Induced neuroprotection by remote ischemic perconditioning as a new paradigm in ischemic stroke at the acute phase

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Abstract

Remote ischemic conditioning during cerebral ischemia (remote ischemic perconditioning, RIPerC) refers to the application of several cycles of brief ischemia and reperfusion (I/R) commonly to a limb, and it represents a new paradigm in neuroprotection with multiple mechanisms of action in ischemic stroke (IS) patients during acute phase. A systematic review of published research papers and/or registered clinical trials since 2000 was performed. Eighteen studies were identified and only four studies were completed. All of them have demonstrated that RIPerC is secure, feasible and well tolerated in IS patients. However, a high heterogeneity of clinical trial characteristics was observed: five (27.8%) RCTs included only thrombolytic-treated patients, three (16.7%) only thrombectomy-treated patients, and five (27.8%) required radiological confirmation of IS. Temporal inclusion criteria vary from 4h to 48h. Most of the clinical trials used 4 cycles of RIPerC in the upper non-affected limb. Interestingly, only three (16.7%) RCTs applied RIPerC during the transportation at the ambulance. In studies that endovascular therapy was applied, neuroimaging outputs were the main endpoints; functional outcome is also the main endpoint in big-medium size studies. This review summarizes the completed and ongoing clinical trials on RIPerC in IS patients that may be used alone or in combination with recanalization therapies. Ongoing clinical trials will provide new information on the best RIPerC intervention strategy and potentially improve the functional outcome of IS patients, and definition of new RIPerC strategies would ideally aim at enhancing tissue preservation, promoting neurological recovery, and stratify patients to improve treatment feasibility.

Background

Stroke is one of the leading causes of death and disability worldwide (1), with 10.3 million of new strokes and 113 million of disability-adjusted life years (DALYs) per year (2). Stroke victims face an uncertain future and a life severely affected by disability. The most common type of stroke is the ischemic stroke (IS), accounting for 87% of all strokes. It is characterized by the occlusion within an arterial vessel supplying blood to an area of the brain, resulting in a corresponding loss of neurological function. It mainly occurs in elderly patients of both sexes with often multiple comorbidities (diabetes mellitus, hypertension, hyperlipidemia, obesity) (3). Currently, the only treatments available in the acute phase that have demonstrated safety and effectiveness are intravenous fibrinolytic treatment (4, 5) and mechanical thrombectomy (6). Unfortunately, even today many patients cannot benefit from these treatments due to contraindications, time of evolution of the symptoms or restricted access to mechanical therapies that are currently only offered in highly sophisticated hospitals. Thus, there is a need of better and wider therapies to boost patient adherence.

The effectiveness of neuroprotective therapies has a great potential to not only increase the benefits of available reperfusion therapies but also to provide an advisable medical procedure for patients who are not eligible for current treatments. However, translation of most neuroprotective trials from the bench to the emergency room has failed so far, and it did not demonstrate efficacy within IS patients, against promising results in a few preclinical studies (7). One of the main explanations for this failure is that the majority of neuroprotective drugs studied only act on a level of the complex cascade of phenomena that occur in ischemia/reperfusion (7–9). The question of practicability of neuroprotection in IS is unresolved. To date, all trials of neuroprotectant compounds have failed to provide basis and build better trials.

Remote ischemic perconditioning (RIPerC) represents a new paradigm in neuroprotective therapies (10, 11) and it has the potential ability to protect the ischemic brain from injury until reperfusion and, later to protect the brain from reperfusion injury. RIPerC consists of short and controlled cycles of ischemia-reperfusion applied to one limb during the establishment of cerebral ischemia (11). The underlying remote ischemic conditioning mechanisms include neurovascular protection, induced anti-inflammatory action and neuronal protection against excitotoxicity; paired with mitochondrial physiology, circulating inflammasome activation and/or transcriptional regulation of neuroprotective pathway (12). However, there is limited data about the clinical translation of RIPerC in IS patients.

Endogenous cerebral neuroprotection for IS patients by RIPerC is a new paradigm aimed at enhancing the brain resilience to ischemia and with the potential to improve the clinical outcome of affected individuals. For that, a systematic review of the published articles and clinical trials on RIPerC applied to IS patients was performed to evaluate and summarize the findings.

Search Strategy And Selection Criteria

A systematic review of prospective cohort studies was conducted (prehospital-based and hospital-based cohorts) of acute ischemic stroke and remote ischemic perconditioning, and placebo-arms of randomized controlled trials. Studies published from January 2000 to September 2019 were included. PRISMA recommendations were followed (13).

Identification, screening and eligibility for included studies was performed by two reviewers (F.P., G.A.). Bias analysis was unable to be performed because of the ongoing clinical trials. The search was conducted using the electronic databases: Pubmed and ClinicalTrials.gov. Search limits used were English language, human and 2000-current. The search terms used were: ‘remote ischemic conditioning’ AND ‘acute ischemic stroke’ OR ‘remote ischemic perconditioning’ AND ‘acute ischemic stroke’ OR ‘remote ischemic postconditioning’ AND ‘acute ischemic stroke’. Prospective human cohort studies that applied RIPerC in IS patients were included. Studies accepting inclusion beyond 48 hours from the onset of symptoms were excluded. The last database search was conducted on September 2019. Following screening of abstracts, full-text copies of potentially eligible papers were retrieved and assessed for eligibility.

Results

Electronic database search yielded 25 publications and 27 clinical trials of which 18 studies (5 research articles and 13 clinical trials) were finally included in the systematic literature review (Fig. 1). Among the 25 publications identified on Pubmed search, nine articles were not related to stroke (36%), four articles applied chronic PostRIC (16%), three articles were reviews of literature, two articles were the description of studies, two articles were on subarachnoid

hemorrhage patients, one article was a sub-study and four articles were not eligible. After applying the inclusion criteria (acute ischemic stroke-AIS patients and application of remote ischemic per-conditioning-RIPerC) and exclude the studies that accept inclusion beyond 48 hours from the onset of symptoms, a total of 5 articles, which were previously registered clinical trials, were finally included and analyzed (14–18). Twenty-seven randomized clinical trials (RCT) were identified on clinicaltrials.gov. Of these RCT, 6 (22%) applied PostRIC and 17 (62%) were not considered once inclusion/exclusion criteria were applied. 13 RCT were further considered in the present systematic review (SERIC-AIS, SERICT-AIS, RIC-SIID, REVISE-2, PROTECT I, RICE PAC, RICAMIS, rtPA-RIC, REMOTE-CAT, RESIST, TRIPCAIS, ReCAST-2, ICARUS).

Table 1 provides a summary of study design characteristics of the 5 research papers and 13 clinical trials of remote ischemic per-conditioning (RIPerC) application on IS patients. All included research papers were related to completed clinical trials and only one described the trial protocol (18)[Che, 2019, rt-PA with remote ischemic postconditioning for acute ischemic stroke][Che, 2019, rt-PA with remote ischemic postconditioning for acute ischemic stroke].

The first research paper was published by Hougard et al. in 2014 (14). Of the 443 randomized patients, 247 received manual remote ischemic conditioning (mRIC) during transportation in the ambulance to the hospital. After adjustment for baseline multimodal magnetic resonance imaging (MRI) findings, voxel-wise logistical analysis showed better radiological evolution of mRIC treated patients than non-treated patients. However, there were no significant differences in clinical neurological outcome between the mRIC and control groups. It was focused on rt-PA subjects, as Che et al. (17), which only included 30 patients. Zhao et al. (16) demonstrated that RIC is safe in 20 patients who were treated by thrombectomy. Moreover, England et al. (15) confirmed the applicability and feasibility of RIC in 13 patients with ischemic stroke within 24 hours of evolution. Furthermore, RIC was associated with changes in the concentration of plasma biomarkers related to the phenomenon of ischemic tolerance (IT), such as HSP27 and phosphorylated HSP27, when both arms (control vs experimental) of the trial were compared (n = 13) (15). These four publications had a limited and small number of recruited subjects (14–17). Finally, in contrast to the previous studies, RESCUE-BRAIN trial (18) was not only focused on IS patients who received or were candidate for revascularization therapies. It included 200 patients with IS with less than 6 hours evolution of symptoms and it demonstrated ischemic damage on MRI. RESCUE-BRAIN's results were presented at the last European Stroke Organization Conference'19 (19) and showed that RIC applied on affected lower extremity had a futile effect on functional evolution and infarct volume.

Up to now, there are 18 RCT identified and 17 (94.4%) of them registered in clinicaltrials.gov. Among them, 13 (72.2%) have been registered in the last 3 years, 9 (50%) have been developed in China, 8 (44.4%) in Europe and one (5.6%) in United States. Regarding the estimated number of enrolled patients, we highlight RICAMIS (n = 1800), RESIST (n = 1500), SERIC-AIS (n = 912) and REMOTE-CAT (n = 572). There is a high variability in the inclusion and exclusion criteria among trials. Only 6 trials (33.3%) set up an upper age limit as an inclusion criterion. As in the previous RCT of Hougard et al. (14) and Che et al. (17), three on-going RCTs (SERICT-AIS, rtPA-RIC, TRIPCAIS) are focused on the RIC's role as an adjuvant treatment of thrombolytic therapy. In contrast, REVISE-2, PROTECT I and REVISE-1 (16) included patients who went under thrombectomy. Despite the low estimated sample size (n = 15), ICARUS trial wants to reveal the feasibility of RIC application on thrombectomy candidates who are transported to comprehensive stroke centers by aircraft. Five studies require radiological confirmation of acute cerebral infarction regardless of the subsequent treatment received (SERIC-AIS, RIC-SHD, RICAMIS, RECAST, RESCUE BRAIN). Finally, Danish RESIST study, Spanish REMOTE-CAT and British RECAST-2 include patients with stroke code criteria. Both REMOTE-CAT and RESIST consider the score of prehospital scales: RACE scale (20) and Prehospital Stroke Score (PreSS), respectively. In both trials as in the previous published by Hougard et al. (14), the application of RIC begins already in the ambulance transportation of the patient to the hospital.

Certain variability of inclusion time window is observed within the 18 RCTs. Concretely, in the RESIST trial, temporal inclusion criterion is set at < 4 hours while in RIC-SIID and RICAMIS is extended to 48 hours. RCTs focused on patients treated with intravenous fibrinolysis set the maximum time for the evolution of symptoms to 4.5 hours. Instead, among RCTs assessing the effect of RIC on thrombectomy, the time is set up at 6 hours. The Spanish REMOTE-CAT trial includes patients with less than 8 hours evolution of symptoms. Heterogeneity is also evidenced by the number of cycles of RIC application: 7 (38.9%) RCTs use 5 cycles, one (5.6%) RCTs uses between 3 and 5 cycles, and the rest of the trials use 4 cycles. Thirteen (72.2%) trials perform a single application of RIC. Conversely, SERIC-AIS and RESIST plan up to two applications throughout seven days. The application of RIC is located in the non-paretic lower limb only in one RCT (18), on both upper extremities in five (27.8%) RCTs, and on upper or lower non-paretic extremities in one (5.6%) RCT. In most cases, the application is restricted to the unaffected upper limb. The application of the RIC is manual in 4 (22.2%) RCTs: two research articles (14, 15) and RECAST 2 and RICE PAC. A simulated control group is only included on half of the considered RCTs.

The high heterogeneity within RCTs is also observed on the main endpoints (Fig. 2). The RCTs yielding the highest number of enrolled patients are still on-going as REMOTE-CAT, SERIC AIS, RESIT and RICAMIS, that consider the clinical endpoint as main endpoint. In medium-size studies (18) and endovascular therapy related studies, the main endpoints are infarct volume and/or neuroimaging outputs. On the first research published paper on the application of RIC on IS patients, the main endpoint considered was the neuroimaging outcome (14). Ischemic tolerance-related biomarkers are included in TRIPCAIS and RIC-SIID trials. However, other RCTs would also study biomarkers to detect differential expression changes. Small-size recruited patients studies demonstrate whether RIC application is feasible in AIS patients and AIS patients treated with rt-PA and/or endovascular therapy (15–17) (Fig. 2).

Discussion

The current systematic review of remote ischemic preconditioning (RIPerC) in IS patients has revealed a noticeable number of trials registered and designed in clinicaltrials.gov, especially in the last three years. Globally, a broad heterogeneity is observed among RCTs on the number of recruited patients, inclusion criteria, number of RIPerC applied cycles, location of application, and the main endpoints. However, each RCTs would contribute to a piece of knowledge and puzzle it together.

The first published evidence of RIPerC in IS patients was limited to patients underwent intravenous alteplase therapy (rt-PA) (14). According to new advances in stroke, five new studies have been focused on patients treated with endovascular therapy. However, preclinical data have demonstrated that RIC during

acute ischemia is effective when applied both alone and in combination with revascularization therapies (21). For that, results of the biggest RCTs (REMOTE-CAT, SERIC AIS, RESIST and RICAMIS), which include IS patients regardless of the acute applied treatment, would be of enormous interest.

A drawback of applying RIC manually in Hougaard et al. study (14). was that only one out of three patients complete the cycles. Therefore, 14 out of 17 new trials use automatic devices. Another important issue is the number of cycles and the place of application. Most RIC trials in Cardiology (22, 23) and the first trials in IS used the four-cycle protocol, probably due to literature tradition. Preconditioning was first demonstrated in a dog model of myocardial ischemia using a four-cycle protocol (24). Afterwards, both RIC before ischemia (25) and RIC during ischemia were first documented using the same protocol (26). The neutral clinical results of Hougaard et al. (14) and Pico et al. (19) trials arise the need to increase the RIC stimulus and repetitions. Recent studies in preclinical models also addressed it, in order to optimize the efficacy and duration of RIPerC (27). In a rat model of cerebral ischemia, Ren et al. reported that repeated remote post-conditioning during 14 days after reperfusion significantly decrease the volume of infarction by acting again reperfusion injury (28). There are some successful experiences in chronic postconditioning among intracranial stenosis patients (29) and in patients with cerebral small-vessel disease (30) using five-cycle protocol. REMOTE-CAT and RESIST trials proposed a five-cycle protocol. RIPerC and postconditioning combined during 4 to 7 days is included in one arm of RESIST trial, ReCAST-2 (15) and SERIC-AIS trial. Although, the quantity of muscle mass affects the efficacy of the intervention (31), only one study proposed RIC application in a leg (18). It has been described that one in four IS patients has silent peripheral arterial disease (32), for that it has suggested that the upper arm would be the best location because of safety reasons. One and two-limb conditioning were equally protective according to preclinical models (27). Transfer of the cerebral protective stimulus is not well understood (33), sensory signal is crucial for the remote signaling to the brain (34), for that tourniquet should be performed in the non-affected arm.

A prehospital administration of RIC in the ambulance transportation of the IS patients was first proposed by Hougard et al. (14) and it is established in REMOTE-CAT and RESIST trials due to lack of RIC effect by time (35). An increased proportion of patients with transient symptoms in the intervention group was observed in the Hougard et al. (14) trial, nonetheless, only the Face Arm Speech Test was used. It was not clear if it was a RIC's effect or there was a bias in the selection. Now, both trials (REMOTE-CAT and RESIST) have a pre-hospital screening performed by RACE and PreSS scores. Patients should be properly balanced using prehospital stroke scores.

Implications for further research

Recent published data highlight that RIC is safe and feasible (14–17, 19), similarly to RCTs involving patients with myocardial infarction (22). According to preclinical data and results from pilot studies, RIC should be applied as soon as possible, preferable during the patient transportation to the hospital and could be effective not only in patients who receive reperfusion therapies. Ongoing trials will clarify the effect of RIC in IS patients and the optimal RIC protocol application.

Conclusions

The summary of the completed and ongoing RCTs on RIPerC in IS patients shows that RIC can be initiated during pre-hospital transport, it can be used alone or in combination with current recanalization therapies. The time window and the primary RIC protocol in neuroprotection are still not fully determined. However, ongoing CTs will provide new information on the best RIPerC intervention strategy and the improvement of functional outcome of IS patients.

Declarations

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Author contributions

FP, CG, GM, CP, CT, DV-J, MV-P, AV and GA have made substantial contributions to the design of the review. FP and GA have analyzed the data. FP and GA have drafted the work. CG, GM, CP, CT, DV-J, MV-P and AV substantively revised the manuscript.

Declaration of conflicting interests

The authors declared no conflicts of interest regarding research, authorship, and/or publication of this article.

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Table

NTC Number Acronym/Ref	Country	Registered year	Estimated enrollment	Age	Criteria	Time before inclusion	Prehospital intervention	Application # cycles Pressure	Application of RIC	Interventio
NCT0097596(14)	Denmark	2009	120	>18	Ischemic stroke and rtPA therapy candidate, cerebral infarct showed on MRI	4.5h	Yes	Manual rIPerC, 4 x 5' Up to 25mmHg above systolic BP	Non-affected upper extremity	One time Control group: not RIC simulation
NCT02189928 **RESCUE-BRAIN(18)**	France	2014	200	>18	Carotid ischemic stroke, confirmed by MRI, NIHSS ³5 and ≤25	<6h	No	Device, 4 x 5' 110mmHg	Non-affected lower extremity	One time after initial MRI Control group: RIC simulation (no pressure)
RECAST (15)	UK	-	26	>18	Ischemic stroke with motor deficits on arm and/or leg	<24h	No	Manual RIC, 4 x 5' Up to 20mmHg above systolic BP	Non-affected upper extremity	One time Control group: manual RI simulation (30 mm Hg)
NCT03210051 **REVISE-1 (16)**	China	2017	20	18 – 80	Ischemic Stroke and endovascular recanalization	<6h	No	Device, 5 x 5' 200mmHg	Both upper extremities	One time No control group
NCT03231384 **rtPA-RIC1 (17)**	China	2017	30	> 18	Confirmed Ischemic Stroke and rtPA therapy on going	<4.5h	No	Doctormate device, 5 x 5' 200mmHg	Both upper extremities	One time 2 hours after rtPA therapy; twice daily for 6 days. Control group: not RIC simulation
NCT02779712 **ReCAST-2**	UK	2016	120	>18	Ischemic stroke	6h	No	Manual, 4 x 5' Up to 20mmHg above systolic BP	Non-affected upper extremity	Group1: one time. Group2: two times (repetition after 60 min). Group3: twice daily for 4 days. Control group: manual RI simulation (30 mm Hg)
NCT02886390 **rtPA-RIC**	China	2016	60	18 – 80	Clinical sign and symptoms of acute ischemic stroke and rtPA therapy candidate, NIHSS score ³4 and ≤15	4.5h	No	Doctormate device, 5 x 5' 200mmHg	Both upper extremities	One time within 2 hours after rtPA therapy Control group: not RIC simulation

NTC Number Acronym/Ref	Country	Registered year	Estimated enrollment	Age	Criteria	Time before inclusion	Prehospital intervention	Application # cycles Pressure	Application of RIC	Interventio
NCT03375762 REMOTECAT	Spain	2017	572	>18	Clinical signs and symptoms of acute ischemic stroke, RACE >0, RACE motor >0, known-onset stroke	<8h	Yes	Device, 5 x 5', 200mmHg	Non-affected upper extremity	One time i the ambulanc Control group: RIC simulation (no pressure)
NCT03218293 TRIPCAIS	China	2017	120	all	Confirmed ischemic stroke by neuroimaging, accordance with GTAIS and accomplish rtPA therapy	<4.5h	No	RIPC Device, 5 x 5'	Non-affected upper extremity	One time after rtPA therapy Control group: not RIC simulation
NCT03045055 REVISE-2	China	2017	180	18 – 80	Confirmed Ischemic Stroke, NIHSS ³6, Endovascular recanalization	<6h	No	Device, 4 x 5' 200mmHg	Upper extremity	One time Control group: RIC simulation (60 mm Hg)
NCT03152799 RICE PAC	UK	2017	60	> 18	Ischemic Stroke, proximal anterior occlusion, endovascular recanalization	<6h	No	Manual	Non-affected upper/lower extremity	One time Control group: RIC simulation
NCT03669653 SERIC-AIS	China	2018	912	18 – 80	Confirmed Ischemic Stroke, NIHSS score >5 and ≤25	<12h	No	Device, 4 x 5' 200mmHg	Both upper extremities	Twice daily x 7 days Control group: twice daily x 7 days (60 mm Hg)
NCT03740971 RICAMIS	China	2018	1800	> 18	Confirmed Ischemic Stroke by neuroimaging, NIHSS score ³6 and ≤16	48h	No	—	—	Twice one day Control group: not RIC simulation
NCT03481777 RESIST	Denmark	2018	1500	>18	Clinical signs and symptoms of stroke, PreSS ³ 1	<4h	Yes	Device, 5 x 5', 200mmHg	Non-affected upper extremity	Two times one at the ambulanc and one 6 hours afte in the hospital. Some patients ge twice daily for 7 days. Control group: RIC simulation (20 mm Hg)

NTC Number Acronym/Ref	Country	Registered year	Estimated enrollment	Age	Criteria	Time before inclusion	Prehospital intervention	Application # cycles Pressure	Application of RIC	Interventio
NCT03481205 **ICARUS**	US	2018	10	18 – 85	Ischemic stroke, air transportation to a Stroke unit for endovascular recanalization, NIHSS ³6	–	No	Doctormate Device, 3-5 x 5' 200mmHg	Both upper extremities	One time i route (airplane) to Stroke center No control group
NCT04027621 **SERICT-AIS**	China	2019	50	18 – 80	Confirmed Ischemic Stroke and rtPA therapy, NIHSS score >5 and ≤25	—	No	Device, 4 x 5' 200mmHg	Non-affected upper extremity	Twice within 6-24 hours from rtPA therapy, Control group: twice within 6-24 hours from rtPA therapy (60 mm Hg)
NCT04069546 **RIC-SIID**	China	2019	30	> 18	Confirmed Ischemic Stroke, NIHSS ≤15	<48h	No	Device, 5 x 5' 180mmHg	Upper extremity	One time <48 hours from stroke symptom onset Control group: not RIC simulation
NCT03915782 **PROTECT I**	France	2019	126	> 18	Ischemic Stroke, full occlusion of the MCA (occlusion of M1 and/or proximal M2), confirmed by MRA and DWI Endovascular recanalization	<6h	No	Device, 4 x 5' 200mmHg	Upper extremity	One time after first MRI Control group: RIC simulation (30 mm Hg)

Table 1. Summary of study design characteristics of 18 clinical trials and research papers of remote ischemic per-conditioning application on acute ischemic stroke patients.

Abbreviations: bFGF: basic fibroblast growth factor; DWI: diffusion weighted imaging; GTAIS: guideline of thrombolysis in Acute Ischemic Stroke; MCA: middle cerebral artery; MRI: magnetic resonance imaging; mRS: Modified Rankin Scale (mRS) Score; NIHSS: National institute of Health Stroke Scale; PreSS: prehospital Stroke score; PWI-DWI: perfusion-weighted imaging-diffusion-weighted imaging; RACE: rapid arterial occlusion evaluation scale; RIC: remote ischaemic conditioning; RLIC: remote limb ischemic conditioning; rt-PA: recombinant tissue plasminogen activator; VEGF: Vascular endothelial growth factor.

Figures

Figure 1

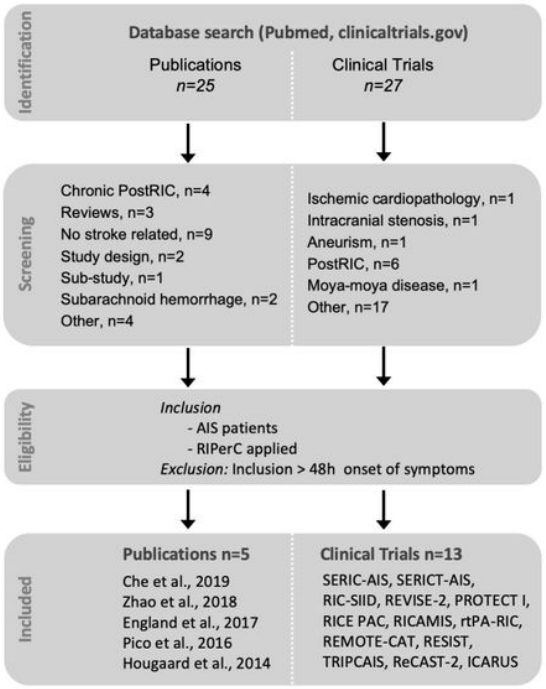

Figure 1

PRISMA workflow describing the number of papers collected during the systematic literature review based on the PRISMA statement.

Figure 2

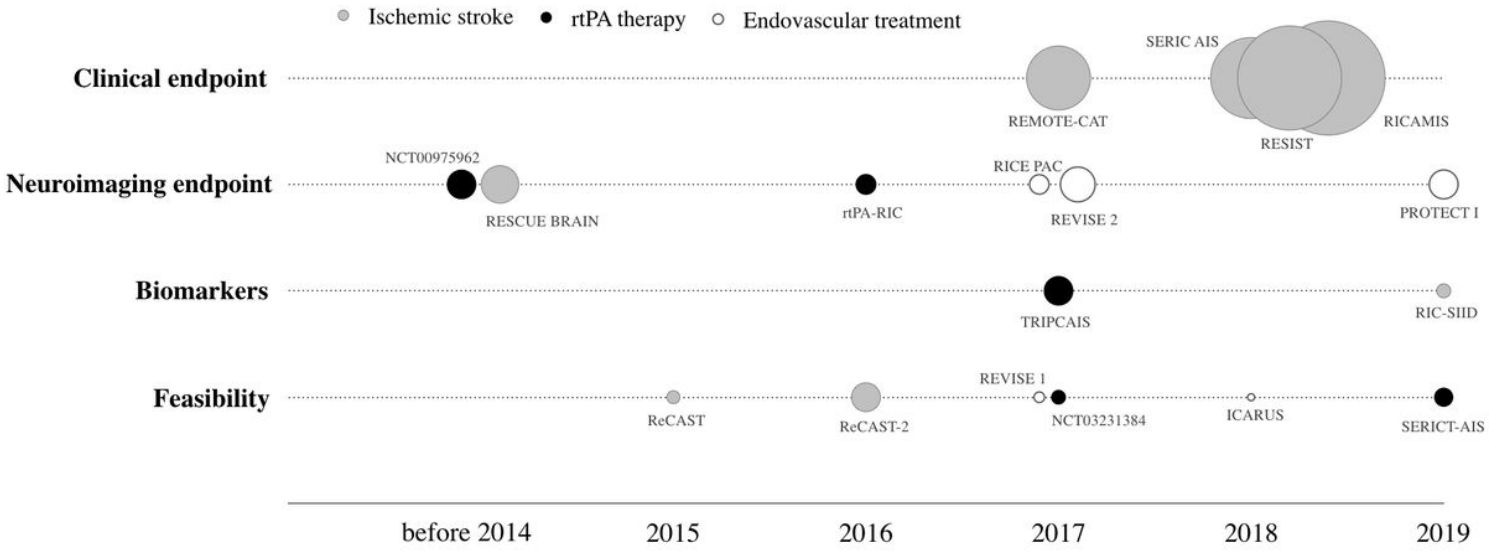

Figure 2

Forest plot of included clinical trials and research papers by ischemic stroke (grey dots), rt-PA therapy (black dots) and endovascular treatment (white dots). Dots height are proportional to estimated enrollment. The analysis included data from 18 studies by four variables: clinical endpoints, neuroimaging endpoint, biomarker discovery and feasibility.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAchecklistPurroyetal.doc