Purpose of review
The introduction of clot removal by endovascular treatment (EVT) in 2015 has improved the clinical outcome of patients with acute ischemic stroke (AIS) due to a large vessel occlusion (LVO). Anesthetic strategies during EVT vary widely between hospitals, with some departments employing local anesthesia (LA), others performing conscious sedation (CS) or general anesthesia (GA). The optimal anesthetic strategy remains debated. This review will describe the effects of anesthetic strategy on clinical and radiological outcomes and hemodynamic parameters in patients with AIS undergoing EVT.

Recent findings
Small single-center randomized controlled trials (RCTs) found either no difference or favored GA, while large observational cohort studies favored CS or LA. RCTs using LA as separate comparator arm are still lacking and a meta-analysis of observational studies failed to show differences in functional outcome between LA vs. other anesthetic strategies. Advantages of LA were shorter door-to-groin time in patients and less intraprocedural hypotension, which are both variables that are known to impact functional outcome.

Summary
The optimal anesthetic approach in patients undergoing EVT for stroke therapy is still unclear, but based on logistics and peri-procedural hemodynamics, LA may be the optimal choice. Multicenter RCTs are warranted comparing LA, CS and GS with strict blood pressure targets and use of the same anesthetic agents to minimize confounding variables.

Keywords
anesthesia, endovascular treatment, large vessel occlusion, sedation, stroke
KEY POINTS

- The choice which anesthetic regimen: local anesthesia (LA), conscious sedation (CS) or general anesthesia (GA) optimizes clinical outcome after endovascular treatment (EVT) for stroke therapy is unknown.
- Single center randomized controlled trials (RCTs) showed no difference or favored GA, while large observational studies favored CS or LA, with faster door-to-groin time and less hypotension during CS and LA.
- Blood pressure drops during EVT, in severity and duration, are associated with worse functional outcome and strict blood pressure targets could probably negate this effect.
- Faster door-to-groin time, less change of blood pressure drops, and less constraints on personal makes LA a valid option in patients undergoing EVT.
- Multicenter RCTs are warranted comparing LA, CS and GA with strict blood pressure targets and use of the same anesthetic agents to minimize confounding variables.

ANESTHETIC STRATEGIES IN ENDOVASCULAR TREATMENT

A recent survey among members of the Society for Neuroscience in Anesthesiology and Critical Care (SNACC) examining the use of CS vs. GA showed that the preferred anesthetic strategy varies substantially between hospitals [11*]. The use of LA was not explicitly asked in the respective survey, but this anesthetic strategy is also employed in multiple CSCs, especially in the Netherlands [12*]. A study by Fröhlich et al. [13] suggested that the choice of GA over CS is influenced by higher disability, clinical impairment such as aphasia and reduced alertness in affected patients. The variation in use of anesthetic strategy is a consequence of current guidelines stating the optimal anesthetic approach remains undetermined [9,10].

Advantages of LA include avoidance of potentially detrimental effects of anesthetic agents on the jeopardized brain, a lower incidence of (aspiration) pneumonia compared to CS, and a shorter onset-to-reperfusion time since anesthetic preparation time to sedate or anesthetize the patient and to secure the ventilation is not needed [12*,14,15]. On the other hand, GA makes the patient completely immobile, possibly decreasing the chance of intra-procedural complications such as arterial vessel perforation or dissection. Also, sedative pharmacological agents could in theory have a neuroprotective effect by decreasing metabolic demand [16], making CS or GA more favorable approaches above LA.

Studies comparing different treatment strategies mainly focus on patients with LVO of the anterior circulation, in which EVT is proven effective [1]. Patients with a posterior circulation LVO more often present with reduced consciousness and respiratory depression, and physicians more often opt for GA in these patients [17,18*]. In posterior circulation, results of the BASICS trial showed that EVT combined with medical treatment was not superior to best medical treatment alone in the respective patients [19*].

ANESTHETIC STRATEGIES AND OUTCOMES

Multiple observational nonrandomized cohort studies have been conducted evaluating the effect of different anesthetic approaches on functional outcome. A meta-analysis containing seven posthoc analyses of RCTs, a composite of LA and CS (the non-GA group) compared with GA, found that GA was associated with significantly worse functional outcome – as measured by the modified Rankin Scale (mRS) at 90 days [14]. Multiple nonrandomized (mainly retrospective) cohort studies comparing CS and GA mostly favored CS over GA, showing significantly higher rates of good functional outcome at 90 days (a mRS of 0–2) when CS was applied [20*,21–26,27*].

This is in contrast with five single-center randomized controlled trails (RCTs) regarding CS vs. GA, reporting worse functional outcome following CS or no difference between the two anesthetic strategies [28**,29–32]. A recent meta-analysis of these five RCTs showed an overall relative risk of good functional outcome at 90 days of 1.28 (95% confidence interval [CI] 1.05–1.55) in favor of GA. This difference in functional outcome may be explained partly by the higher recanalization rates in GA vs. CS in these studies (relative risk [RR] 1.13, odds ratio [OR] 95% CI 1.04–1.23) [33**]. Pneumonia following EVT was more prominent in GA than in CS (RR 1.97 95% CI 1.18–3.30). The occurrence of interventional complications (RR 1.06 95% CI 0.67–1.68) and postprocedural intracerebral hemorrhage (RR 0.78, 0.41–1.50) did not differ between groups.

The results of the nonrandomized studies could be affected by selection bias. Indeed, GA may be chosen for patients with more severe neurological impairment [13]. However, the results of the RCTs should also be interpreted with caution in terms of generalizability. Time delays in door-to-reperfusion due to GA varied substantially between RCTs. In the SIESTA trial, median door-to-reperfusion time for the
GA group was 187 min vs. 195 min in the CS group, while the GOLIATH trial (58 min GA vs. 44 min CS) and the study by Ren et al. (58 min GA vs. 49 min CS) showed the fastest median door-to-reperfusion times [28**,31]. Differences in door-to-reperfusion times ranged from a median of 22 min favoring CS to 7 min favoring GA, albeit nonsignificant. In the HERMES study, the time delay from randomization to reperfusion was 20 min longer with GA (105, interquartile range [IQR] 80–149) compared to CS (85, IQR 51–118) [14].

Time delays in door-to-groin puncture times were relatively low in the RCTs, except for the SIESTA trial [29]. Ren et al. even showed a similar door-to-arterial puncture times in both groups, namely 11 min [28**]. These fast door-to-puncture times may reflect the highly specialized anesthesia team providing 24-h EVT coverage, which may not be present in every CSC center. Furthermore, only the SIESTA trial showed a significant relative risk reduction for functional independence in favoring GA in the meta-analysis of these five RCTs. The small sample sizes of these single-center RCTs, ranging from 40 to 150 patients, are further hindering the external validity of the results. Therefore, multi-center RCTs are necessary to further elucidate if GA is favored above CS or LA in EVT.

Although LA is used in multiple CSCs, RCTs comparing LA with other anesthetic approaches are lacking. In a recent meta-analysis, eight non-randomized studies comparing LA with CS and/or GA were evaluated [34**]. In this meta-analysis of LVO of the anterior circulation, adjusted for possible confounders including baseline NIHSS, onset-to-door time, age, sex, collaterals, intravenous thrombolysis and blood pressure (BP), no differences were found in good functional outcome between either LA vs. GA (OR = 1.24, 95% CI 0.74–1.17; four studies) or LA vs. CS (1.20, 95% CI 0.53–2.70). Successful reperfusion was also similar between LA (70.4%) and CS (75.1%; OR 0.92 [95% CI 0.56–1.50]), as well as between LA and GA (74.6%; OR 0.90 [95% CI 0.54–1.49]). Symptomatic cerebral intracerebral hemorrhage (sICH) and mortality did not differ between the three anesthetic approaches.

Door-to-groin puncture time was significantly faster when LA was employed (53.4 ± 36.8 min) compared to GA (70.8 ± 37.1 min; mean difference −14.36 [95% CI −20.91 to −7.81]), and seemed faster compared to CS (81.3 ± 49.7 min, although only one study in the meta-analysis looked at door-to-groin puncture time). No significant differences were found in groin puncture-to-reperfusion time. Selection bias in previous observational studies could have influenced these results. There were differences in the approach to data analysis between studies, further impeding adequate interpretation of the results: four studies had an intention-to-treat analysis and three studies a per-protocol analysis. Until today, there is only one multicenter RCT regarding anesthetic modalities, but this study limited its intervention arms to CS and GA [35]. Based on these findings, the superior door-to-groin time in LA could make it the most viable option in EVT. However, much remains to be elucidated.

ANESTHETIC APPROACH AND HEMODYNAMICS

Autoregulation of cerebral blood flow (CBF) to the affected brain region is compromised in LVO stroke, which makes the penumbra, i.e. the salvageable ischemic brain tissue, highly dependent on the mean arterial blood pressure (MAP) [36]. Preintubation hypotension caused by any induction agent for GA, and hypotension during EVT potentially decreases the CBF and increases the speed of core conversion of the ischemic penumbra, resulting in larger infarct volumes [37]. In different RCTs comparing GA with CS, drops in BP variables were more profound when GA was employed [28**,30,32,38].

Guidelines state that systolic BP drops should be avoided during EVT and systolic BP above 150 mmHg could be useful in keeping adequate collateral blood flow, but these recommendations are based on limited data [9,10].

A systematic review concerning the effect of BP in sedated or anesthetized patients (i.e., patients receiving CS or GA) during EVT on functional outcome showed significant discrepancies regarding the methods of BP monitoring and definitions of BP variability [39]. Due to the heterogeneity of hemodynamic parameters used, meta-analysis of these studies was not possible.

Five of the nine studies in the systematic review [39] showed an association between (changes of) hemodynamic parameters and functional outcome three months after the stroke event [30,40–42]. Four of these five studies concerned only patients undergoing GA for stroke therapy [23,30,40,42], while one study involved CS patients only [41]. No predefined BP targets were maintained during EVT in all these studies. The MAP-drop from baseline (ΔMAP), as well as differences between baseline MAP and lowest MAP (ΔLMAP) were inversely associated with good functional outcome, with OR’s of 0.95 (95% CI 0.92–0.99) and 0.97 (95% CI 0.95–1.00), respectively [42]. A fall of 40% in MAP compared to baseline was associated with poor functional outcome (mRS 3–6) (OR 2.8; 95% CI 1.09–7.19) [37]. Lower minimum diastolic BP (P = 0.03) [23], higher maximum systolic BP variability...
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(P = 0.01) [23] and higher MAP variability (P = 0.03) [23], as well as a longer duration of systolic BP < 100 mmHg (P = 0.02) [40] also showed an association with poor functional outcome. Thus, maintaining hemodynamic stability is of major concern for functional outcome in patients with AIS undergoing EVT.

The study involving CS patients only [41] used a systolic BP target between 140 and 180 mmHg with the target set before reperfusion, but not formally protocolized. Patients with absolute MAP drops of >15 mmHg from baseline, as well as MAP drops >10% from baseline, had a higher chance for poor functional outcome. MAP values under a certain threshold, such as a MAP below 80 mmHg (OR 2.21; 95% CI 1.12–4.19), also indicated a higher chance for poor functional outcome.

The other four studies from the systematic review did not show any association between hemodynamic parameters and functional outcome [38,43–45]. Interestingly, 3 of these 4 studies used predefined BP targets: a systolic BP between 140 and 160 mmHg in two studies [43,44] while the third study aimed at a systolic BP ≥140 mmHg and a MAP of ≥70 mmHg [38]. It may be possible that meticulous monitoring and maintaining predefined BP values with adequate medical therapy negates the negative effects of BP drops.

Rasmussen et al. performed a posthoc analysis of the GOLIATH trial in which strict BP targets were applied and no effect of BP on functional outcome was found: median time of a systolic BP < 140 mmHg was 13 min in the GA (IQR 8–29) and 14 min in the CS (IQR 14–29) group [38]. These relatively short intervals of BP below thresholds are also seen in other RCTs concerning GA vs. CS in EVT. The ANSTROKE trial showed a median duration of MAP >20% below baseline of 22 (IQR 5–57) min in the GA group and 15 min (0–55) in the CS group, with no BP values observed under a MAP >40% of baseline [30]. Another RCT showed patients with similar short times spent in MAP >20% below baseline in the CS group (IQR 5.25–15.00 min) and GA group (IQR 6.00–15.00) of just 9 min [28**]. This is in contrast to a study including GA-treated patients without using predefined BP targets, where the median time of systolic BP <140 mmHg of patients with good functional outcome was 34 min (IQR 21–97) and in those patients with poor outcome 48 min (16–95), showing an association between worsened hemodynamic parameters and worse functional outcome [40].

A pooled analysis of multiple RCTs comparing GA and CS found that having a MAP of <70 mmHg for more than 10 min was associated with poor functional outcome (OR 1.62; 95% CI 1.15–2.27, P = 0.005) [46**]. The extension of the collateral circulation may also modify the association between BP and functional outcome: one study suggested that increased hypotension time showed a trend towards worse outcome only in patients with poor collateral status [47]. Additionally, a recent study in GA patients found that the number of hypotensive periods is associated with poor functional outcome [48*]. In this study, duration of hypotension was not found to be associated with poor functional outcome, but the duration of hypotensive periods in this study were extremely short because of strict BP monitoring and treatment of hemodynamic changes.

The studies above mentioned are restricted by anesthetic modality, with in all studies lacking a LA group. A study examining hemodynamic parameters during EVT with LA as anesthetic approach demonstrated that the area under curve for the predefined MAP-threshold – determined by the MAP at admission – in mmHg × minute (thereby combining depth and duration of a hypotensive period) was significantly higher (e.g. less well maintained BP) in CS patients compared to LA patients [49]. ΔMAP was also more pronounced in patients undergoing CS than those receiving LA. Nonetheless, this BP drop could not fully explain the worse functional outcome in the CS compared to the LA group [49].

In summary, all until now published studies indicate that BP drop during EVT should be avoided, independent of the anesthetic strategy used. There is a tremendous need for RCTs including all three anesthetic strategies to understand which targets need to be set for BP in EVT. The INDIVIDUATE study is currently ongoing to analyze the effect of different BP targets during EVT on outcome in patients with AIS [50*].

ANESTHETIC AGENTS AND VENTILATION MANAGEMENT

The anesthetic of choice differs between centers, with European hospitals showing a strong preference for intravenous propofol, while hospitals in the United States have a preference for volatile anesthetics [11*]. In the majority of trials comparing GA and CS, propofol was used in CS as well as in all GA cases, to minimize bias from the administration of different anesthetic agents [28**].

Neuroprotective effects are ascribed to certain volatile anesthetics and propofol, with propofol showing higher cerebral perfusion pressure in elective craniotomies [51–54]. No studies have specifically looked at the role of different anesthetic agents during EVT on functional outcome.
A peripheral arterial oxygen saturation (SpO₂) of >94% should be maintained during the procedure, but supplemental oxygen for nonhypoxic patients is not recommended. Patients with decreased consciousness or bulbar dysfunction should get airway support [9,10]. Lower end-tidal carbon dioxide (etCO₂) levels were associated with worse functional outcome [40,55], so normocapnia should be maintained or targeted for.

PRACTICAL CONSIDERATIONS

The role of the anesthesiologist in CSCs that have LA or CS as preferred anesthetic strategy is often limited, and often only required to be directly present in patients with hemodynamic instability or those in whom GA is employed. Besides the time-delay incurred by sedating and intubating patients, involvement of anesthesiologists may cause extra time-delay by itself, as they have to physically come to the neuroradiological intervention suite. Scarcity of personnel is a practical consideration and might argue to prefer LA and, by lesser extent, CS over GA [56]. In only a minority of patients, conversion from either LA or CS to GA was needed, with studies reporting a range of 6.3–15.6% patients [29–31,57]. Conversion to GA did not lead to worse clinical outcome compared to primary induction of GA in patients at risk for emergency conversion [57]. LA might also be the most practical choice with regard to BP maintenance, as any sedation may lead to more BP drops, certainly if not monitored and treated adequately.

CONCLUSION

The optimal anesthetic strategy for EVT remains unclear, with contrasting results comparing CS and GA between observational cohort studies and single center RCTs. There is a need for multicenter RCTs with LA as a distinct comparator arm: on practical and hemodynamic bases, LA seems a promising approach. Strict monitoring and targets for BP are associated with better functional outcome, but the optimal BP target has not been determined. The effect of different anesthetic agents needs to be further elucidated in EVT patients. Large multicenter trials, using the same predefined BP targets and the same anesthetic agents are warranted to fully understand the relation between anesthetic strategy and functional outcome in patients with AIS undergoing EVT. The effectiveness of thrombectomy in more distal vessel occlusion needs further evaluation [58][9], again making studies necessary for the most appropriate anesthetic management in the respective patients.

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Conflicts of interest

There are no conflicts of interest.

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