Periprocedural Management During Stroke Thrombectomy

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Abstract

Purpose of Review
Endovascular therapy (EVT) for acute ischemic stroke caused by large vessel occlusion is a powerful and evidence-based tool to achieve reperfusion and results in improved neurologic outcome. Focus has now shifted toward optimizing the procedure. We reviewed the relevant current literature on periprocedural stroke care such as pretreatment with IV tissue plasminogen activator (tPA), choice of anesthesia, ventilation strategy, and blood pressure management.

Recent Findings
IV tPA should not be withheld in a patients with stroke eligible for EVT. A meta-analysis of randomized trials on general anesthesia (GA) vs procedural sedation has shown better neurologic outcomes with protocol-based GA in centers with dedicated neuroanesthesia teams. There are no data from randomized trials on blood pressure control, but according to available evidence, systolic blood pressure should probably be held at >140 mm Hg during the procedure and <160 mm Hg after reperfusion. In ventilated patients, extreme deviations from normoxemia and normocapnia should be avoided.

Summary
Periprocedural care influences the outcome after EVT for large vessel ischemic stroke. More evidence from prospective ongoing and future studies is urgently needed to identify its optimization.
Reperfusion therapy is still the only evidence-based treatment for acute ischemic stroke (AIS). Modern stroke treatment has been revolutionized by initially the medical approach with IV tissue plasminogen activator (tPA)\(^1\) and subsequently by endovascular therapy (EVT).\(^2\) In 2015, randomized controlled trials convincingly demonstrated that EVT for patients with large vessel occlusion (LVO) in the anterior circulation was associated with improved outcome compared to medical treatment alone. Since then, EVT has been considered the treatment of choice in patients with AIS due to LVO (Class I Level of Evidence).\(^3\) Subsequently, the focus has now been directed to factors related to how to deliver EVT fast and safely while maintaining the ischemic penumbra until reperfusion occurs. Particularly, tPA bridging therapy before EVT, choice of anesthetic strategy, and hemodynamic management are currently subject to intense research because these factors appear to influence functional outcome after EVT. In this article, we review the latest advances in periprocedural care with emphasis on these aspects.

### Treatment With tPA

Giving IV tPA to an eligible patient before EVT is referred to as bridging. The recently updated guidelines for the early management of patients with AIS specify that bridging with IV tPA should be performed in a patient eligible for EVT before the procedure (Class I) and recommend against observing for a clinical response before continuing with EVT (Class III).\(^4\)

Thrombolysis with IV tPA is an evidence-based treatment that benefits all subtypes of stroke.\(^5\) However, successful reperfusion of an LVO with IV tPA is much lower (≈10% of LVOs are reperfused acutely)\(^6\) than the likelihood of reperfusion with EVT (≈85% in the recent trials).\(^7\) These findings have been used as an argument for omitting tPA before EVT (direct to EVT approach).\(^8\) Other arguments have been that the treatment potentially infers a higher risk of symptomatic intracranial hemorrhage (sICH) and a delay of groin puncture and hence a longer time before initiation of the more effective treatment.

Current data come from thrombectomy trials and meta-analyses of observational studies. The latest and largest meta-analysis\(^9\) shows an increased odds ratio (OR) for good outcome in the bridging group of 1.52 (95% confidence interval [CI] 1.32–1.76) for achieving functional independence (defined as a modified Rankin Scale [mRS] score 0–2). Mortality was also significantly lower with bridging therapy, and the risk of sICH was not different between the 2 groups.

The recently published Direct Intra-Arterial Thrombectomy in Order to Revascularize AIS Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals (DIRECT-MT) trial showed noninferiority for the direct to EVT approach compared with bridging but a better successful reperfusion rate in the bridging group.\(^10\) Other ongoing studies are currently investigating whether EVT without bridging will yield an equivalent or better outcome (Branding Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke [NCT03192332], Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN NO IV], and A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval [NCT03494920]).

The studies include patients coming to an EVT-capable center (mothership). If the patients need transfer, they will be treated with tPA because 10% of patients with an LVO proven on CT angiography are reperfused on IV tPA alone, with clot dissolution by the time EVT is performed. In the Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial randomized patients with LVO to either alteplase or tenecteplase (a tPA mutant with greater fibrin specificity and a longer half-life that is administered as a single bolus instead of a bolus and hour-long infusion) before EVT. In the tenecteplase group, 22% of patients were already reperfused at bolus instead of a bolus and hour-long infusion) before EVT. In the tenecteplase group, 22% of patients were already reperfused at bolus instead of a bolus and hour-long infusion) before EVT. 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Multiple trials are evaluating the role that tenecteplase will play in stroke care, with a data-driven expansion anticipated in the near future for either patients with LVO or all patients with stroke (A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion [NCT02398656], Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance [NCT04071613], Tenecteplase in Wake-up Ischaemic Stroke Trial [NCT03181360], Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis [NCT02814409], Alteplase Compared to Tenecteplase in Patients with Acute Ischemic Stroke [NCT03889249], Tenecteplase in Stroke Patients Between 4.5 and 24 Hours [NCT03785678], Norwegian Tenecteplase Stroke Trial 2 [NCT03854500], and Chinese Acute Tissue-Based Imaging Selection for Lysis in Stroke–Tenecteplase [NCT04086147]).

Proposed benefits of PS include stable hemodynamics, a potentially shorter time delay to reperfusion, and, depending on the depth of sedation, the option of clinical neurologic monitoring during the procedure. The main disadvantages of PS are an unprotected airway and uncontrolled patient movements, which may increase the risk of procedural complications (aspiration, respiratory failure, longer time to reperfusion, not achieving successful reperfusion, vessel perforation, embolization to nonaffected territory, etc.)

A meta-analysis of 7 randomized EVT trials showed an OR of 1.53 (95% CI 1.14–2.04, \(p = 0.0044\)) for worse outcome in the GA group.\(^{19}\) GA in these trials was chosen either because of institutional protocols or by request from the treating physician. Reasons for the request of GA were typically due to excessive patient movements or because the medical condition necessitated tracheal intubation (loss of airway/aspiration).

Although the patients appeared comparable, it was possible that outcome in patients undergoing EVT under GA were confounded by indication. This concern likely applies to most observational studies that assessed the influence of anesthetic strategy on outcome because patients with increased stroke severity and poor clinical presentation were more likely to be treated under GA. This influence of selection bias was seen in data from Interventional Management of Stroke III, one of the early large thrombectomy trials; worse outcomes were seen in the GA patient cohort, but if the patients requiring GA for

Suggested advantages of GA are complete patient immobilization, full airway protection, and a pain-free procedure. The main disadvantages of GA include a higher risk of hemodynamic instability and procedure delay because the induction of anesthesia and tracheal intubation is more time-consuming.
medical reasons were excluded, there was no difference on outcome, emphasizing the influence of selection bias.20

A further concern was that most retrospective studies lacked specific anesthetic and blood pressure protocols and did not report blood pressure measurements during the procedure. Because anesthetic drugs produce hypotension, an important question is whether the worse outcome was a result of GA itself or mediated by lower blood pressure, as illustrated by Davis et al.21 in Figure 2.

One retrospective study assessed the effect of local anesthesia at the puncture site only with PS and reported worse functional outcome and increased mortality in the PS group. However, in this study, PS was requested when the procedure could not be performed under local anesthesia, again indicating a confounder by indication similar to above.22

Randomized Studies
The suggestion raised by the observational studies that GA produces worse outcomes has been challenged by 3 single-center trials in which patients were randomized to either GA or PS. The Sedation vs Intubation for Endovascular Stroke Treatment (SIESTA),23 Sedation vs General Anesthesia for Endovascular Therapy in Acute Stroke–Impact on Neurological Outcome (ANSTROKE),24 and General or Local Anaesthesia in Intra Arterial Therapy (GOLIATH)25 trials all included patients with AIS caused by an LVO in the anterior circulation who were eligible for EVT. All trials included strict protocols of periprocedural care for both treatment groups, including management by a neuroanesthesia/neurocritical care specialist, rapid anesthesia induction, and aiming at a systolic blood pressure (SBP) >140 mm Hg during the procedure. The primary endpoint differed in each trial: in SIESTA, early neurologic improvement (difference in 24-hour NIHSS score); in ANSTROKE, long-term functional outcome (90-day mRS score); and in GOLIATH, infarct growth measured on MRI. All studies reported equivalent primary outcomes between the 2 anesthetic strategies, with no disadvantage of GA. As secondary outcome, both SIESTA and GOLIATH reported improved 90-day mRS scores in the GA group. A successive individual patient data meta-analysis showed improved 90-day outcome for the patients receiving GA with an OR for shift to a lower mRS score group of 1.58 (95% CI 1.09–2.29)26 (Table 1).

This improved outcome associated with GA was seen despite a 10-minute-longer time period from symptom onset to groin puncture and a higher incidence of hypotension in the GA group.26 Outcome in the GA group was probably mediated by a higher rate of successful reperfusion in the GA group (defined as modified Thrombolysis in Cerebral Infarction grade 2b–3), which was 85.2% in the GA arm and 75.7% on the PS arm (OR 2.02, 95% CI 1.16–3.53, p = 0.01). The Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke (HERMES) meta-analysis on GA vs PS did not specify the degree of successful reperfusion in the 2 arms, but in another large thrombectomy trial, Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke (THRACE),27 successful reperfusion was very close to being significantly higher in the GA arm than in the PS arm (76% vs 62%, respectively, p = 0.059). This and other putative explanations for the success for GA are outlined in Table 2.

A small pilot study from China also randomized between GA and PS before EVT, showing no deleterious effect of GA compared to PS. With 43 patients, similar reperfusion rates and outcomes were seen, with 55% reaching independence after 90 days in the GA arm and 50% in the PS arm (p = 0.26).28 These randomized trials constitute the best available evidence to date and essentially point to outcome advantages of GA if applied in a protocol-based fashion. Similar studies are ongoing (General Anesthesia Versus Sedation During Intra-Arterial Treatment for Stroke [NCT02822144], Sedation Versus General Anesthesia for Endovascular Therapy in Acute Ischemic Stroke [NCT03263117], and Impact of Anesthesia Type on Outcome in Patients With Acute Ischemic Stroke [AIS] Undergoing Endovascular Treatment [NCT0267741S]). A standard operative procedure for patients undergoing EVT is outlined in Figure 3.

The most recent American Heart Association guideline recommends that either method of anesthetic technique is reasonable and that the decision should be based on individualized assessment of patient risk factors, technical performance of the procedure, and other clinical characteristics (Class II).4

Procedural Sedation
The objective of PS is to facilitate a rapid EVT procedure without discomfort in a spontaneously breathing patient.
Currently, no comparative studies are available on the optimal choice of sedative and analgesic drugs in PS. Optimal sedation and analgesia depend heavily on the experience of the anesthesia provider and, in particular experience, with sedative drugs in patients with AIS, in whom cerebral autoregulation is often impaired and control of cerebral hemodynamics may be very challenging. In this specific group of patients, both too light and too heavy sedation may have adverse consequences for the outcome of the EVT procedure.

The drugs administered for PS in the randomized trials included remifentanil in ANSTROKE or fentanyl boluses supplemented with a low-dose propofol infusion in GOLIATH (Table 3).

Dexmedetomidine, an α2-adrenergic agonist, has been suggested and studied as a sedative for safe PS,29 although it is not approved in acute stroke in Europe. Low-dose midazolam and ketamine are other options. In some centers, sedative drugs are administered by the interventionalist; in other centers, they are administered by anesthetic nurses or by anesthetic physicians.30 No studies have assessed the influence of the type of anesthesia provider on outcome after EVT performed under PS.

### GA and Ventilation Strategy

GA is not a generic treatment. Anesthetic agents have different effects on physiologic parameters and cerebral hemodynamics31 that are certainly dose dependent. Currently, there are no randomized data to recommend 1 form of GA over another. ANSTROKE used volatile anesthetics (sevoflurane) in combination with remifentanil, while SIESTA and GOLIATH used IV anesthetics (propofol) in combination with remifentanil, and these studies had comparable outcomes. One retrospective study reported its single-center experience with improved outcome in patients with AIS sedated with volatile anesthetics.32 However, a recent and similar study showed a better outcome among patients treated with propofol compared to volatile anesthetics.33 Both types of drugs are cardiovascular depressants in higher doses and often have to be accompanied by fluids or vasopressors.

A survey of anesthesia practice patterns for EVT revealed a discrepancy between Europe and the United States. While 88% of European centers favor the use of propofol as maintenance anesthesia, this is the case for only 5% of US centers. In contrast, 51% of US centers favor volatile anesthetics compared to 13% of the European centers.34 Only 33% of the institutions (overall) reported that they had access to a dedicated neuroanesthesia team for EVT.

The notion that GA may provide a form of neuroprotection has been suggested in many experimental studies, but currently there is no clinical evidence to confirm this hypothesis.35

The optimal ventilation strategy is unknown. Hyperventilation (most often inadvertently) with low PaCO2 is a frequent problem,36 that may cause vasoconstriction and decreased cerebral blood flow and has been proved harmful in patients with head trauma.37 Along that line, a study has shown an association between a higher end-tidal CO2 level (i.e., hypoventilation) and a good outcome after EVT.38 Currently, it is probably reasonable to maintain...
normocapnia because hypoventilation-associated hypercapnia may also theoretically redirect blood from affected brain regions (steal effect). It is also reasonable to aim for normoxemia and apply lung-protective ventilation. The patient should be extubated immediately or very soon after the procedure unless there is a specific airway concern. This was the strategy for most of the patients in the 3 randomized trials and also an observation from other studies.\textsuperscript{38}

### Blood Pressure and EVT

Hypertension is the most important risk factor for stroke, but it is also related to outcome. It is a long-standing observation that a U-shaped relationship exists between mortality/morbidity and either very low or very high admission blood pressure. This has also been observed in patients with LVO undergoing EVT.\textsuperscript{39} A poor outcome has been reported in patients with LVO with hypertension both at presentation\textsuperscript{40} and in the 24 hours after EVT.\textsuperscript{41} It is unclear whether the relationship between blood pressure and outcome is causation or correlation. If the relationship is causal, modifying blood pressure may modify outcome.

### Preprocedural Blood Pressure

Hypertension on admission may be a physiologic response to support collateral flow to the penumbra. Unfortunately, it is difficult to assess the effectiveness in the acute patients because collateral status and impairment of cerebral autoregulation are individually highly variable. Data on induced hypertension in stroke have not focused on patients with LVO as a specific subset, but this therapeutic intervention may be expected to particularly benefit this stroke population.\textsuperscript{42} Hypertension on presentation may also just be an epiphenomenon reflecting stroke severity. Guideline recommendations are currently to allow autoregulation within certain limits.\textsuperscript{4} Use of thrombolytic therapy before EVT is an important threshold of hypertensive limits. Hemodynamic intervention is necessary not only in patients undergoing EVT under GA but also in patients treated under PS.\textsuperscript{43}

### Intraprocedural Blood Pressure

Low blood pressure during the EVT procedure (i.e., before reperfusion) has been shown in observational studies to cause worse outcomes, either as a reduction from baseline or as excessive blood pressure variability. Physiologically, this would support the hypothesis that penumbral perfusion is pressure passive, dependent on stable, elevated blood pressure.\textsuperscript{44} Furthermore, a recent analysis of hemodynamic and interventional data from the GOLIATH trial suggested that mean arterial blood pressure (MAP) <70 mm Hg is associated with poor collateral filling, which may further compromise the penumbra.\textsuperscript{45}

Typically, 2 different strategies are applied to blood pressure management under EVT. One strategy is the individual or relative approach whereby blood pressure is managed relative to a baseline blood pressure (often measured at admission or when the patient enters the neurointerventional suite). Blood pressure during the procedure is then allowed to fluctuate only 10% to 20% around the baseline.

The second strategy could be called the fixed threshold approach. In this approach, blood pressure is targeted above/within fixed thresholds. The Society for Neuroscience in Anesthesiology and Critical Care consensus recommends that SBP should be >140 mm Hg during the procedure.\textsuperscript{46} The aforementioned stroke guidelines suggest maintaining blood pressure <180/105 mm Hg, which is related mainly to the respective safety threshold of thrombolysis, but make no recommendation as to the lower end of the range (Class III).\textsuperscript{4}

As an example of a baseline-guided management, 1 study showed that a 40% drop in MAP is associated with worse outcome,\textsuperscript{47} and more recent studies have shown that even a 10% drop is associated with worse outcome.\textsuperscript{48} In MR CLEAN, an analysis in the patients under GA also showed a relationship between drop in blood pressure and outcome, but because the baseline SBP was only 130 mm Hg and thus

### Table 2 Potential Explanations for the Good Outcome in the Randomized Trials (SIESTA, ANSTROKE, GOLIATH) Related to EVT Under GA

<table>
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<th>Explanation</th>
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<td>Availability of neuroanesthesia team</td>
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<td>Detailed knowledge of EVT procedure and the importance of optimizing</td>
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<td>anesthesia logistics to minimize time delay to anesthesia induction</td>
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<td>General anesthetics reduce cerebral metabolic rate of oxygen and may provide</td>
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<td>Higher rate of successful reperfusion under general anesthesia</td>
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<td>Improved conditions for neurointerventional instrumentation, probably due</td>
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<td>Observational studies were biased</td>
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<td>Physiologic control and neuroanesthetic logistics may not have been well</td>
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<td>organized in the observational studies.</td>
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<td>No blood pressure protocols in the observational studies.</td>
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Abbreviations: ANSTROKE = Sedation vs General Anesthesia for Endovascular    |           |
| Therapy in Acute Stroke–Impact on Neurological Outcome; EVT = endovascular  |           |
| therapy; GA = general anesthesia; GOLIATH = General or Local Anaesthesia   |           |
| in Intra Arterial Therapy; SIESTA = Sedation vs Intubation for Endovascular  |           |
| Stroke Treatment.
lower than advised, the poor outcome may be seen as a violation of the fixed threshold criteria. In a recent study from Petersen et al., worse outcome correlated with even small (10%) drops in MAP in a dose-response relation with worse outcome in more severe drops in MAP from admission MAP.

Blood pressure management strategies in the 3 randomized trials on anesthetic strategy for EVT were very similar and followed the fixed threshold principle whereby SBP was aimed at >140 mm Hg and MAP at >70 mm Hg. These thresholds were partly according to the recommendations from Society for Neuroscience in Anesthesiology and Critical Care (Class III). Specific post hoc analyses of the relationship between blood pressure and outcome were performed in the SIESTA and GOLIATH studies. These analyses could not demonstrate a relationship between drops in blood pressure and outcome as long as SBP and MAP were kept above the thresholds mentioned above. An analysis of blood pressure data from all 3 studies (n = 365) showed worse outcomes if MAP was <70 or >90 mm Hg. The study
Further demonstrated that cumulated periods of a minimum of 10 minutes with MAP <70 mm Hg or a minimum of 45 minutes with MAP >90 mm Hg were associated with a shift toward higher 90-day mRS scores. These findings may suggest that blood pressure recordings outside targets are acceptable as long as they are immediately adjusted and support the application of strict blood pressure protocols to avoid too extreme variations (Figure 4).

A recent systematic review has summarized the findings that (relative) blood pressure drops are associated with poor outcome. The review also reported that studies with strict blood pressure protocols (SBP 140–180 mm Hg) did not find an association between blood pressure and outcome provided that the hemodynamic criterion was upheld. Survey data found that 35.7% of centers apply the absolute strategy and keep SBP between 140 and 180 mm Hg, while the rest of the centers apply a relative strategy in which MAP was not allowed to drop a certain percent relative to a baseline value. The hope is that future studies will guide us on optimal blood pressure targets.

### Postprocedural Blood Pressure

After the procedure, the physiologic argument for a high blood pressure being related to poor outcome is the increased risk of hemorrhagic transformation after reperfusion. The well-known U-shaped relationship was found in non-reperfused patients, while patients successfully reperfused did worse with higher postprocedural blood pressure, supporting the approach of many interventionalists to lower blood pressure after successful reperfusion. Of note, these signals from retrospective studies are yet to be confirmed by prospective studies.

Both SBP and blood pressure variability have been associated with functional outcome and risk of sICH. In a study by Kim et al., both absolute SBP and variability after EVT were associated with sICH. In the sICH group, a maximum SBP of 167.2 mm Hg was seen, while it was 155.0 mm Hg in the group with no sICH (p = 0.033). A relationship was also seen with the amount of time spent with a higher SBP.

In the newly published Blood Pressure After Endovascular Therapy for Ischemic Stroke trial, a peak SBP of 158 mm Hg was found to be the best discriminator between favorable and unfavorable outcome in the unadjusted but not in the adjusted analyses because patients were younger and had milder strokes in the <158 mm Hg group.

In summary, it seems reasonable to keep SBP >140 mm Hg or MAP between 70 and 90 mm Hg during EVT and SBP <160 mm Hg after EVT, but this needs to be investigated prospectively.

### Other Elements of Periprocedural Care

Multiple other factors likely play a role in periprocedural care but are beyond the scope of this article and hence are just
brieﬂy summarized here. The logistics of EVT, that is, organization, communication, and distribution of roles and tasks, are an essential component of improved stroke outcomes by more rapid onset to treatment times. Logistics of EVT may even extend to prehospital interventions (including controversies such as drip-and-ship vs mothership) because stabilization of the patient and mastering the interface to the emergency room inﬂuence planning for the angiography suite.

Neuroprotection in AIS has been investigated in countless animal studies but never successfully translated to the clinical setting. With the expectation of improved reperfusion by EVT, several approaches may now see a renaissance. One of these might be hypothermia, which is being investigated in a systemic and focal fashion in ongoing EVT studies. Until these yield results, normothermia should probably be the goal. Other neuroprotective strategies are being investigated in the prehospital and emergency room settings. A recent study (Safety and Eﬃcacy of Nerinetide [NA-1] in Subjects Undergoing Endovascular Thrombectomy for Stroke) showed the eﬀect of a neuroprotective agent in the subgroup of patients not receiving tPA.58

Hyperglycemia has a well-known association with worse outcome and higher risk of sICH after EVT.59 However, it is not known whether aggressive glycemic management improves outcomes. Continues insulin drip was not better than a sliding scale in a study on patients with ischemic stroke (all subtypes) with hyperglycemia.60 It may by prudent to measure glucose and stabilize it to normoglycemia during EVT.

Conclusion
EVT is a highly eﬀective therapy, and optimized periprocedural management may further improve patient outcomes. Particular consideration is given to the role of thrombolysis, choice of anesthetic strategy, and modulation of blood pressure. Additional randomized data are needed to improve these important factors. Integration of care systems and neuroprotective strategies may represent a near-term horizon. Both are under active study. While data-directed guidance is currently available, it is essential to continue eﬀorts to explore and understand these crucial, sometimes underappreciated, aspects of EVT care.

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Appendix Authors

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<th>Name</th>
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<tr>
<td>Claus Z. Simonsen, MD</td>
<td>Aarhus University Hospital, Denmark</td>
<td>Drafted manuscript, data acquisition, analysis and interpretation</td>
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<tr>
<td>Julian Bösel, MD</td>
<td>Klinikum Kassel, Germany</td>
<td>Revision of the manuscript, data acquisition, analysis and interpretation</td>
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<tr>
<td>Mads Rasmussen, MD</td>
<td>Aarhus University Hospital, Denmark</td>
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Periprocedural Management During Stroke Thrombectomy
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