Variations in Modeling for Treating All Patients With Stroke With Suspected Large Vessel Occlusion

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Published in:
Jama neurology

DOI:
10.1001/jamaneurol.2019.0348

Publication date:
2019

2. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

3. Polman C, Kappos L, Freedman MS, et al; BENEFIT investigators. Subgroups of the BENEFIT study: risk of developing MS and treatment effect of interferon beta-1b. *J Neurol*. 2008;255(4):480-487. doi:10.1007/s00415-007-0733-2

4. O'Connor P; CHAMPS. The effects of intramuscular interferon beta-1a in patients at high risk for development of multiple sclerosis: a post hoc analysis of data from CHAMPS. *Clin Ther*. 2003;25(11):2865-2874. doi:10.1016/S0149-2918(03)80339-9

5. Giovannoni G, Cook S, Rammohan K, et al; CLARITY study group. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. *Lancet Neurol*. 2011;10(4):329-337. doi:10.1016/S1474-4422(11)70023-0

6. Hutchinson M, Kappos L, Calabresi PA, et al; AFFIRM and SENTINEL Investigators. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol*. 2009;256(3):405-415. doi:10.1007/s00415-009-0093-1

Variations in Modeling for Treating All Patients With Stroke With Suspected Large Vessel Occlusion

To the Editor We read the article by Holodinsky et al,[1] who reported the results of a modeling study to identify the optimal triage and transport strategy for patients suspected of having large-vessel occlusion, with interest.

This study adds input for discussing and redesigning care for patients with acute stroke by highlighting the tradeoffs in patient routing to the nearest thrombolysis center vs a center that offers thrombolysis and endovascular therapy. The authors suggest that prehospital triage, subsequent treatment allocation, and routing patterns can be modeled using data from clinical trials and that delivery of endovascular treatment should be centralized regionally. Input data for the model were obtained from clinical trials that were published by large comprehensive academic stroke centers. However, an important question on how well the trial setting reflects the clinical stroke pathway operational in their own region remains unanswered. The variability in triage instruments used, diagnostic accuracy attained, availability of sufficiently trained personnel, and how factual the distributions of the time intervals along the pathway were may not reflect the local situation. We support using simulation modeling to support redesign of care.[2] However, we stress carefully selecting and validating model parameters before suggesting general application and implementing a prehospital triage scale according to the promising results obtained. The results obtained in a dedicated academic trial setting might be overly optimistic projections that once compared with factual results would undermine policymakers' trust in modeling.

Also, by using a deterministic modeling approach, outcomes may appear quite fixed and robust (ie, not reflecting the real-life degree of precision and flexibility typically observed in acute stroke care pathways). Thus, as the effectiveness of acute stroke therapies is highly time sensitive,[3] the (parameterization) approach used may have led to an overestimation or underestimation of clinical outcomes. We propose stochastic modeling using patient-level data, as previously adopted for acute stroke care systems by Lahr et al,[4] which allows for the inherent randomness typically reflecting patient logistics from symptom onset to treatment in the hospital.

Furthermore, a seemingly obvious question regarding the scenarios compared was not answered, which is what would be the effect of a fast diagnostic workup and treatment with alteplase in thrombolysis centers and subsequent transportation for endovascular treatment compared with bypassing and immediate admission to overall more slowly operating comprehensive stroke centers?

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Published Online: March 25, 2019. doi:10.1001/jamaneurol.2019.0348

Conflict of Interest Disclosures: None reported.

1. Holodinsky JK, Williamson TS, Demchuk AM, et al. Modeling stroke patient transport for all patients with suspected large-vessel occlusion. *JAMA Neurol*. 2018;75(12):1477-1486. doi:10.1001/jamaneurol.2018.2424

2. Lahr MM, van der Zee DJ, Vroomen PC, Luijckx GJ, Buskens E. Thrombolysis in acute ischemic stroke: a simulation study to improve pre- and in-hospital delays in community hospitals. *PLoS One*. 2013;8(11):e79049. doi:10.1371/journal.pone.0079049

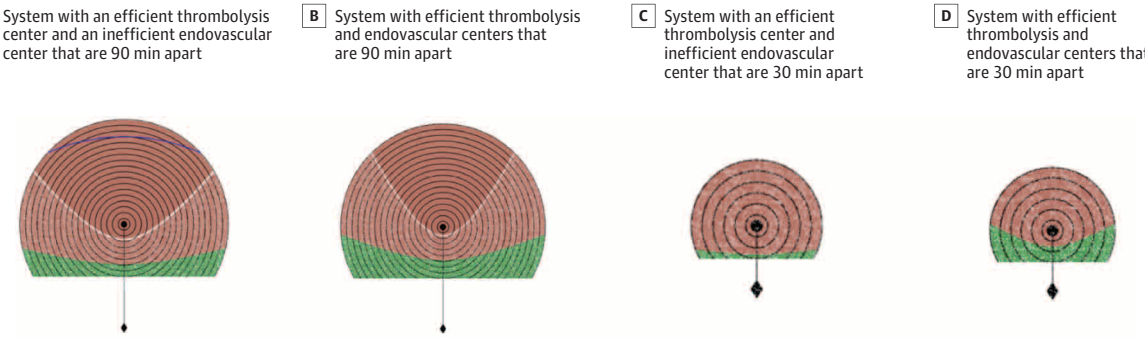
3. Saver JL, Goyal M, van der Lugt A, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316(12):1279-1288. doi:10.1001/jama.2016.13647

4. Lahr MM, van der Zee DJ, Luijckx GJ, Vroomen PC, Buskens E. A simulation-based approach for improving utilization of thrombolysis in acute brain infarction. *Med Care*. 2013;51(12):1101-1105. doi:10.1097/MLR.0b013e3182a3e505

In Reply We thank Maas et al for commenting on our recent article.[1] We would like to emphasize that this modeling is intended to be a framework for prehospital decision making, particularly for systemwide planning. Our approach comes from the reality that transport decision making must be made with system and geographic context and the realization that there can never be randomized clinical trials of drip and ship vs mothership in all regions globally. The main advantage of a modeling approach is that these context-specific factors can be considered, entered into a model, and varied appropriately to ensure that the models results are reflective of the system.

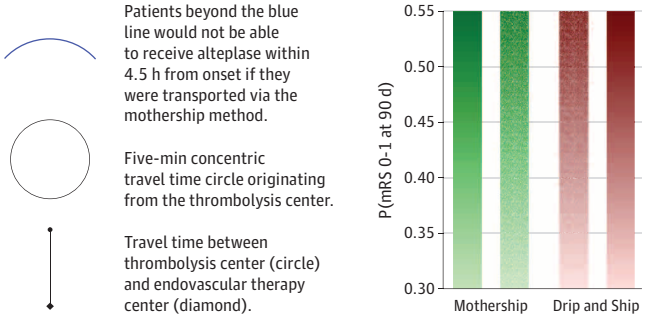
One of these system-level considerations is the extrapolation of randomized clinical trial data to real-life treatment practice. We acknowledge that data from explanatory trials may not always be generalizable to real-world practice. In this case, the data relating the average probability of good outcome to onset to treatment times allow for individual onset to treatment times within a real-life workflow to be simulated. Similarly, the trial data are from a highly selected group of patients (small infarct core, good collateral circulation, functionally independent prestroke). However, the model is adaptable and flexible and as results of more pragmatic trials or registries of endovascular therapy treatment (eg, MR-CLEAN registry[2]) become available, such data can be in-

Figure. Comparison of Drip-and-Ship vs Mothership Transport



E Time parameters used in panels A-D

Time Parameter	Panel A	Panel B	Panel C	Panel D
Onset to first medical contact	30	30	30	30
Ambulance response and scene time	30	30	30	30
DTN at thrombolysis center	30	30	30	30
DIDO at thrombolysis center	50	50	50	50
DTN at EVT center	45	30	45	30
DTP at EVT center (mothership)	90	60	90	60
DTP at EVT center (drip and ship)	60	30	60	30
Travel time between centers	90	90	30	30



In a completely efficient system (B and D) and one with less efficient endovascular therapy centers than thrombolysis centers (A and C) using a Los Angeles Motor Scale score of greater than or equal to 4 patient distribution. Green indicates that the mothership model predicts the greatest probability (P) of a good outcome, defined as modified Rankin scale (mRS) score of 0 to 1 (P[mRS 0-1]). Red indicates that the drip-and-ship model predicts the greatest P (mRS, 0-1). Stippling indicates the following equation: |P(mRS 0-1 | mothership) − P(mRS 0-1 | drip-and-ship)| < .01. DIDO indicates door-in–door-out time; DTN, door-to-needle time; DTP, door-to-puncture time; EVT, endovascular therapy.

corporated into the modeling. However, this type of data may be reflective of this specific local practice and regional customization is the key to modeling local circumstance in this kind of model.

Maas et al also identify a scenario not explored in the article, which is the efficient thrombolysis center and the less efficient endovascular therapy center. The model's flexibility allows for these scenarios to be examined; see the **Figure** for an example comparing transport in a system with efficient thrombolysis centers and nonefficient endovascular therapy centers (Figure, A and C) with transport in a totally efficient system (Figure, B and D). As expected in this scenario, the drip-and-ship method is predicted to result in better patient outcomes because of the early alteplase administration at the efficient thrombolysis centers.

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Published Online: March 25, 2019. doi:10.1001/jamaneurol.2019.0367

Conflict of Interest Disclosures: Ms Holodinsky reported funding from a graduate studentship from Alberta Innovates and has partial equity ownership of DESTINE Health Inc. Dr Hill reported grants from Medtronic LLC, Boehringer Ingelheim, and NoNO Inc. Dr Kamal reported grants from the Society of NeuroInterventional Surgery, Health and Social Care Board of Northern Ireland, and Hyogo Medical College and is a part equity owner for DESTINE Health Inc.

1. Holodinsky JK, Williamson TS, Demchuk AM, et al. Modeling stroke patient transport for all patients with suspected large-vessel occlusion. *JAMA Neurol*. 2018;75(12):1477-1486. doi:10.1001/jamaneurol.2018.2424

2. Mulder MJHL, Jansen IGH, Goldhoorn RB, et al; MR CLEAN Registry Investigators. Time to endovascular treatment and outcome in acute ischemic stroke: MR CLEAN Registry results. *Circulation*. 2018;138(3):232-240. doi:10.1161/CIRCULATIONAHA.117.032600

CORRECTION

Error in Discussion Section: In the Original Investigation titled "Pioglitazone Therapy in Patients With Stroke and Prediabetes: A Post Hoc Analysis of the IRIS Randomized Clinical Trial,"[1] published online February 7, 2019, there was an error in the Discussion section. The second-to-last sentence before the Limitations section should read: "Myocardial infarction and stroke are very costly, so the balance of NNTs for beneficial outcomes and numbers needed to harm for adverse outcomes would suggest cost utility for pioglitazone, but we have not yet conducted a cost-utility calculation." This article was corrected online.