Mortality Risk in Acute Ischemic Stroke Patients With Large Vessel Occlusion Treated With Mechanical Thrombectomy

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Background—Recent randomized controlled clinical trials have provided solid evidence that mechanical thrombectomy (MT) coupled with best medical therapy (BMT) improve functional outcomes of acute ischemic stroke patients with large vessel occlusion compared with BMT alone. However, they provided inconclusive evidence on the benefit of MT on mortality.

Methods and Results—We evaluated the association of MT+BMT compared with BMT with the risk of 3-month mortality using aggregate data from all available randomized controlled clinical trials. We also sought to identify potential predictors on the mortality risk and performed univariate meta-regression analyses. Our literature search identified 11 eligible randomized controlled clinical trials, including a total of 2460 patients. The pooled rates of 3-month mortality were 15% (95% CI:12%–19%) and 19% (95% CI:16%–23%), respectively, in the MT+BMT and BMT groups. In the overall analysis MT+BMT was associated with a significantly lower risk for 3-month mortality compared with BMT (risk ratio=0.83, 95% CI:0.69–0.99; P=0.04), without heterogeneity across included studies (I²=3%, P for Cochran Q=0.41). No evidence of publication bias was present in funnel plot inspection and Egger statistical test (P=0.762). In meta-regression analyses no moderating effect on the aforementioned association was detected with patient age (P=0.254), sex (P=0.702), admission systolic blood pressure (P=0.601), admission glucose (P=0.277), onset-to-groin puncture time (P=0.985), administration of intravenous alteplase before MT (P=0.804), MT under general anesthesia (P=0.735), and successful reperfusion following MT (P=0.663).

Conclusions—Our meta-analysis provides evidence that MT+BMT reduces the risk of 3-month mortality compared with BMT alone. This association appears not to be moderated by individual patient or procedural characteristics. (J Am Heart Assoc. 2019;8: e014425. DOI: 10.1161/JAHA.119.014425.)

Key Words: ischemic stroke • mortality • thrombectomy

Despite the significant decrease of stroke mortality risk during the past decade, stroke still remains the second global cause of mortality.¹ Recent randomized controlled clinical trials (RCTs) have provided solid evidence that mechanical thrombectomy (MT) coupled with best medical therapy (BMT) improve functional outcomes of acute ischemic stroke (AIS) patients with large vessel occlusion (LVO) compared with BMT alone. However, except for one, they were inconclusive on the benefit of MT+BMT on mortality.²

In the present systematic review and meta-analysis, we evaluated the association of MT+BMT compared with BMT alone with the risk of 3-month mortality in AIS patients with LVO using data from eligible RCTs.

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Accompanying Data S1, Tables S1 through S3 and Figures S1 through S6 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014425

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Clinical Perspective

What Is New?

- Recent randomized controlled clinical trials have provided inconclusive evidence on the benefit of mechanical thrombectomy (MT) on mortality of patients with acute ischemic stroke attributable to large vessel occlusion.
- Our meta-analysis provides evidence that MT reduces by 17% the risk of 3-month mortality of acute ischemic stroke patients with large vessel occlusion.
- The reduction of mortality risk with MT appears not to be moderated by individual patient or procedural characteristics.

What Are the Clinical Implications?

- MT should be performed in ≥31 acute ischemic stroke patients with large vessel occlusion to save the life of 1 more patient.
- MT is also associated with improved functional outcomes, and therefore the reduction in mortality by MT does not seem to be associated with increased likelihood for functional disability.

Methods

The present systematic review and meta-analysis adheres to the Journal of the American Heart Association’s (JAHA) implementation of the Transparency and Openness Promotion guidelines, and is presented according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses statement.

We searched for RCTs providing 3-month mortality rates in LVO patients randomized to MT+BMT or BMT alone. Literature search in MEDLINE, SCOPUS and CENTRAL (the Cochrane Central Register of Controlled Trials) was performed using the following terms in combination: “endovascular therapy,” “endovascular treatment,” “endovascular reperfusion therapy,” “mechanical thrombectomy,” “thrombectomy,” “acute ischemic stroke,” “cerebrovascular ischemia” and “stent retriever,” “thromboaspiration,” “stroke,” and “large vessel occlusion.” The complete algorithm used in MEDLINE database search is available in Data S1. Eligible studies were also sourced from the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. No language or other search restriction was applied. Last literature search was performed on June 11, 2019.

No time or protocol restrictions were implemented, and thus we included all RCTs providing mortality rates on the 3-month follow-up. Per study protocol we excluded from further evaluation all observational studies, case reports, case series, and studies not providing 3-month mortality rates. We also excluded studies using first generation thrombectomy devices and studies with possibility of enrolling patients without LVO. Reference lists of all articles that met the inclusion criteria and of relevant review articles were examined to identify studies that may have been missed by the initial database search.

We performed quality control for each eligible study with the Cochrane risk of bias assessment tool. Literature search, data abstraction, and bias identification were independently performed by 2 authors (AHK, KM) and all emerging conflicts were resolved after consultation of the senior author (GT).

Using aggregate data from available RCTs we performed random-effects meta-analyses on the risk of 3-month mortality and the probability of functional improvement at 3 months in the ordinal scale between patients randomized to MT+BMT or BMT alone. Mortality rates in each group were calculated after implementing the variance-stabilizing double arc sine Freeman-Tukey transformation. Heterogeneity was assessed with the $I^2$ and Cochran Q statistics. Number needed to treat was calculated using the formula number needed to treat=$1/[(1-Risk Ratio) \times mortality rate in BMT alone group]$. To identify potential predictors of mortality risk we performed univariable meta-regression analyses for all baseline characteristics reported as percentages or mean values (for continuous variables) and being provided in ≥10 publications. Publication bias across individual studies was graphically evaluated by funnel plot inspection and with the Egger statistical test.

All statistical analyses were conducted using the Cochrane Collaboration’s Review Manager (RevMan 5.3) Software Package (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and the Stata Statistical Software Release 13 for Windows (College Station, TX, StataCorp LP).

Data Availability Statement

All data used for analyses are available within the main manuscript and its associated supplemental file.

Results

Our literature search identified 11 eligible RCTs, including a total of 2460 patients (Figure S1). Excluded studies with reasons for exclusion are outlined in Table S1. Patient characteristics receiving MT+BMT or BMT alone are summarized in Table. Risk of bias was considered low in most domains, except for the risk of performance bias because of the open blinded design (Figures S2 and S3), while marked as unclear in the corresponding domains of one RCT that could
# Table

Characteristics of patients randomized to receive mechanical thrombectomy within included studies.

| Study Name | Publishing, y | Enrollment, y     | n, Patients | Mean Age (y) | Women (%) | Median NIHSS Score | Median ASPECTS Score | IVT Pretreatment (%) | General Anesthesia (%) | Mean/Median SBP | Mean/Median Glucose (mmol/L) | Mean/Median Onset to Groin Puncture (min) | Successful Reperfusion (%) |
|------------|---------------|-------------------|-------------|--------------|------------|--------------------|----------------------|----------------------|------------------------|----------------|----------------------------|----------------------------------|---------------------------|
| DAWN⁴      | 2017          | 2014 to 2017      | 107         | 69.4         | 61         | 17                 | N/A                  | 5                    | 10                     | 147            | 6.9                       | 768                              | 84                        |
| DEFUSE ³⁵   | 2018          | 2016 to 2017      | 92          | 70           | 50         | 16                 | 8                    | 11                   | 28                     | N/A            | N/A                      | 688                              | 76                        |
| ESCAPE²     | 2015          | 2013 to 2014      | 164         | 71           | 52.1       | 16                 | 9                    | 72.7                 | 9.1                    | 147            | 6.6                       | 185                              | 72.4                      |
| EXTEND-IA⁶  | 2015          | 2012 to 2014      | 35          | 70.2         | 51         | 13                 | N/A                  | 100                  | 36                     | N/A            | 7.6                       | 210                              | 86                        |
| MR CLEAN⁷   | 2014          | 2010 to 2014      | 233         | 65.8         | 42.1       | 17                 | 9                    | 87.1                 | 37.8                   | 146            | N/A                       | 260                              | 58.7                      |
| PISTE⁸      | 2017          | 2013 to 2015      | 33          | 67           | 61         | 18                 | 9                    | 100                  | 31                     | 147            | 8                         | 209                              | 87                        |
| RESILIENT⁹  | N/A           | 2017 to 2019      | 111         | 65           | 46         | 18                 | 8                    | 69                   | N/A                    | N/A            | 170                      | N/A                              | 75                        |
| REVASCAT¹⁰  | 2015          | 2012 to 2014      | 103         | 65.7         | 46.6       | 17                 | 7                    | 68                   | 6.7                     | 142            | 6.8                       | 269                              | 65.7                      |
| SWIFT PRIME¹¹ | 2015       | 2012 to 2014      | 98          | 65           | 45         | 17                 | 9                    | 100                  | 37                     | N/A            | 7.3                       | 224                              | 88                        |
| THERAPY¹²   | 2016          | 2012 to 2014      | 50          | 67           | 38         | 17                 | 7.5                  | 100                  | 64                     | 148            | 6.2                       | 227                              | 73                        |
| THRACE¹³    | 2016          | 2010 to 2015      | 202         | 66           | 43         | 18                 | N/A                  | 100                  | 49                     | 140            | 6.7                       | 250                              | 69                        |

ASPECTS indicates Alberta stroke program early CT score; DAWN, DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo; DEFUSE, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial; IVT, intravenous thrombolysis; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; PISTE, Pragmatic Ischaemic Stroke Thrombectomy Evaluation; RESILIENT, Randomisation of endovascular treatment with stent-retriever and/or thromboaspiration versus best medical therapy with acute ischaemic stroke due to large vessel occlusion; REVASCAT, Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset; SBP, systolic blood pressure; SWIFT PRIME, Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment; THERAPY, The Randomized, Concurrent Controlled Trial to Assess the Penumbra System’s Safety and Effectiveness in the Treatment of Acute Stroke; THRACE, Thrombectomie des Artères Cérébrales.
not be sufficiently assessed because of the lack of full-text publications at the time of our literature search.\(^9\)

In the overall analysis, MT+BMT was associated with a significantly lower risk of all-cause mortality at 3 months compared with BMT alone (risk ratio=0.83, 95% CI: 0.69–0.99; \(P=0.04\); Figure 1), without heterogeneity across the included studies (I\(^2\)=3%, \(P\) for Cochran \(Q=0.41\)). No evidence of publication bias was present in both funnel plot inspection (Figure S4) and Egger statistical test (\(P=0.762\)). The pooled rates of 3-month mortality were 15% (95% CI: 12%–19%; Figure S5) and 19% (95% CI: 16%–23%; Figure S6), respectively, in the MT+BMT and BMT alone groups. MT+BMT was also associated with a higher probability of functional improvement in the whole distribution of the modified Rankin Scale scores at 3 months (common odds ratio=2.13, 95% CI: 1.77–2.57), with no significant heterogeneity within studies (I\(^2\)=38%, \(P\) for Cochran \(Q=0.10\); Figure 2).

In meta-regression analyses (Table S2) no moderating effect on the aforementioned association was detected with patient age (\(P=0.254\)), sex (\(P=0.702\)), admission systolic blood pressure (\(P=0.601\)), admission glucose (\(P=0.277\)), onset-to-groin puncture time (\(P=0.985\)), administration of intravenous alteplase before MT (\(P=0.804\)), MT under general anesthesia (\(P=0.735\)), and successful reperfusion following MT (\(P=0.663\)).

**Discussion**

Our meta-analysis provides evidence that MT coupled with BMT reduce the risk of 3-month mortality. This association appears not to be moderated by individual patient or procedural characteristics. Based on the risk reduction and pooled 3-month mortality rates of BMT (19%) in the 11 RCTs, it appears that MT should be performed in 31 AIS patients with LVO in addition to BMT to save the life of 1 additional patient. MT was also associated with improved functional outcomes across all ranks of modified Rankin Scale (ordinal shift analysis), and therefore the reduction in mortality by MT does not seem to be associated with increased likelihood for functional disability.

Our results are in accordance with a previous nationwide US study suggesting a steady decrease in the mortality risk of AIS patients after the introduction of MT.\(^14\) Although numerous clinical and procedural parameters have been reported as potential predictors of all-cause mortality risk following MT,
we uncovered no moderating effect in our meta-regression analyses. Despite the fact that futile recanalization was associated with increased mortality risk in a North-American stroke registry, proximal vessel occlusion, high National Institutes of Health Stroke Scale scores, and the need for rescue therapy emerged as the only independent predictors of mortality, posing an increased risk independent of successful reperfusion.15

The present meta-analysis is the first to date to have the adequate statistical power to answer the question on the impact of MT on 3-month mortality (Table S3). Despite the strengths of the present report several limitations also need to be acknowledged. First, it should be highlighted that we combined studies with heterogeneous clinical and neuroimaging inclusion criteria to provide an estimate of the cumulative impact of MT on all-cause mortality in different settings. Despite the disparities between study protocols of included studies, no evidence of heterogeneity was detected between study estimates. Second, it should be acknowledged that we were unable to assess the causes of mortality in included RCTs that further limited conducting subgroup analyses according to the corresponding cause (ie, cardiovascular mortality versus mortality associated with neurological deterioration). Finally, the lack of significant associations in meta-regression analyses could also be attributed to the potential presence of aggregation bias (ecological fallacy).

Figure 2. Forest plot on the probability of functional improvement at 3 months between patients randomized to mechanical thrombectomy plus best medical treatment vs best medical treatment alone. BMT indicates best medical therapy; DAWN, DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo; DEFUSE, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT toRecanlization Times; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MT, mechanical thrombectomy; PISTE, Pragmatic Ischaemic Stroke Thrombectomy Evaluation; RESILIENT, Randomisation of endovascular treatment with stent-retriever and/or thromboaspiration versus best medical therapy with acute ischaemic stroke due to large vessel occlusion; REVASCAT, Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset; SWIFT PRIME, Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment; THERAPY, The Randomized, Concurrent Controlled Trial to Assess the Penumbra System’s Safety and Effectiveness in the Treatment of Acute Stroke; THRACE, Thrombectomie des Arères Cérébrales.

Conclusions

MT combined with BMT provide survival benefits in addition to functional independence in AIS patients with LVO. The relative risk reduction in 3-month mortality corresponds to 17% with a number needed to treat of 31.

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Disclosures

Dr Cordonnier reports personal fees from Boehringer-Ingelheim during the conduct of the study; personal fees from Biogen and grants from French ministry of health outside the submitted work; and is a member of the DSMB (Data and Safety Monitoring Board) for ATTEST-2 (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis) trial (unpaid).
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SUPPLEMENTAL MATERIAL
Data S1.

**Complete search algorithm used in MEDLINE search**

((endovascular[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) OR (endovascular[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) OR (endovascular[All Fields] AND ("reperfusion"[MeSH Terms] OR "reperfusion"[All Fields] OR ("reperfusion"[All Fields] AND "therapy"[All Fields]) OR (mechanical[All Fields] AND ("thrombectomy"[MeSH Terms] OR "thrombectomy"[All Fields]))) OR ("thrombectomy"[MeSH Terms] OR "thrombectomy"[All Fields]) OR ("stents"[MeSH Terms] OR "stents"[All Fields] OR "stent"[All Fields]) AND retriever[All Fields] OR thromboaspiration[All Fields]) AND ((acute[All Fields] AND ("ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischemic"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields]))) OR ("brain ischemia"[MeSH Terms] OR ("brain"[All Fields] AND "ischemia"[All Fields]) OR "cerebrovascular"[MeSH Terms] OR "cerebrovascular ischemia"[All Fields]) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields]) OR (large[All Fields] AND ("blood vessels"[MeSH Terms] OR ("blood"[All Fields] AND "vessels"[All Fields]) OR "blood vessels"[All Fields] OR "vessel"[All Fields]) AND ("dental occlusion"[MeSH Terms] OR ("dental"[All Fields] AND "occlusion"[All Fields]) OR ("dental occlusion"[All Fields] OR "occlusion"[All Fields]))) AND (Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms])
Table S1. Excluded studies from the meta-analysis with reason(s) for exclusion.

| Study name     | Reason for exclusion                                                                 |
|----------------|--------------------------------------------------------------------------------------|
| IMS III [1]    | first generation thrombectomy devices used                                          |
| MR RESCUE [2]  | first generation thrombectomy devices used                                          |
| SYNTHESES [3]  | first generation thrombectomy devices used / possibility of enrolled patients without LVO |
| EASI [4]       | possibility of enrolled patients without LVO (baseline vascular imaging was available in 80% of patients)/ neither masking nor blinding were required |

LVO: large vessel occlusion
Table S2. Meta-regression analyses on the association of all-cause mortality at 3 months with patient and procedure characteristics.

| Variable                                | Coefficient (95% CI) | p-value |
|------------------------------------------|-----------------------|---------|
| Age                                      | -0.05 (-0.15, 0.04)   | 0.254   |
| Female sex                               | 0.01 (-0.03, 0.04)    | 0.702   |
| Systolic blood pressure on admission     | -0.02 (-0.12, 0.08)   | 0.601   |
| Admission glucose                        | -0.39 (-0.40, 1.17)   | 0.277   |
| Onset to groin puncture time             | 0.01 (-0.06, 0.06)    | 0.985   |
| IVT pretreatment                         | 0.01 (-0.01, 0.02)    | 0.804   |
| General anesthesia                       | -0.01 (-0.02, 0.01)   | 0.735   |
| Successful reperfusion                   | -0.01 (-0.03, 0.02)   | 0.663   |

IVT: intravenous thrombolysis, 95%CI: 95% confidence interval
Table S3. Overview of meta-analyses on the association of mechanical thrombectomy with 3-month mortality according to sample size.

| Study           | N of studies | N of patients | Mortality (MT)         | Mortality (BMT)         | RR (95% CI)   |
|-----------------|--------------|---------------|------------------------|------------------------|--------------|
| Goyal et al, 2016 [5] | 5            | 1309          | 15.3% (97/633)         | 18.9% (122/646)        | 0.82 (0.63–1.07) |
| Roman et al, 2018 [6] | 7            | 1754          | 14.7% (128/870)        | 17.3% (153/884)        | 0.85 (0.69-1.05)  |
| Katsanos et al  | 11           | 2460          | 15.8% (194/1228)       | 19.3% (238/ 1232)      | 0.83 (0.69-0.99)  |

MT: mechanical thrombectomy, BMT: best medical treatment, RR: risk ratio
Figure S1. Flow chart presenting the selection of eligible studies.
Figure S2. Risk of bias summary that reviews authors’ judgments about each risk of bias item for each included study.
Figure S3. Risk of bias graph that reviews authors’ judgments about each risk of bias item presented as percentages across all included studies.
Figure S4. Funnel plot of included studies.
Figure S5. Mortality rate in patients receiving mechanical thrombectomy plus best medical treatment, calculated using double arcsine Freeman-Tukey transformation (FTT).
Figure S6. Mortality rate in patients receiving best medical treatment alone, calculated using double arcsine Freeman-Tukey transformation (FTT).

| Study     | Mortality (95% CI) | Weight |
|-----------|--------------------|--------|
| DAWN      | 0.18 (0.12, 0.27)  | 9.59   |
| DEFUSE 3  | 0.25 (0.18, 0.35)  | 8.96   |
| ESCAPE    | 0.19 (0.14, 0.24)  | 11.13  |
| EXTEND-IA | 0.20 (0.10, 0.36)  | 5.63   |
| MR CLEAN  | 0.22 (0.18, 0.27)  | 13.45  |
| PISTE     | 0.13 (0.05, 0.22)  | 4.72   |
| RESILIENT | 0.30 (0.22, 0.39)  | 9.86   |
| REVASCAT  | 0.16 (0.10, 0.24)  | 9.57   |
| SWIFT PRIME| 0.12 (0.07, 0.20) | 9.30   |
| THERAPY   | 0.24 (0.14, 0.38)  | 5.67   |
| THRACE    | 0.13 (0.09, 0.18)  | 12.50  |
| Overall   | 0.19 (0.15, 0.23)  | 100.00 |
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