on the evaluation of treatment effects as much as possible free of the effect on the degenerative component of cognitive impairment. Should data on beneficial effect of some interventions emerge from our systematic review, these data might be translated to mixed cases as these interventions might be adaptable to the vascular components of mixed cases.

On the other hand, our study strengths may be found in its systematic approach, which is based on PRISMA guidelines for Systematic Reviews, which is both embedded within our study design and in the COVIDENCE platform itself.

Analysis and report on efficacy measures for each intervention and assessed outcomes, together with in-depth study quality analysis, have not been reported here and will be the object of a second article, stemming from this systematic review.

5 | CONCLUSION

Considering the data reported above, a great heterogeneity seemed to have affected clinical trials in VCI. To obtain more robust results, future studies in VCI should focus on treatments with plausible

pathophysiological rationale in homogeneous patient groups, employing reproducible outcomes.

CONFLICTS OF INTEREST STATEMENT

Federico Masserini, Giacomo Baso, and Claudia Gendarini: none to disclose. Leonardo Pantoni: member of the editorial boards of *Neurology, Stroke, European Stroke Journal, Cerebrovascular Diseases, Cerebral Circulation – Cognition and Behavior*. Associate editor of *Neurological Sciences*. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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