

1 **Impact of Clinical Trial Enrolment on Thrombolysis Workflow in a Mobile Stroke Unit:**

2 **Results from the AcT Trial**

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21

22 **Highlights**

- 23 • The University of Alberta Hospital-based mobile stroke unit (MSU) enrolled patients in
24 the Intravenous Tenecteplase Compared with Alteplase for Acute Ischemic Stroke (AcT)
25 trial.
- 26 • All eligible patients were randomized to the study without MSU workflow issues.
- 27 • An MSU is a feasible site for clinical trials in the hyperacute phase.

28 Abstract

29 **Background:** The Edmonton-based mobile stroke unit (MSU), which transports patients to the
30 University of Alberta Hospital (UAH), enrolled patients in the Intravenous Tenecteplase
31 Compared with Alteplase for Acute Ischemic Stroke (AcT) trial. We examined the feasibility of
32 trial enrolment in MSU, its impact on acute stroke workflow metrics, and functional outcomes at
33 90-120 days.

34 **Methods:** In this post-hoc analysis, patients were divided into three groups based on enrolment
35 site (MSU (n=43), UAH (n=273), and non-UAH (n=1261)). All patients were enrolled with a
36 deferred consent process. The primary outcome for this analysis was the feasibility of enrolment
37 defined as the proportion of patients receiving intravenous thrombolysis (IVT) during the study
38 period who were enrolled in the trial. Multiple linear and binary logistic regression was used to
39 evaluate the adjusted effect of the study groups on acute stroke workflow metrics and functional
40 outcomes at 90-120 days.

41 **Results:** 100% of eligible IVT-treated patients in the MSU during the study period were enrolled
42 in the AcT trial. Covariate-adjusted linear regression showed shorter door-to-needle [17.2 (9.7-
43 24.6) min] and CT-to-needle [10.7(4.2-17.1) min] times in the MSU compared to UAH and non-
44 UAH sites. There was no difference in the proportion of patients with an excellent functional
45 outcome (mRS 0-1) at 90-120 days or symptomatic ICH at 24 hours between groups.

46 **Conclusions:** Enrolment in the AcT trial from the MSU was feasible. MSU-enrolled patients
47 demonstrated faster door-to-needle and CT-to-needle times resulting in earlier IVT
48 administration, and similar rates of symptomatic intracerebral hemorrhage.

49
50 **Keywords:** mobile stroke unit, acute ischemic stroke, intravenous thrombolysis, tenecteplase

51 52 Introduction

53 Intravenous thrombolysis (IVT) is the first-line treatment for eligible patients with acute
54 ischemic stroke within the first 4.5 hours of symptom onset.¹ IVT is typically delivered in the
55 emergency department of a primary or comprehensive stroke center supervised by a neurologist.
56 Rapid administration of IVT closer to symptom onset is associated with better short and long-
57 term functional outcomes than delayed treatment.² The time-limiting step for IVT delivery is the
58 need for a computed tomography (CT) scan before IVT and the availability of a trained

59 multidisciplinary team. Mobile stroke units (MSUs) are specially designed ambulances equipped
60 with a CT scanner and trained personnel that may include a physician, nurse, CT technologist,
61 and paramedics. The MSU can assess a patient with acute stroke syndrome at the scene of the
62 stroke, at a rendezvous point with another ambulance, or a community hospital without access to
63 a CT scanner. The MSU hastens time to neurological assessment after symptom onset, provides
64 dedicated access to a CT scanner, and allows for rapid administration of IVT.³ Challenges exist
65 in the recruitment of patients in clinical trials in the prehospital setting with respect to the
66 consent process and clinical trial workflow.^{4,5} Few clinical trials have enrolled patients in
67 MSUs.⁶

68
69 The pivotal Intravenous Tenecteplase Compared with Alteplase for Acute Ischemic Stroke (AcT)
70 trial was a multicenter, randomized controlled trial that demonstrated non-inferiority of
71 tenecteplase (TNK) compared to alteplase within the first 4.5 hours from stroke onset.⁷ The
72 Edmonton-based MSU transports patients to the University of Alberta Hospital (UAH) and was
73 involved in enrolling patients in the AcT trial.⁸ We examined the feasibility, impact on
74 workflow, and functional outcomes with MSU enrolment in the AcT trial.

75

76 **Methods**

77 **The AcT Trial**

78 This is a post-hoc analysis of the AcT trial; the protocol and main results have been previously
79 published.^{7,9} Briefly, the AcT trial was a Canadian, pragmatic, multicenter, parallel-group, open-
80 label, registry-linked, randomized, controlled, non-inferiority study comparing the efficacy of
81 TNK versus alteplase in eligible patients with acute ischemic stroke. In the AcT trial, patients
82 were recruited in 1 MSU, 5 primary stroke centers, and 17 comprehensive stroke centers between
83 November 2020 and January 2022. Eligibility for IVT and post-thrombolysis care was based on
84 the Canadian Stroke Best Practices Guidelines.^{1,10} Patients were randomized 1:1 to receive either
85 TNK at a dose of 0.25 mg/kg according to weight brackets up to a maximum of 25 mg as bolus
86 dose or alteplase 0.9 mg/kg up to a maximum of 90 mg (10% as bolus dose and the remaining
87 90% over 1 hour as an infusion). The primary outcome for the AcT trial was the proportion of
88 patients with a modified Rankin score (mRS) of 0-1 at 90-120 days after randomization.

89

90 **Workflow of Edmonton Mobile Stroke Unit**

91 The Edmonton MSU has been operational since February 2017 and services both urban and rural
92 areas within a 250 km radius of the UAH in Alberta, Canada.¹¹ The MSU team consists of a
93 stroke fellow, emergency department nurse, CT technologist, primary care paramedic, and
94 advanced care paramedic. The MSU operates on weekdays between 8 am to 4 pm and is alerted
95 by the Emergency Medical Services (EMS) dispatch or a critical care phone consultation service
96 regarding patients with an acute stroke syndrome who are within 4.5 hours of symptom onset or
97 last known well time. For calls within the city of Edmonton, both a regular ambulance and MSU
98 are co-dispatched. For rural locations, the MSU and EMS ambulance meet at a rendezvous point
99 approximately midway between the site of the initial assessment and the UAH. On arrival, if the
100 patient is suspected to be an acute stroke eligible for thrombolysis, the patient is then transferred
101 to the MSU for a CT scan. Once completed, the team reviews the case and CT scan with a
102 telestroke physician. If eligible for IVT, alteplase or tenecteplase is delivered in the field and if
103 required the infusion is continued as the patient is transported to the comprehensive stroke center
104 for further evaluation and admission.

105

106 **Workflow of Trial Enrolment**

107 The UAH MSU was included as a site in the AcT trial and screened consecutive patients for trial
108 enrolment between November 2020 and January 2022. Patients evaluated on the MSU, similar to
109 other sites in the AcT trial, were enrolled using a deferred consent process in accordance with the
110 Tri-Council Policy Statement – Ethical Conduct for Research involving human guidelines and
111 the Helsinki Declaration.¹² The deferred consent process was designed to allow for rapid
112 treatment of time-critical conditions for patients being enrolled in randomized clinical trials. The
113 deferred consent process was approved at all sites in the AcT trial except for two centers in
114 Quebec. Patients were screened for trial eligibility by stroke fellows who were on board the
115 MSU. If the patient was deemed eligible for IVT, the stroke fellow randomized the patient with
116 the help of a secure, real-time, web-based server that could be accessed via a web browser on a
117 mobile phone. Randomization was also available through secure text messaging and automated
118 telephone calls. The randomizing physician received instant information about the treatment
119 allocation and dose. The study drug was stored on the MSU. The study coordinator would meet

120 the patient and/or the family member(s) on arrival at the UAH site at the earliest feasible time to
121 obtain written informed consent.

122

123 **Study Outcome Measures**

124 The primary outcome was the proportion of MSU administered IVT patients during the study
125 period who were enrolled in the trial. Secondary outcomes were door-to-needle time (min), CT-
126 to-needle time (min), the proportion of patients with symptomatic intracerebral hemorrhage
127 (ICH) at 24 hours, and mRS 0-1 at 90-120 days.

128

129 **Statistical Analyses**

130 The study participants were divided into MSU-treated, UAH site, and non-UAH sites. Age was
131 described as mean \pm SD. Baseline NIHSS and workflow metrics were non-normally distributed
132 and described as median with interquartile range (IQR). Sex, presence of intracranial occlusion,
133 patients undergoing endovascular thrombectomy (EVT), symptomatic ICH, and patients with
134 mRS of 0-1 and 0-2 at 90-120 days were expressed as proportions. Univariable analysis to
135 compare proportions was performed with the Chi-Square test. To assess between-group
136 differences in workflow measures (min) a linear regression was used. Logistic regression
137 assessed between-group differences on 90-day mRS 0-1. Similarly, a binary logistic regression
138 was used to assess between-group differences in patients achieving excellent outcomes (mRS 0-
139 1), good outcomes (mRS 0-2), and deaths. The reference category was a non-UAH site. All
140 regression analyses were adjusted for prespecified variables, including age (years), sex, baseline
141 NIHSS, visible symptomatic arterial occlusion site, and IVT drug type (TNK or alteplase).
142 Statistical significance was defined as a p-value <0.05 . All analyses were conducted using
143 STATA 18.0 BE (StataCorp LLC, Texas, USA).

144

145 **Results**

146 Of the 1577 patients (after excluding the 23 patients who did not consent) in the AcT trial, 43
147 (2.7%) were MSU-treated, 273 (17.3%) were treated at the UAH site, and 1261 (80%) were
148 treated at non-UAH sites. 100% of eligible MSU patients during the data collection period of the
149 AcT trial were enrolled. No issues were noted with randomization or internet connectivity during
150 enrolment. There were no issues related to drug availability or drug administration on the MSU.

151 The baseline characteristics of participants in the MSU-treated, UAH, and non-UAH groups are
152 described in Table 1 and outcomes in Table 2.

153
154 On linear regression, door-to-needle-time (min) was lower in the MSU-treated group by 17.2
155 (95% Confidence Interval (CI) 9.7-24.6) min compared to the non-UAH sites (Supplementary
156 Table 1). CT-to-needle time (min) was lower in the MSU-treated group compared to the non-
157 UAH site by 10.7 (95% CI 4.2-17.1) min (Supplementary Table 2; Figure 1). CT-to-needle time
158 was higher at the UAH site than the non-UAH sites by 3.1 (95%CI 0.4-5.9) min. There was no
159 statistically significant interaction noted between study groups and IVT drug type.

160
161 Symptomatic ICH at 24 hours, odds of excellent outcome (mRS 0-1), odds of good outcome
162 (mRS 0-2) showed no difference between the MSU-site and non-UAH site (Supplementary
163 Table 3-4; Figure 2). A total of 241 (15.3%) died during the study period. The odds of death
164 were increased in the UAH-treated group (aOR 1.57 (1.08-2.26)) (Supplementary Table 5)
165 compared to non-UAH site.

166
167 **Discussion**

168 This post-hoc analysis of MSU-enrolled patients included in the AcT trial indicates that it is
169 feasible to rapidly screen and enroll patients with acute ischemic stroke into clinical trials on an
170 MSU without significantly disrupting thrombolysis workflow. During the study period, all stroke
171 patients eligible for IVT evaluated by the MSU were enrolled in the trial. The MSU-enrolled
172 participants had faster workflow metrics, such as CT-to-needle time (min) and door-to-needle
173 time (min) allowing rapid delivery of reperfusion therapy after symptom onset. No difference
174 was observed in functional outcome measures assessed at 90-120 days. No safety concerns were
175 observed.

176
177 The prehospital stroke trial enrolment with an emergency medical systems ambulance is
178 challenging due to the issues of consent, CT scanner availability, and randomization.^{13,14} The
179 Prehospital Acute Neurological Treatment and optimization of medical care in Stroke study
180 (PHANTOM-S) conducted in Germany, and the Benefits of Stroke Treatment Delivered by an
181 MSU Compared with standard management by Emergency Medical Services (BEST-MSU) trial

182 conducted in the United States of America consistently demonstrated it is possible to enroll
183 patients safely in the CT equipped MSU.^{15,16} Both the BEST MSU trial and PHANTOM-S
184 prospectively designated weeks of enrolment by MSU vs standard of care in a quasi-
185 experimental fashion. These primary studies randomized patients to receive IVT either in MSU
186 or in the closest stroke center and observed the efficacy of MSU in delivering acute care. In the
187 comparison of TNK with alteplase for the early treatment of ischemic stroke in the Melbourne
188 MSU (TASTE-A) trial the investigators were able to conduct an MSU-only trial.⁶ The
189 investigators randomized 104 patients 1:1 with the help of sealed, opaque envelopes that
190 contained the treatment allocation, organized in sequential order as internet connectivity
191 concerns were expected. The TASTE-A study was able to randomize all eligible patients. In the
192 AcT study, patients were randomized in the MSU as a site along with the other stroke centers,
193 thus allowing MSU participation in the acute stroke multicenter trial. In this analysis, we
194 demonstrated the feasibility of randomizing patients in the MSU with the help of a web browser.
195 rFVIIa for Acute hemorrhagic Stroke administered at the earliest Time (FASTEST) is another
196 ongoing global study randomizing patients with acute spontaneous ICH in the first 2 hours of
197 symptom onset to either receive rFVIIa or placebo.¹⁷ The study is enrolling patients at 15 MSUs
198 worldwide. Like the AcT trial, a deferral of consent is used at applicable sites. The
199 randomization procedure involves the delivery of a fixed number of predetermined drug kits to
200 each site which are sequentially numbered, blinded, and dispensed by the site pharmacy. Thus,
201 the MSU will carry only one sequential kit at any given time. This is an example of the
202 innovative ideas that can be successfully implemented in recruiting patients in the MSU
203 environment. The deferral of the consent and presence of stroke fellow may have facilitated the
204 enrolment process. In the absence of a physician in the MSU enrollment is still possible if a
205 study stroke physician is available via telehealth and patient is being transferred to a study-site
206 ED. It is also possible to enroll patients in implementation studies by time-based cluster
207 randomization, where the intervention and control can be provided on certain days of week.

208

209 MSU allows for faster and earlier delivery of thrombolysis in eligible acute ischemic stroke
210 patients. MSU has been associated with better utility-weighted disability outcomes derived from
211 the mRS at 90 days.¹⁸ Furthermore, it has also been demonstrated that IVT with TNK is
212 associated with better early reperfusion than alteplase on the MSU.⁶ In our analysis, CT-to-

213 needle time and door-to-needle times were quicker than other sites. Faster CT-to-needle time
214 could be MSU workflow related as the patient is not moved from the stretcher bed, and the MSU
215 team can deliver dedicated care to one patient without simultaneity, which may be presented in
216 ED care.¹⁹ The AcT was conducted during the COVID-pandemic, it may have affected workflow
217 metrics. In a study from Alberta, the first year of COVID-pandemic was associated with delays
218 in CT-groin puncture, door-to-groin puncture and groin-puncture-to-reperfusion times compared
219 to the pre-pandemic period. However, no delays were noted in the door-to-CT and door-to needle
220 times during the first year of the pandemic.²⁰ Our results demonstrated that there was no
221 significant difference between the site of enrolment and the proportion of patients that had an
222 mRS of 0-1 at 90-120 days. Due to the small sample size, the results can only be considered
223 exploratory.

224

225 With respect to measures of safety, the proportion of symptomatic ICH was not different
226 between groups, and proportion of favorable outcomes (mRS 0-1 or mRS 0-2) was not different
227 among groups (Table 2). Interestingly, the rates of visible occlusions were significantly lower in
228 the MSU (45.2%) compared to UAH (64.6%) and non-UAH sites (68.2%) as well as the
229 proportion of patients that received EVT: MSU 23.3%, UAH 26.4%, and non-UAH 33.6%.
230 Recent evidence that TNK reduces perfusion lesion volume as compared to alteplase does not
231 explain this group difference as the proportion of TNK use was similar among groups: MSU
232 51.2%, UAH 49.1%, and non-UAH 51.5%. In a recent meta-analysis, IVT resulted in successful
233 reperfusion in 1 in 10 patients averting the need for EVT.²¹ However sub-group analyses of time
234 interval from stroke onset to IVT did not significantly change rates of successful reperfusion, and
235 thus faster onset-to-needle times cannot adequately explain the proportional differences in visible
236 occlusions and EVTs in our MSU group from existing data. As the MSU is treating earlier than
237 patients included in the above analyses it is possible that ultra-early thrombolysis could have a
238 higher recanalization rate in the setting of a threshold effect but that remains unproven. In this
239 exploratory analysis there was increased death in UAH ED treated group compared to the non-
240 UAH site and MSU site. Possible consideration are patients treated in MSU-site have stable
241 hemodynamic parameters, in the current observation maybe younger, had a lower intracranial
242 occlusion, mild-moderate severity of baseline neurological deficits as assessed by NIHSS (Table
243 1).

244 Our study has limitations. First, this is a secondary analysis of the AcT trial and as such is
245 underpowered to detect differences in patients' functional outcomes treated via the MSU in
246 relation to other sites, though point estimates favor the MSU. Furthermore, the small sample size
247 also limits the evaluation of workflow metrics beyond door-to-needle and CT-to-needle times.
248 Unexplained lower proportions of visible occlusions and EVT may be confounding the lower
249 rates of death observed in the MSU group. As MSU care expands globally, the feasibility of
250 enrollment will enhance the inclusion of stroke patients in the pre-hospital space and ultra-early
251 time period in trials of important stroke therapies.

252

253 **Conclusion**

254 Enrolment into the AcT trial from the MSU was feasible. MSU-enrolled patients demonstrated
255 no difference in a favorable outcome but had faster door-to-needle and CT-to-needle times
256 resulting in earlier IVT, similar rates of symptomatic intracerebral hemorrhage. Clinical trial
257 enrollment in MSU will allow for the inclusion of patients in the hyperacute phase of stroke.

258

259 **Statement of Authorship**

260 GC and AP contributed equally as first authors. MK led conceptualization and creation of study
261 design with assistance from GC and AP. AP and MK led statistical analysis with critical input
262 from TTS and TJ. GC, AP, and MK prepared the first draft. BHB, TJ, AS, MA, RS, AB, LC, NS,
263 AT, TTS, and BKM critically revised the final manuscript.

264

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267

268 **Competing Interests Disclosure Statement**

269 MA has received grants from CIHR and has participation on a data safety monitoring board or
270 advisory board with Palmera Medical and Fluid Biomed. RS discloses salary support from
271 Sunnybrook Research Institute, grants from CIHR, participation on an advisory board for
272 Hoffman-La Roche (<\$5000), and stock ownership in FollowMD Inc. BKM discloses grants
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274 honoraria from Roche and Boehringer Ingelheim, participation on an advisory board with

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277 Medical Protective Association. AS discloses honoraria from Bayer Daiichi, advisory board
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281

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350

351 **Table 1:** Baseline characteristics in MSU-treated, UAH site and non-UAH site groups.

	MSU-Treated (n=43, 2.7%)	UAH Site (n=273,17.3%)	Non-UAH site (n=1261, 80%)	p
Mean Age \pm SD, years	69 \pm 14	72 \pm 14	72 \pm 14	0.3
Female Sex, n (%)	15(34.9)	131(48)	609(48.3)	0.2
Median (IQR) NIHSS	9 (6,13)	11(6, 17)	9 (6, 17)	0.5
Median Onset-to-CT time, min	87(60, 123) *	101 (77, 145)	103(71, 159)	0.1
Median Onset-to-needle time, min	100 (79, 139) *	129(102,184)	131(93,189)	0.01
Median Door-to-needle time, min	26 (22,30) *	40(31,54) **	36(28,49)	<0.00 01
Median CT-to-needle time, min	13 (9,17) *	22(14,33) **	19(12,30)	<0.00 1
Visible Occlusion, n (%)	19 (45.2) *	175(64.6)	851(68.2)	0.005
Tenecteplase, n (%)	22(51.2)	134(49.1)	650(51.5)	0.7
Endovascular Thrombectomy, n (%)	10(23.3) *	72(26.4)	424(33.6)	0.03

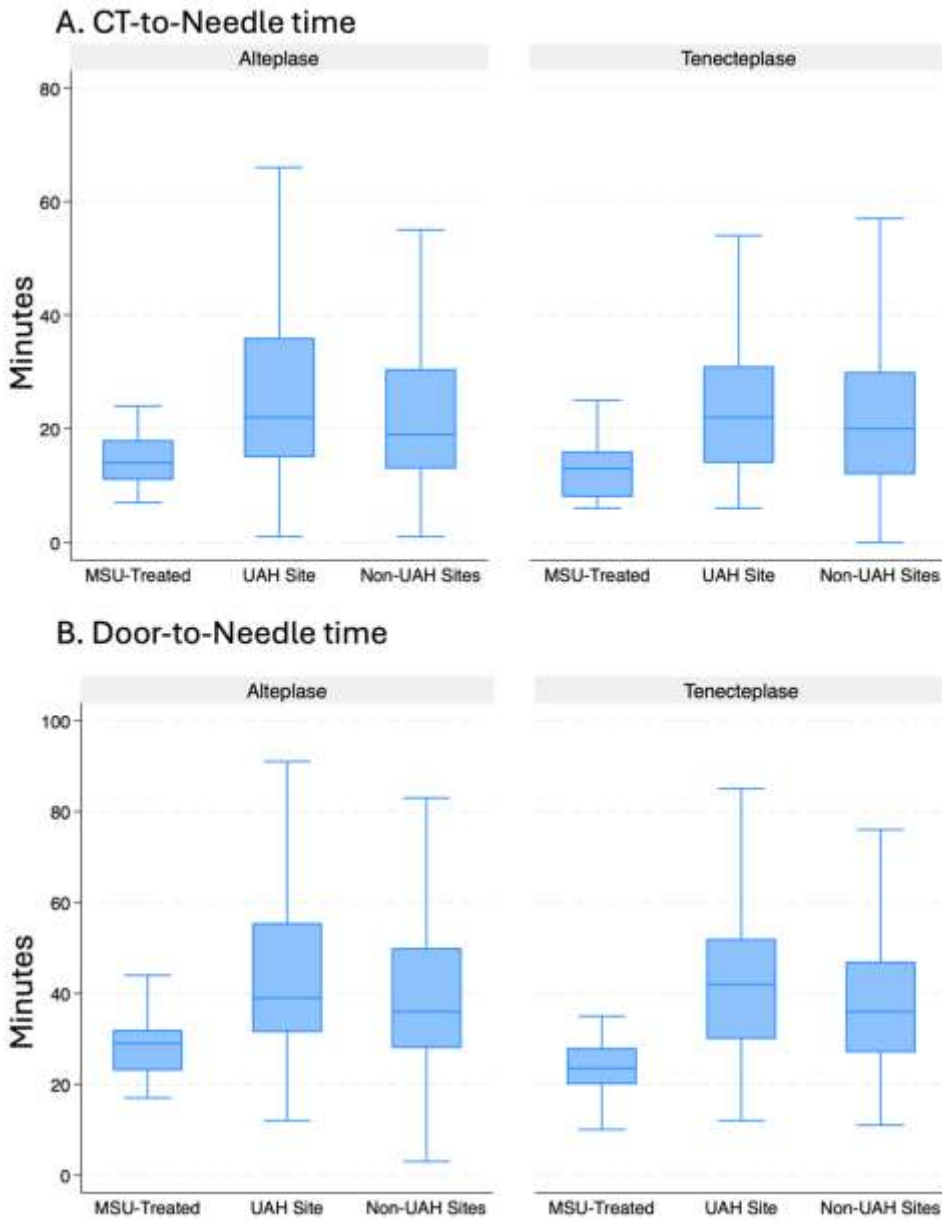
352 MSU- Mobile stroke unit, UAH-University of Alberta Hospital, NIHSS-National Institute Health
 353 Stroke Scale, CT- Computed tomography, *p<0.05 in MSU compared to other groups, **p<0.05
 354 in UAH compared to non-UAH

355 Table 2: Outcomes in MSU-treated, UAH site and non-UAH site groups.

	MSU-Treated (n=43, 2.7%)	UAH Site (n=273,17.3%)	Non-UAH site (n=1261, 80%)	p
Endovascular Reperfusion, n (%)	5(50)	56(77.8)	331(78.1)	0.1
Symptomatic intracerebral hemorrhage, n (%)	1(2.3)	9(3.3)	41(3.3)	0.9
mRS 0-1, n (%)	22(51.2)	96(35.7)	444(35.4)	0.1
mRS 0-2, n (%)	31(72.1)	148(55)	698(55.6)	0.09
Death, n (%)	2(4.7) *	53(19.4)	186(14.8)	0.02

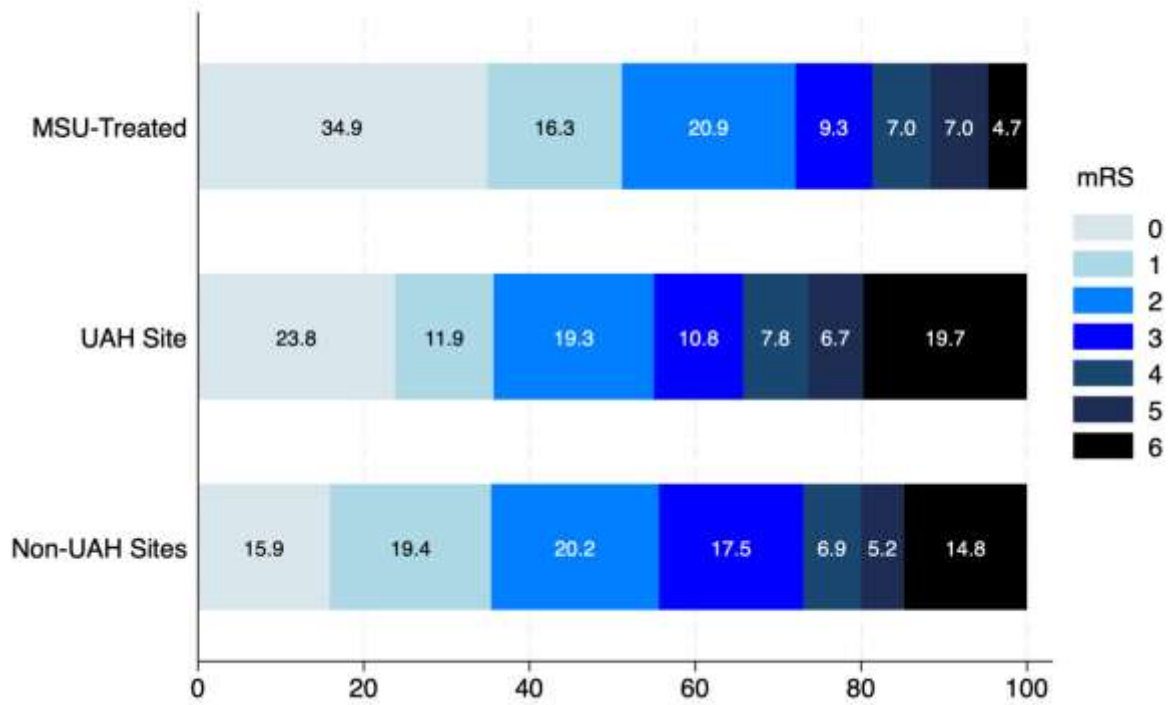
356 MSU- Mobile stroke unit, UAH-University of Alberta Hospital, mRS-modified Rankin scale,

357 *p<0.05 in MSU compared to other groups



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359 Figure 1: Box plot A: CT-to-needle time (min) in different groups (MSU-treated, UAH site, non-
 360 UAH site) and different intravenous thrombolysis groups (Alteplase, Tenecteplase); B: Door-to-
 361 needle time (min) in different groups (MSU-treated, UAH site, non-UAH site) and in different
 362 intravenous thrombolysis groups (Alteplase, Tenecteplase).



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365 Figure 2: Distribution of the modified Rankin Scale scores at 90-120 days in MSU-treated, UAH
 366 site, non-UAH site.