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ABSTRACT

BACKGROUND: Infarct volume inversely correlates with good recovery in stroke. The magnitude and predictors of infarct growth despite successful reperfusion via endovascular treatment are not known.

PURPOSE: We aimed to summarize the extent of infarct growth in patients with acute stroke who achieved successful reperfusion (TICI 2b–3) after endovascular treatment.

DATA SOURCES: We performed a systematic review and meta-analysis by searching MEDLINE and Google Scholar for articles published up to October 31, 2020.

STUDY SELECTION: Studies of >10 patients reporting baseline and post-endovascular treatment infarct volumes on MR imaging were included. Only patients with TICI 2b–3 were included. We calculated infarct growth at a study level as the difference between baseline and follow-up MR imaging infarct volumes.

DATA ANALYSIS: Our search yielded 345 studies, and we included 10 studies reporting on 973 patients having undergone endovascular treatment who achieved successful reperfusion.

DATA SYNTHESIS: The mean baseline infarct volume was 19.5 mL, while the mean final infarct volume was 37.5 mL. A TICI 2b reperfusion grade was achieved in 24% of patients, and TICI 2c or 3 in 76%. The pooled mean infarct growth was 14.8 mL (95% CI, 7.9–21.7 mL). Meta-regression showed higher infarct growth in studies that reported higher baseline infarct volumes, higher rates of incomplete reperfusion (modified TICI 2b), and longer onset-to-reperfusion times.

LIMITATIONS: Significant heterogeneity among studies was noted and might be driven by the difference in infarct growth between early- and late-treatment studies.

CONCLUSIONS: These results suggest considerable infarct growth despite successful endovascular treatment reperfusion and call for a faster workflow and the need for specific therapies to limit infarct growth.

ABBREVIATIONS: EVT = endovascular treatment; mTICI = modified TICI

Final infarct volume is a known predictor of clinical outcome in acute ischemic stroke: The larger the infarcted area on follow-up imaging, the worse the outcome is.[1-3] The goal of reperfusion therapies like intravenous alteplase and endovascular treatment (EVT) is to minimize infarct progression as much as possible, thereby ultimately improving clinical outcomes. Arterial occlusion leads to hypoperfusion of downstream brain tissue. The area of irreversible damage will grow unless recanalization is achieved and normal blood flow is restored. Restoration of blood flow would, in theory, arrest infarct growth. It is, however, increasingly recognized that infarcted brain keeps growing even after blood flow has been restored; this is reperfusion injury.[4] To

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date, it is not entirely clear to what extent infarct growth occurs after reperfusion because serial brain imaging after reperfusion is not feasible in clinical routine.[5,6] Quantifying infarct growth following successful reperfusion would allow a better understanding of these different mechanisms of infarct growth and provide valuable information for studies on neuroprotective agents that aim to reduce infarct growth.

Thus, we aimed to summarize published evidence on the extent of infarct growth measured on MR imaging from baseline imaging to posttreatment follow-up imaging in patients with acute ischemic stroke who achieved successful reperfusion after EVT.

MATERIALS AND METHODS

Search Strategy

We conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7] Using MEDLINE and the Google Scholar data base, we reviewed clinical studies published in full length from inception to April 2020 and updated on October 31, 2020. Keywords included "stroke" AND ("thrombectomy" OR "endovascular" OR "aspiration" OR "stent-retriever" or "recanalization") AND ("infarct" OR "core" OR "lesion") AND ("growth" OR "volume" OR "change"). Bibliographies of key articles were reviewed to identify additional relevant publications.

Study Selection

Studies were included if they enrolled ≥10 patients with acute ischemic stroke, were published in English, and reported infarct volume on MR imaging performed at baseline (before or within 12 hours post-EVT) and after EVT (≥24 hours) according to endovascular reperfusion quality using the modified TICI (mTICI) score. Only patients with mTICI 2b–3 were eligible for inclusion in this analysis. We included studies that reported baseline volumes on early post-EVT MR imaging because we hypothesized that infarct growth would be minimal between pre- and immediate post-EVT MR imaging in patients who achieved rapid and successful reperfusion.

Three reviewers (F.B., J.O., M.A.A.) independently screened the identified abstracts and jointly extracted the following information for each study: first author's name, year of publication, study design (prospective versus retrospective), number of patients, number of male/female patients, mean/median age, median NIHSS score, proportion of occlusion of the first segment of the middle cerebral artery (M1), proportion of tandem occlusion, treatment with intravenous alteplase, reperfusion quality (final mTICI score on the last angiography run), and final infarct volume at baseline and on follow-up imaging. We directly contacted the corresponding authors of the studies that did not report complete details.

Outcome

The primary outcome of this analysis was the assessment of infarct growth, defined as infarct volume on MR imaging follow-up minus infarct volume at baseline MR imaging in patients with successful reperfusion (mTICI 2b–3).

Statistical Analysis

The estimates of mean infarct growth (in milliliters) were calculated from the baseline and final mean infarct volumes and pooled across all studies using random effects analysis. If the mean volumes were not reported, we obtained them directly from the study authors or calculated their closest approximation using the methods of Luo et al[8] and Shi et al.[9] In addition, percentage infarct volume change from baseline was calculated [(final baseline / baseline) × 100].

Subgroup and sensitivity analyses were performed for studies according to the time of baseline imaging in relation to the start of EVT for patients with complete reperfusion (mTICI 3) and for patients with onset-to-reperfusion ≤ 6 hours versus >6 hours.

Heterogeneity among studies was assessed using the I^2 index. Meta-regression models were fitted to explore sources of heterogeneity and associations of infarct growth with baseline infarct volume, speed of treatment, completeness of reperfusion, and intravenous tPA use.

Publication bias was assessed with the Egger test and illustrated with a funnel plot. Two-tailed P values <.05 were considered statistically significant. Statistical analysis was conducted in STATA MP 15.1 (StataCorp).

Risk of Bias and Quality Assessment. The risk of bias was assessed by 2 authors independently using the Risk Of Bias in Non-Randomized Studies of Interventions assessment tool. In case of disagreement, a consensus was reached.[10,11]

The tool addresses preintervention (confounding and selection bias), at-intervention (misclassification of interventions), and postintervention features of the study, which cover biases due to deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. The risk of bias judgment for each bias domain and for the overall risk of bias was low, moderate, serious, or critical risk of bias, with a supplementary option of "no information."[10,11]

RESULTS

Study and Participant Characteristics

A total of 10 studies (n = 973 patients) were identified.[6, 12-20] The Online Supplemental Data show the selection flow chart.

Three studies were prospective and 7 were retrospective analyses of prospectively collected data (Online Supplemental Data). Six of the included studies (60%) were multicenter. The mean age was 68 years, and the median NIHSS score was 16. Women represented 48% of participants. All patients had anterior circulation strokes with occlusion of the terminal ICA and/or MCA. Isolated MCA occlusion was described in 54% of cases (reported in 8 studies). Tandem cervical occlusion was noted in 15% of patients (reported in 4 studies). The mean time from symptom onset to baseline imaging was 246.3 minutes (reported in 7 studies).

Treatment Characteristics

Intravenous tPA was administered in 46% of patients. All patients in this analysis received endovascular therapy and achieved successful reperfusion (mTICI 2b–3 scores). Complete or near-complete reperfusion (mTICI 3 or expanded TICI 2c, 3) was achieved in 76% of patients. Three studies reported ≥90 reperfusion status

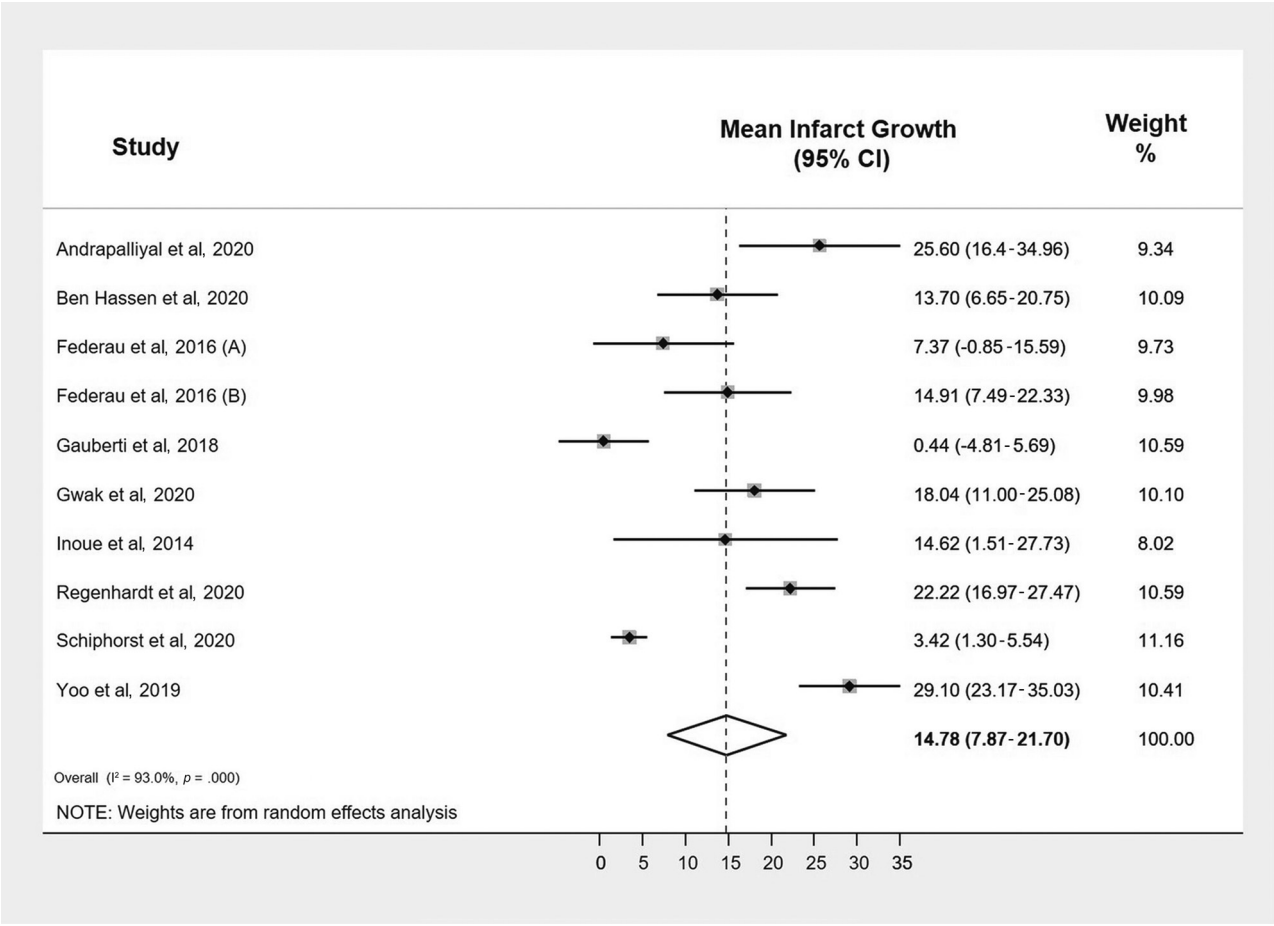

FIG 1. Forest plot with a random effects model showing the overall mean infarct growth.

on perfusion-weighted imaging performed post-EVT. The mean time from symptom onset to the start of the endovascular procedure was 295 minutes (reported in 8 studies).

Times of Baseline and Follow-up Imaging Assessments

All included studies assessed infarct volumes (baseline and follow-up) on diffusion-weighted MR imaging except 1 study[14] that used 5-day follow-up FLAIR to estimate the final infarct volume. Baseline volumes were measured on MR imaging performed before the EVT procedures in all studies except 2 that used early post-EVT (within 12 hours) for baseline infarct volumes. The median time from onset to imaging was 135 minutes in the studies that used pre-EVT scans versus 714 minutes for studies with early post-EVT studies. Final infarct volumes were assessed at a median of 24 hours post-EVT. Three studies used 5-day follow-up MR imaging, while 1 study used 2-week follow-up for final infarct volumes.

Meta-analysis of Infarct Growth and Sensitivity Analyses. The mean baseline infarct volume was 19.5 (SD, 7) mL, while the mean final infarct volume was 37.5 (SD, 15.4) mL. The pooled mean infarct growth was 14.8 mL (95% CI, 7.9–21.7 mL) (Fig 1). There was no difference in the mean infarct growth between the studies that performed the follow-up MR imaging in the first 24 hours (18.8 mL; 95% CI, 14.7–22.8 mL) versus in the first 5 days post-EVT (19.7 mL; 95% CI, 15.6–23.7 mL) versus within 2 weeks (18.0 mL; 95% CI, 11.0–25.1 mL).

Significant heterogeneity existed among the included studies (I^2 = 93%). However, subgroup analyses according to the onset-to-reperfusion time suggest that the heterogeneity is driven by the variability of infarct growth in the early-treatment studies (onset to reperfusion <6 hours) (pooled mean growth: 9.7 mL; 95% CI, 4.3–15.0 mL) compared with those with an onset-to-reperfusion time of ≥6 hours (pooled mean growth: 25.4 mL; 95% CI, 20.9–30.0 mL) (Fig 2).

When the analysis was restricted to studies that included only patients with complete reperfusion (reperfusion ≥90%; *n*= 6), the pooled mean infarct growth was relatively lower than the overall pooled growth at 11.6 mL (95% CI, 5.3–17.8 mL). In the studies that assessed final infarct volumes within 24 hours post-EVT, the pooled mean infarct growth was not notably different, with a pooled mean infarct growth of 13.3 mL (95% CI, 2.3–24.3 mL). On the basis of the time of baseline MR imaging, mean infarct growth did not significantly differ between studies reporting initial infarct volume on MR imaging performed immediately post-EVT versus those with pre-EVT MR imaging (*P* = .6).

The percentage infarct growth from baseline also varied among the included studies (pooled mean growth: 80.4%; 95% CI, 57.8%–103.0%) and was lower in the studies in the early (<6 hours) treatment window (pooled mean growth: 69.4%; 95%

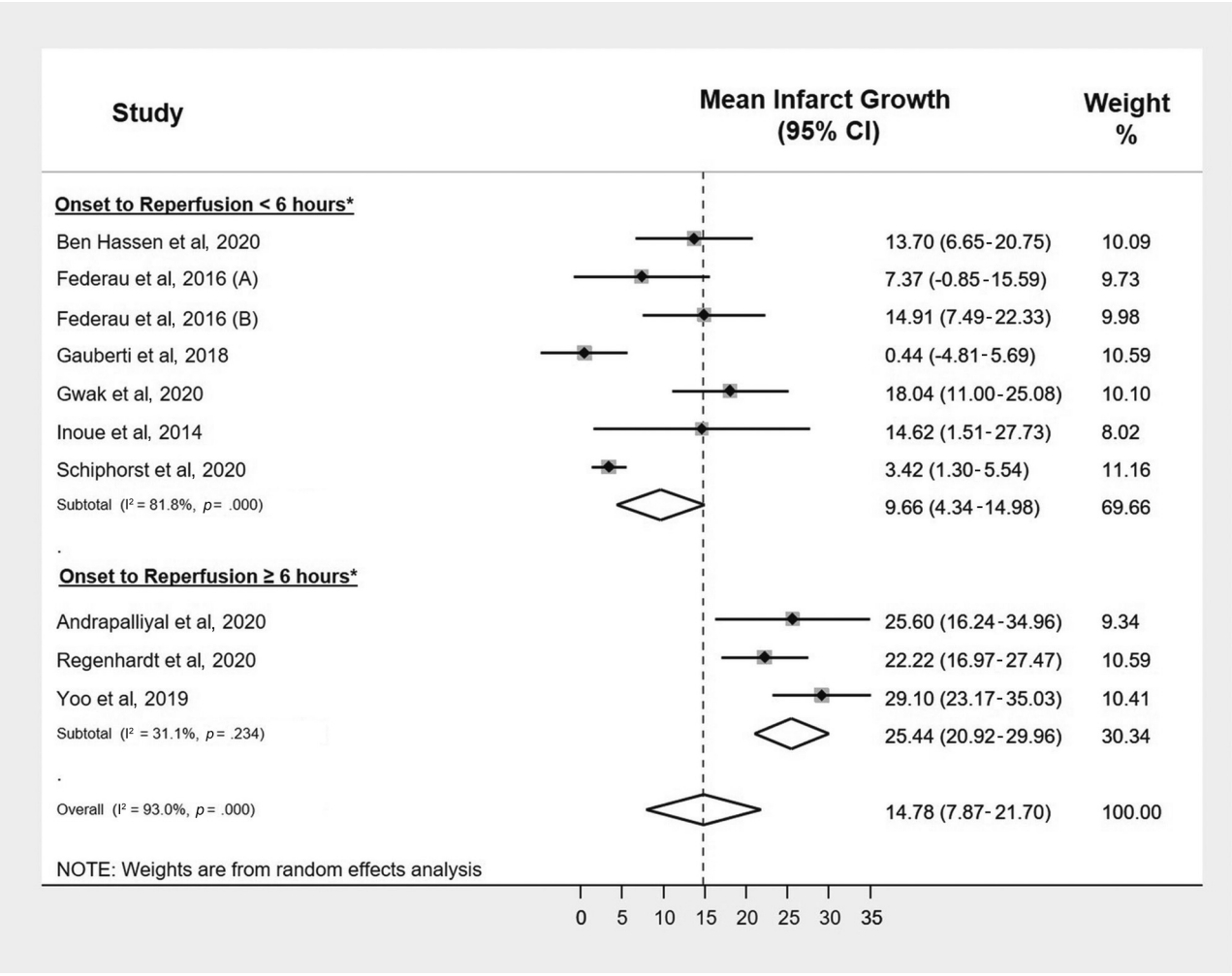

FIG 2. Forest plot with a random effects model for mean infarct volume according to dichotomized onset-to-reperfusion time (<6 versus ≥6 hours).

CI, 41.2%–97.6%) versus studies with onset to reperfusion of ≥6 hours (pooled mean growth: 107.8%; 95% CI, 78.6%–137.0%).

Meta-regression

To assess the potential effects of various predictors on infarct growth, we conducted a series of random effects meta-regression analyses. These showed a significant association between the pooled mean infarct growth and the baseline infarct volume (coefficient = 1.02; 95% CI, 0.2–1.9; $P = .022$), indicating increasing infarct growth in studies with higher baseline infarct volumes (Fig 3).

There was a higher mean infarct growth in the studies that reported higher proportions of patients with incomplete reperfusion (mTICI 2b) (coefficient = 0.22; 95% CI, 0.1–0.4; $P = .019$), while studies with higher complete reperfusion (mTICI 3 or ≥90% reperfusion) reported lower mean infarct growth (coefficient = 0.21; 95% CI, −0.4 to −0.03; $P = .026$). Similarly, the mean infarct growth increased in the studies that reported longer onset-to-reperfusion times (coefficient = 0.1; 95% CI, 0.01–0.2; $P = .028$). Other factors such as onset-to-imaging time and the use of intravenous tPA did not influence infarct growth in the included studies.

Study Quality and Risk of Bias. The quality of included studies ranged between moderate and high (Online Supplemental Data).

Testing for publication bias showed significant small-study effects (Egger statistic, $P = .045$). The funnel plot also suggests skewing of studies, indicative of publication bias toward reporting higher mean infarct growth (Online Supplemental Data).

DISCUSSION

We summarized available estimates of infarct growth despite successful endovascular reperfusion in patients with acute stroke. Our findings suggest that ischemic stroke evolves despite successful reperfusion. The degree of infarct growth appears to positively correlate with the initial stroke volume and negatively with the completeness and speed of reperfusion. The observed heterogeneity among the included studies was partially explained by the difference in the onset-to-reperfusion times.

In a pooled individual patient data meta-analysis of 7 randomized clinical trials, reduction of final infarct volume explained only 12% of the treatment effect of EVT.[21] Our finding of continued infarct growth despite successful recanalization might be 1 explanation for this phenomenon. Possible mechanisms of infarct growth

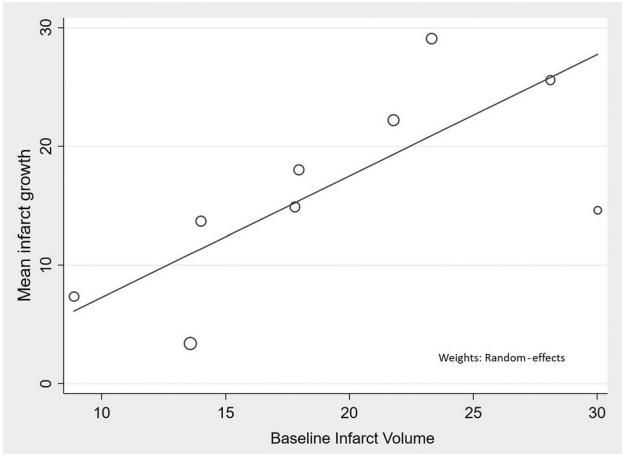

FIG 3. The relationship between infarct growth and baseline infarct volume using meta-regression analysis.

include ischemic reperfusion injury, overestimation of final infarct due to edema, progression of infarction due to delays or failure to achieve complete reperfusion, or vascular reocclusion post-EVT. Ischemic reperfusion injury is thought to result from numerous processes, including endothelium activation, oxidative stress, inflammatory responses causing leukocyte infiltration, platelet activation, and blood-brain barrier breakdown, engendering apoptosis, brain edema, and hemorrhagic transformation.[22,23] While the restoration of blood flow mitigates hypoxia, subsequent irreversible cell death might still occur. This mechanism plays an important role in experimental stroke models,[24,25] despite discrepant results between animal models and human studies.[26,27] Our findings are in line with the results of a serial MR imaging study after endovascular treatment that described secondary infarct growth despite good recanalization.[28]

Infarct growth may be biased by brain edema, leading to the overestimation of the final infarct volume.[29] A recent study of Harston et al[30] found that edema was responsible for 20% and 36% of lesion expansion at 24 hours and 1 week after acute stroke, respectively. Vasogenic edema occurs because of blood-brain barrier breakdown and may lead to hemorrhagic transformation.[31] Recently, net water uptake was described on CT to discriminate between infarct lesion and edema.[32] Results showed that edema-corrected volumes of early follow-up imaging were in agreement with the true final infarct volume.[33] Another study by the same group reinforced this view and found that infarct volume was overestimated within the first 24 hours owing to edema.[34] Therefore, therapies targeting cerebral edema before reperfusion could be a potential neuroprotective strategy to slow down infarct growth postreperfusion in patients with large-vessel occlusion.

Successful angiographic reperfusion encompasses TICI 2b, TICI 2c, and TICI 3 grades. However, TICI 2c and 3 reperfusions are associated with better outcome than TICI 2b reperfusions.[35] The area of infarct in patients with TICI 2b may continue to grow after EVT. Several studies reported reduced infarct growth in patients with TICI 2c and 3 compared with TICI 2b reperfusions; this finding was confirmed by our analysis.[36,37] Early reocclusion is an infrequent event, with a prevalence estimated between 2% and 11%.[38,39] However, it should still be taken into account when explaining the infarct growth after endovascular treatment. This has been demonstrated by Santana et el,[40] who found that reocclusion is associated with an increased infarct growth (adjusted OR = 8.5; 95% CI, 2.04–34.70). Similarly, distal embolization and infarction in new territory can contribute to the infarct growth.[41,42]

Potential Strategies to Slow Down Infarct Growth

Our analysis confirms the need for therapies to limit the infarct expansion after successful endovascular reperfusion and improve the clinical outcomes of these patients. Strategies targeting the possible pathways leading to infarct growth have been described, including slowing down the ischemic reperfusion process and/or enhancing the collateral blood flow. Novel approaches have demonstrated the ability to enhance collateral blood flow, including sphenopalatine ganglion stimulation and remote ischemic conditioning.[43-45]

Some agents (nerinetide and uric acid) showed encouraging results in large clinical trials of patients with acute stroke treated by reperfusion therapy.[46,47] In addition, therapeutic hypothermia has shown promising results in reducing infarct volume and, therefore, improving clinical outcome.[48] A recent study of intra-arterial selective cooling infusion showed a lower average final infarct volume (63.7 [SD, 31.8] mL) compared with controls (77.9 [SD, 44.7] mL) ($P = .038$).[49]

Limitations

Our analysis has several limitations. First, we did not include studies that used CT to estimate the initial and/or final stroke volumes; however, it is well-known that MR imaging is more accurate than CT for infarct detection.[50] Second, we used aggregate patient data, which may lead to ecologic bias. Third, the collateral status was not always available in the included studies, and the mean baseline infarct volume in the included studies was relatively low; therefore, our results might not be generalizable to patients with large baseline volumes. Fourth, serial imaging was not available in the included studies, thus, raising the possibility that infarct growth noted in these studies could have happened during the time from baseline imaging to reperfusion. Fifth, not all covariables were reported in the included studies. Thus, we were unable to account for some differences in unreported confounders, which may impact some of our results of analyses. Sixth, the definition of infarcted-versus-noninfarcted tissue on MR imaging might be less accurate owing to the high variability of interindividual tissue vulnerability and to selective neuronal loss.[51] Recently the term "severely ischemic tissue of uncertain viability" was introduced to replace the erstwhile "ischemic core" to account for its uncertainty in determining tissue state.[52]

CONCLUSIONS

This meta-analysis reported substantial infarct growth in patients with acute stroke despite successful reperfusion after EVT. Patients with low baseline infarct volume, those who achieve fast complete or near-complete reperfusion, and those presenting in the early time window had lower infarct growth. Continuous

effort is needed to improve treatment workflow and to develop therapies that aim to reduce infarct growth postreperfusion.

Disclosures: Fouzi Bala—*UNRELATED*: *Grants/Grants Pending*: Société Francaise de Neuroradiologie and Société Francaise de Radiologie, *Comments*: I had 2 scholarships from the French Society of Neuroradiology and the French Society of Radiology. Bhageeradh Mulpur—*UNRELATED*: *Employment*: Cleveland Clinic Foundation. Bijoy K. Menon—*UNRELATED*: *Board Membership*: Circle NVI; *Stock/Stock Options*: Circle NVI. Mayank Goyal—*UNRELATED*: *Consultancy*: Medtronic, Stryker, Mentice, MicroVention; *Patents (Planned, Pending or Issued)*: GE Healthcare; *Royalties*: GE Healthcare. Muhammad Shazam Hussain—*UNRELATED*: *Consultancy*: Cerenovus, *Comments*: Advisory Board; *Other*: Rapid Medical, Cerenovus, *Comments*: Data and Safety Monitoring Board, Rapid Medical; Clinical Events Committee, Cerenovus. Mohammed Almekhlafi—*UNRELATED*: *Board Membership*: Palmera Medical Inc, *Comments*: Scientific Advisory Board; *Stock/Stock Options*: Palmera Medical Inc.

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