Original research

Influence of intravenous alteplase on endovascular treatment decision-making in acute ischemic stroke due to primary medium-vessel occlusion: a case-based survey study

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ABSTRACT
Background Intravenous alteplase is currently the only evidence-based treatment for medium-vessel occlusion stroke (MeVO; M2/3, A2/3, and P2/3 vessel segment occlusions), but due to its limited efficacy, endovascular treatment (EVT) is increasingly performed in these patients. In this case-based survey study, we examined the influence of intravenous alteplase treatment on physicians’ decision-making for EVT in primary MeVO stroke.

Methods In an international web-based survey among physicians involved in acute stroke care, participants provided their EVT decision for six quasi-identical fictional MeVO case scenarios (three with and without intravenous alteplase administered). Each scenario showed radiological images and clinical information in the form of a short case vignette. We compared EVT decisions (“immediate EVT”, “no EVT”, or “wait for alteplase effect” [in case scenarios with alteplase treatment only]) for case scenarios with and without alteplase treatment. Clustered multivariable logistic regression was performed to assess the effect of alteplase treatment on treatment decision.

Results The survey was completed by 366 physicians from 44 countries, resulting in 2196 responses included in this study. In alteplase-treated cases, 641/1098 (58.4%) responses favored immediate EVT, 279/1098 (25.4%) favored no EVT, and 178/1098 (16.2%) opted to wait for alteplase effect. In non-alteplase-treated case scenarios, 846/1098 (78.7%) were in favor of and 252/1098 (21.3%) against EVT. Intravenous alteplase was associated with a lower chance of a decision in favor of immediate EVT (adjusted OR 0.38 [95%CI 0.31 to 0.46]).

Conclusions Intravenous alteplase is an important factor in EVT decision-making for MeVO stroke. However, even in alteplase-treated patients, more than half of the physicians decided to proceed with EVT without waiting for alteplase effect.

INTRODUCTION
Intravenous alteplase followed by endovascular treatment (EVT) is the standard of care for acute ischemic stroke (AIS) due to large-vessel occlusion (LVO), in alteplase-eligible patients. With regard to AIS due to medium-vessel occlusion (MeVO), that is, M2/3, A2/3, and P2/3 occlusions, there is currently no randomized evidence proving the safety and efficacy of EVT. Thus, intravenous alteplase is the only treatment option with a level 1A guideline recommendation for MeVO patients, although many of them do not qualify for alteplase treatment due to their relatively mild symptoms (National Institutes of Health Stroke Scale (NIHSS) <6). However, alteplase efficacy in MeVO stroke is limited, with early complete recanalization following alteplase administration occurring in less than 50%. Given the overwhelming efficacy of EVT in LVO stroke and encouraging preliminary safety and efficacy data in the MeVO patient population, physicians are increasingly treating MeVO patients with EVT. A well-designed clinical trial to evaluate EVT in MeVO stroke is needed, but a logistical concern for such a trial includes understanding which factors may influence clinical equipoise for EVT.

METHODS
The Conjoint Health Research Ethics Board of the University of Calgary approved this study (REB20-2086). An international, web-based, anonymous survey was conducted to explore current treatment practice and EVT decision-making in AIS due to MeVO among a broad, international audience of physicians involved in acute stroke care. Approximately 1400 stroke physicians of any specialty were invited to participate in the survey, based on their experience with EVT for AIS and their involvement in previous clinical trials on stroke. The online survey tool Qualtrics (Qualtrics.com) was used for survey distribution, data collection, encryption, and secure data storage. Access to the survey data was password-protected and granted to the study investigators only. Incomplete survey entries were excluded to avoid duplicate responses and incomplete data. Study data are available on reasonable request to the corresponding author.
Survey design
Participants were shown 33 MeVO stroke case scenarios, each consisting of a set of imaging findings and accompanying clinical information in the form of short case vignettes that included a fictional patient’s age, baseline NIHSS, baseline ASPECTS, occlusion location of a primary isolated MeVO, and in some cases CT-perfusion-based core and penumbra volumes. Case vignettes were constructed based on combined data from multiple clinical cases and fictional data, and do not represent real patients. Participants were then asked whether they would offer EVT to the patient or not (binary response: yes/no). In case the vignette indicated that the patient received intravenous alteplase, a third response option was provided (“wait for alteplase effect”). This study analyzes response data from six case-scenarios: three in which patients received intravenous alteplase, and three quasi-identical scenarios, the only difference being that the case vignette indicated that the patient was ineligible for intravenous alteplase (table 1). Corresponding anonymous imaging findings as they were provided to the survey respondents are shown in online supplemental figures 1-3.

Survey participants
Stroke physicians (neurologists, interventional neuroradiologists, neurosurgeons, and other physicians directly involved in acute stroke care) were invited to participate in the survey, without restrictions for personal caseload, hospital setting, geographical location, experience, and level of training or career stage. Prior to answering the case scenarios, participants were asked to provide some basic information about their country of practice, years of experience in treating strokes, age range, specialty, and career stage.

Statistical analysis
Participants’ baseline characteristics were summarized using descriptive statistics appropriate to the type of data. EVT decisions overall, with and without intravenous alteplase treatment were calculated and compared between physician specialties, geographic regions, and by occlusion location. Multivariable logistic regression with respondent identity and scenario as cluster variables was performed to assess the independent effect of intravenous alteplase on the decision to treat with EVT. Changes in treatment decision between scenarios with and without intravenous alteplase treatment decision were visualized with Sankey diagrams. Data analyses were performed in Stata 16.1. Figures were created with Microsoft Excel, version 16.45 and Microsoft PowerBI, version 2.88.1682.0.

RESULTS
A total number of 366 physicians from 44 countries completed the survey, resulting in 2196 responses for the six fictional case scenarios included in this study (n=1098 for scenarios with and without intravenous alteplase treatment each). In total, 217 survey entries were incomplete and excluded. Details on participants’ demographics are shown in online supplemental table 1.

Intravenous alteplase and EVT decision
For case scenarios where intravenous alteplase was administered, 641/1098 (58.4%) responses were in favor of immediate EVT, and “no EVT” was the second most common answer (279/1098 responses [25.4%]), while only 178/1098 (16.2%) responses were in favor of waiting for intravenous alteplase effect, as shown in figure 1A. When the patient described in the scenario was not eligible for intravenous alteplase treatment before EVT, immediate EVT was favored by 846/1098 (78.7%), see figure 1B. When stratifying responses by occlusion site, decision

### Table 1 Fictional case scenarios used in this study

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Occlusion site</th>
<th>Age</th>
<th>Sex</th>
<th>NIHSS</th>
<th>Onset to CT time</th>
<th>ASPECTS</th>
<th>CTP imaging findings</th>
<th>Intravenous alteplase</th>
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</thead>
<tbody>
<tr>
<td>1A</td>
<td>M2/3</td>
<td>86</td>
<td>Male</td>
<td>9</td>
<td>130 min</td>
<td>9</td>
<td>CTP core volume (rCBF &lt;30%) 7 mL CTP penumbra volume: not provided</td>
<td>Yes</td>
</tr>
<tr>
<td>1B</td>
<td>M2/3</td>
<td>86</td>
<td>Male</td>
<td>9</td>
<td>130 min</td>
<td>10</td>
<td>CTP core volume (rCBF &lt;30%) 7 mL CTP penumbra volume: not provided</td>
<td>Not eligible</td>
</tr>
<tr>
<td>2A</td>
<td>A3</td>
<td>79</td>
<td>Male</td>
<td>8</td>
<td>135 min</td>
<td>NA</td>
<td>CTP core volume (rCBF &lt;30%) 9 mL CTP penumbra volume (Tmax &gt;6) 30 mL</td>
<td>Yes</td>
</tr>
<tr>
<td>2B</td>
<td>A3</td>
<td>79</td>
<td>Male</td>
<td>8</td>
<td>135 min</td>
<td>NA</td>
<td>CTP core volume (rCBF &lt;30%) 7 mL CTP penumbra volume (Tmax &gt;6) 30 mL</td>
<td>Not eligible</td>
</tr>
<tr>
<td>3A</td>
<td>P2/3</td>
<td>52</td>
<td>Male</td>
<td>8</td>
<td>90 min</td>
<td>NA</td>
<td>CTP core volume (rCBF &lt;30%) 4 mL CTP penumbra volume (Tmax &gt;6) 24 mL</td>
<td>Yes</td>
</tr>
<tr>
<td>3B</td>
<td>P2/3</td>
<td>52</td>
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<td>8</td>
<td>90 min</td>
<td>NA</td>
<td>CTP core volume (rCBF &lt;30%) 4 mL CTP penumbra volume (Tmax &gt;6) 24 mL</td>
<td>Not eligible</td>
</tr>
</tbody>
</table>

*A3, third segment of the anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score for early ischemic changes on CT; CTP, CT perfusion; M2/3, second/third segment of the middle cerebral artery; NA, not applicable (ASPECTS only accounts for middle cerebral artery territory); P2/3, second/third segment of the posterior cerebral artery; rCBF, relative cerebral blood flow.
rates in favor of immediate EVT were lowest in A3 occlusion scenarios and highest in P2/3 occlusion scenarios, both with and without alteplase treatment. In multivariable clustered logistic regression, intravenous alteplase treatment (adjusted OR 0.38; 95% CI 0.31 to 0.46) was strongly negatively associated with the decision to proceed with immediate EVT.

Changes in EVT decision between alteplase-eligible and alteplase-ineligible patients are visualized in figure 2. Among physicians who decided to wait for alteplase treatment effect in eligible patients (n=63/366 [17.2%] in M2/3 occlusions, n=64/366 [17.5%] in A3 occlusions, n=51/366 [13.9%] in P2/3 occlusions), most decided to proceed with immediate EVT in case the described patient was not eligible for alteplase treatment (n=59/63 [93.7%] in M2/3 occlusions; n=57/64 [89.1%] in A3 occlusions; n=49/51 [96.1%] in A3 occlusions).

**Participant’s characteristics and EVT decision**

A comparison of overall and occlusion location-specific EVT decisions between geographic regions, specialties, and career stages is shown in figure 3. Physicians from Europe decided most often in favor of immediate EVT (337/537 [62.8%] with and 451/537 [84.0%] without intravenous alteplase treatment) with a slight, although non-significant, improvement in clinical outcomes following MeVO stroke with intravenous alteplase administration. Our results clearly reflect this alteplase treatment effect, with significantly higher EVT decision rates in alteplase-ineligible patients (79% vs 58%). Furthermore, one out of six physicians stated that they would wait to see whether the patient shows clinical improvement after alteplase before making a decision on EVT. However, probably owing to the rather small effect of alteplase on functional outcome in previous studies, more than half of the survey participants decided to immediately proceed with EVT even in patients who received intravenous alteplase. Out of those who decided to wait for an alteplase treatment effect, the vast majority opted for immediate EVT if alteplase was contraindicated.

However, all described patients in our survey had an NIHSS score of 8 or 9. Guidelines advise EVT in LVO strokes from NIHSS 6: strokes with less neurological deficits are often considered mild. For patients with mild strokes, which account for a relatively large proportion of MeVO patients due to the more distal occlusion location, intravenous alteplase was shown to improve functional independence rates, whereas an additional benefit of EVT in this patient group has not been proven. As such, more physicians might have preferred to wait for the effect of administered alteplase if patients had lower NIHSS scores. In addition, less severe neurologic deficits in MeVO stroke may affect patient triaging, in turn affecting workflow times and alteplase efficacy. In LVO strokes, the role of alteplase in patients presenting directly to an EVT-performing center seems
limited, since direct EVT and alteplase followed by EVT give very similar outcomes.\textsuperscript{35}

Procedural complications of EVT may form a drawback for physicians treating MeVO strokes. Important complications after EVT include intracranial hemorrhage and vessel dissection.\textsuperscript{6} These risks may be increased in MeVO strokes, since the target vessels are smaller and more distally located. However, new techniques, smaller devices, and more flexible catheters specifically designed for distal thrombectomy have improved procedural safety.\textsuperscript{16–18}

EVT decision rates in this study differed based on occlusion location. In scenarios with A2/3 occlusion, immediate EVT was favored only by 51% (alteplase-eligible patients)/71% (alteplase-ineligible patients) of respondents, while these numbers were much higher for scenarios with M2/3 occlusion (57%/83%) and P2/3 occlusion (82%/67%). The relatively high willingness to proceed with immediate EVT in P2/3 MeVOs could potentially reflect the lack of high-level evidence for IV thrombolysis in posterior circulation MeVOS,\textsuperscript{19} though one could argue that this applies to EVT as well. In fact, the safety and efficacy of EVT has not even been formally proven for LVOs in the posterior circulation,\textsuperscript{20} and there is complete paucity of high-level evidence on EVT for MeVOS in posterior circulation. The relatively young patient age (52 years), short onset to CT time (90 min), and small ischemic core volume (4 mL) in the posterior circulation occlusion scenario probably also influenced participants’ treatment decisions. The reason for the relatively low EVT decision rates in the scenarios with A3 occlusion remains unclear. They could be partly related to the fact that the deficits in isolated, more distal anterior cerebral artery occlusions can be relatively subtle and are often not well reflected in the NIHSS. It is however important to note that this impression is often deceptive: common sequelae of anterior cerebral artery strokes such as memory impairment, emotional lability, and isolated sensory deficits are often highly disabling, although they might not immediately become obvious in a focused neurological examination.\textsuperscript{21} The same applies to the validity of the NIHSS in PCA strokes: P2/P3 occlusions often present with lower NIHSS scores, possibly because the NIHSS does not optimally reflect the typical posterior circulation stroke symptoms.\textsuperscript{19} Therefore, we included detailed descriptions of the neurological loss of function for each case scenario, rather than only an NIHSS value (see online supplemental figures 1-3).

We observed an inverse relationship between physician experience and the willingness to proceed with immediate EVT, with physicians in training opting most often for immediate EVT, and board-certified physicians with >10 years of experience deciding least often in favor of immediate EVT. Furthermore, the “gap” between EVT decisions for alteplase-eligible and -ineligible scenarios decreased in less experienced physicians. This may indicate that younger physicians, having seen more of the rise and successes of EVT after the trials of 2015/2016,\textsuperscript{22} and less of the negative trials in the preceding years,\textsuperscript{23} have more positive expectations of EVT outcomes. For alteplase, the same effect may be true for physicians who saw the successes after the trials in the late 1990s.\textsuperscript{24–26} Of note, our case-scenarios specifically referred to intravenous alteplase, which is currently considered the standard of care. Whether physicians’ decisions would have been different with an alternative thrombolytic agent such as tenecteplase, which shows improved recanalization rates than alteplase, remains unclear at this point.\textsuperscript{27,28}

With regard to physician specialties, the highest willingness to proceed with immediate EVT was seen in interventional neuroradiologists and neurosurgeons. A similar effect as for the early vs late-career differences may be present, where neurologists may have been more involved in the alteplase trials, whereas interventionalists were logically only involved in the EVT trials. Confidence and experience in EVT efficacy and especially safety may play a role in this difference as well. Overall however, differences were small, and decision rates were largely similar between specialties.

When stratifying by geographic regions, European physicians showed the highest decision rates in favor of immediate EVT, closely followed by South/Latin America. The reasons for these geography-specific findings are complex and might be among other reasons related to local healthcare policy, guidelines, and medicolegal environment. Another potential explanation is the frequent use of general anesthesia for EVT in Europe.\textsuperscript{29} General anesthesia completely eliminates patient movement and might benefit the safety of MeVO EVT, where vessels are much smaller and more prone to injury than in LVO stroke.

\section*{Limitations}
This study has limitations. First, physicians were invited to this survey based on institutional networks and collaborations, and some geographic regions and specialties were under-represented. Thus, the results may not be representative of the entire stroke community. We collected no data on the number and characteristics of physicians that did not accept the survey invitation. Second, survey data are cross-sectional and thus do not reflect changes in EVT treatment decisions over time, which are invariably bound to happen as existing EVT technologies evolve and new devices are developed. Third, since vascular anatomy plays a key role in EVT decision-making, participants might have been influenced by the specific images provided in each case scenario, and their decision may reflect decision-making for this particular case rather than decision-making for MeVOS in general. We only included a limited number of occlusion locations: for example, we did not include a case with an A3 occlusion, which may have caused underrepresentation of some MeVO patient subgroups with certain occlusion locations in our study findings. Fourth, owing to the high number of responses, almost all findings in this study, for example subspecialty-related differences in EVT decision rates, were statistically significant but the absolute difference was often small and perhaps of no clinical relevance. We therefore deliberately refrained from reporting P-values for these differences. Lastly, simplified clinical case scenarios as they were used in this study can never capture the many dimensions of clinical decision-making in routine practice. For example, all case scenarios had an NIHSS of 8 or 9. A scenario with NIHSS <6, below the current cut-off for guideline-advised EVT for LVO strokes, would have given useful additional information — although the NIHSS may underrepresent in posterior and anterior circulation strokes, as described above. In addition, EVT preference rates in clinical practice may vary between patients with occlusions of the M2 vs M3 segment, or P2 vs P3, or A2 vs A3, and many other individual patient factors may make the decision to treat with EVT markedly more complex than the dichotomization we describe.

\section*{Conclusions}
Intravenous alteplase treatment was an important factor in EVT decision-making for MeVO stroke in this study, but even in alteplase-eligible patients, more than half of the physicians decided to proceed with EVT immediately, without waiting for alteplase effect.
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Data availability statement Data are available from the corresponding author upon reasonable request.

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