

## **SUPPLEMENTAL MATERIAL**

### **Personalized prehospital triage in acute ischemic stroke: a decision-analytic model**

Esmee Venema; Hester F. Lingsma; Vicky Chalos; Maxim J.H.L. Mulder; Maarten M.H. Lahr; Aad van der Lugt; Adriaan C.G.M. van Es; Ewout W. Steyerberg; M.G. Myriam Hunink; Diederik W.J. Dippel; Bob Roozenbeek

**Table I.** Overview of the model parameters used in the probabilistic sensitivity analysis.

**Table II.** Results of the probabilistic sensitivity analysis using 10,000 Monte Carlo simulations.

**Figure I.** Distribution of the baseline modified Rankin Scale (mRS) scores.

**Figure II.** The time-dependent decrease in treatment effect as used in the model.

**Figure III.** Tornado-plot with the effect of changes in model parameters on the optimal transportation strategy.

**Figure IV.** Results of the sensitivity analyses.

**Table I.** Overview of the model parameters used in the probabilistic sensitivity analysis.

Model parameter	Estimated value	SE	Distribution	Source
<i>Treatment characteristics</i>				
Probability of receiving IVT if presenting <4.5h with an ischemic stroke	0.55	±10%	Beta	Expert opinion
Effect of IVT, beta	0.56 at time 0	0.18	Normal	Hacke et al. <sup>1</sup> (n=2763)
Time-dependent decrease in effect of IVT, beta	-0.0019 per minute	0.001	Normal	Hacke et al. <sup>1</sup> (n=2763)
Probability of early reperfusion after IVT	0.11	0.008	Beta	Tsivgoulis et al. <sup>2</sup> (n=1561)
Probability of receiving EVT if presenting <6h with an LVO	0.85	±10%	Beta	Expert opinion
Effect of EVT, beta	1.35 at time 0	0.29	Normal	Saver et al. <sup>3</sup> (n=1275)
Time-dependent decrease in effect of EVT, beta	-0.0026 per minute	0.001	Normal	Saver et al. <sup>3</sup> (n=1275)
<i>Outcome parameters</i>				
Utility values				Dijkland et al. <sup>4</sup>
mRS scores 0	0.95	0.08	Beta	(n=7)
mRS scores 1	0.93	0.04	Beta	(n=36)
mRS scores 2	0.83	0.04	Beta	(n=84)
mRS scores 3	0.62	0.05	Beta	(n=87)
mRS scores 4	0.42	0.04	Beta	(n=133)
mRS scores 5	0.11	0.05	Beta	(n=45)
Death hazard rate ratios				Samsa et al. <sup>5</sup>
mRS scores 0-1	1.00	N/A	N/A	
mRS scores 2	1.11	1.0-1.5	Triangular	
mRS scores 3	1.27	1.2-1.4	Triangular	
mRS scores 4	1.71	1.3-2.0	Triangular	
mRS scores 5	2.37	1.5-4.0	Triangular	

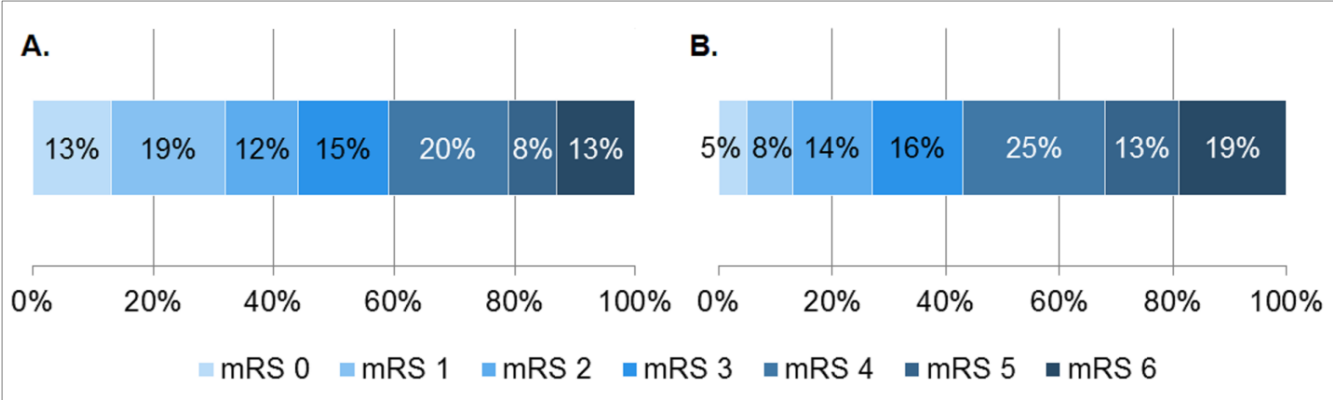
Abbreviations: EVT = endovascular treatment; IVT = treatment with intravenous thrombolytics; mRS = modified Rankin Scale; N/A = not applicable; SE = standard error.

**Table II.** Results of the probabilistic sensitivity analysis using 10,000 Monte Carlo simulations.

<b>Probability of large vessel occlusion</b>	<b>Optimal transportation strategy (percentage of simulations)</b>			<b>Median benefit of direct transportation to intervention center, QALYs (95% credible interval)</b>
	<i>Primary stroke center</i>	<i>Indifferent</i>	<i>Intervention center</i>	
<b>Base case scenario</b>				
Low risk (14%)	58%	36%	6%	-0.03 (-0.09 to 0.03)
Average risk (30%)	17%	44%	39%	0.01 (-0.05 to 0.08)
High risk (66%)	1%	5%	94%	0.09 (0.00 to 0.20)
<b>Urban scenario</b>				
Low risk (14%)	7%	82%	11%	0.00 (-0.03 to 0.03)
Average risk (30%)	1%	31%	68%	0.03 (-0.01 to 0.08)
High risk (66%)	<1%	3%	97%	0.09 (0.02 to 0.19)
<b>Rural scenario</b>				
Low risk (14%)	87%	9%	4%	-0.10 (-0.25 to 0.03)
Average risk (30%)	65%	20%	15%	-0.04 (-0.17 to 0.07)
High risk (66%)	5%	13%	82%	0.07 (-0.04 to 0.20)

The percentage of simulations in which transportation to the primary stroke center or direct transportation to the intervention center was preferred and the median difference in expected outcome between the two strategies is shown for different scenarios and different likelihood of large vessel occlusion. The percentages may not add up to 100% due to rounding. Abbreviations: QALYs = quality-adjusted life years.

**Figure I.** Distribution of the baseline modified Rankin Scale (mRS) scores.

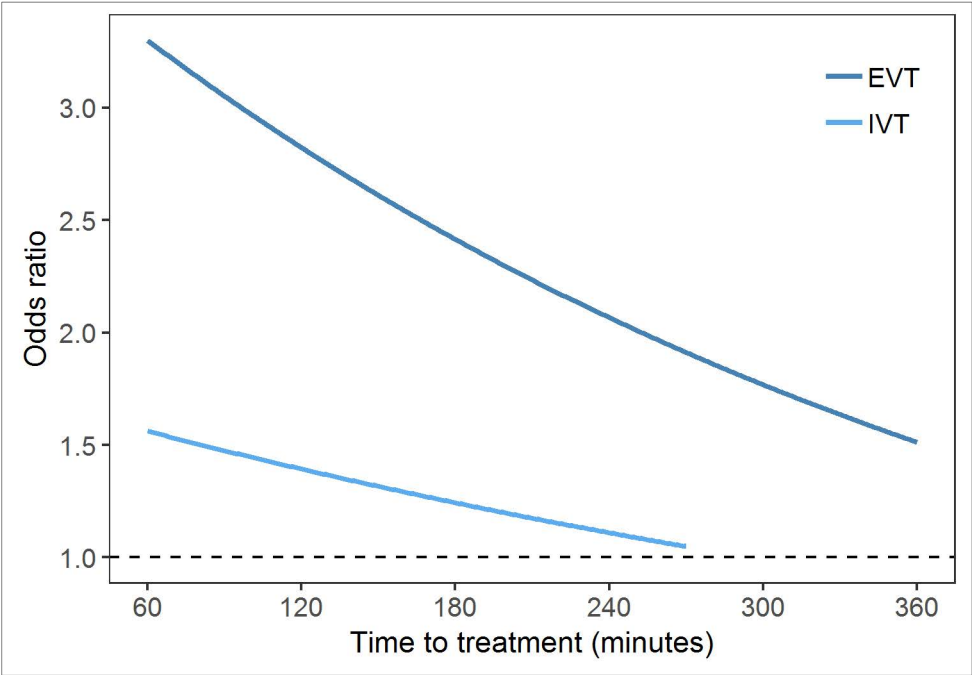


Outcome for untreated ischemic stroke patients without large vessel occlusion (A) and untreated ischemic stroke patients with large vessel occlusion (B).

A. Hacke et al.<sup>1</sup> (placebo group, n=1386); B. Goyal et al.<sup>6</sup> (control group, n=644).

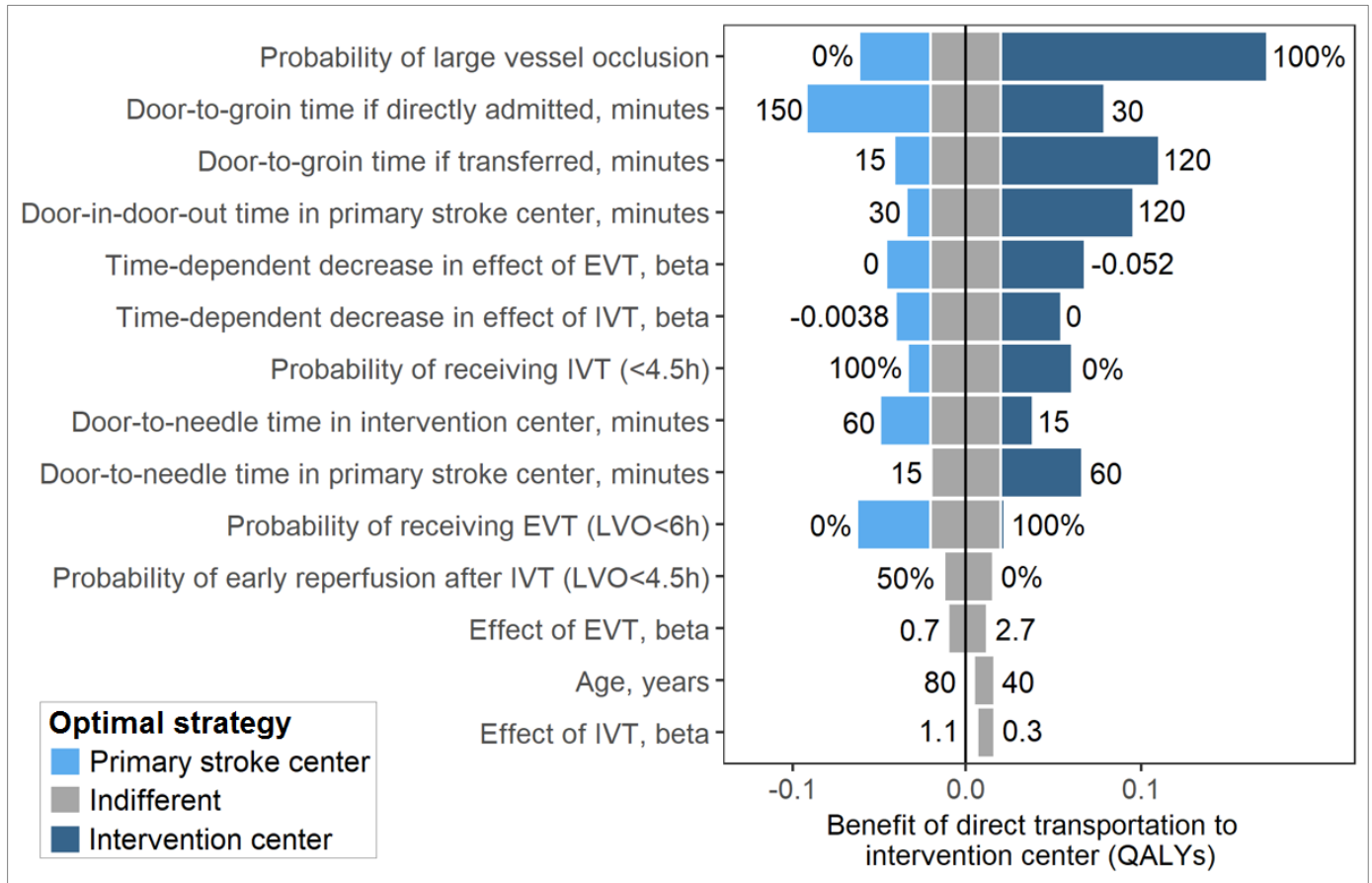
Abbreviations: mRS = modified Rankin Scale.

**Figure II.** The time-dependent decrease in treatment effect as used in the model.



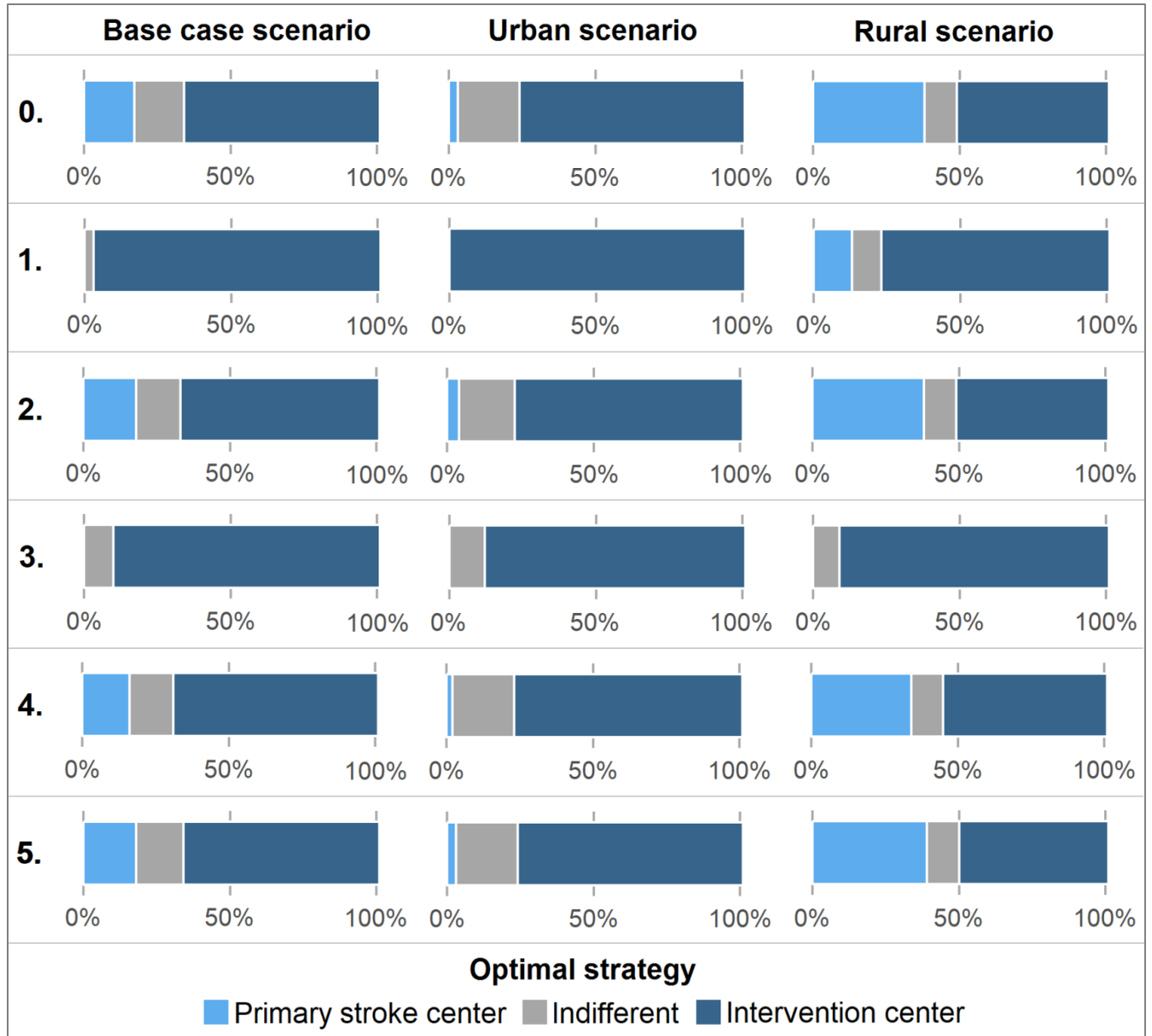
Abbreviations: EVT = endovascular treatment; IVT = treatment with intravenous thrombolytics.

**Figure III.** Tornado-plot with the effect of changes in model parameters on the optimal transportation strategy.



The bars illustrate the effect of changes in the model parameter estimates, within the indicated ranges, on the optimal transportation strategy. The bars are ordered according to their impact on the difference in outcome. Abbreviations: EVT = endovascular treatment; IVT = treatment with intravenous thrombolytics; LVO = large vessel occlusion.

**Figure IV.** Results of the sensitivity analyses.



The bars show the optimal transportation strategy for different likelihood of large vessel occlusion in the base case scenario (primary stroke center at 20 minutes and intervention center at 45 minutes); the urban scenario (10 minutes and intervention center at 20 minutes); and the rural scenario (primary stroke center at 30 minutes and intervention center at 90 minutes).

0. Base case analysis.
1. Sensitivity analysis with increased workflow times in primary stroke center (door-to-needle time 60 minutes and door-in-door-out time 90 minutes).
2. Sensitivity analysis with female patient.
3. Sensitivity analysis with contra-indications for treatment with intravenous thrombolytics.

4. Sensitivity analysis with absent effect of treatment with intravenous thrombolysis for patients with a large vessel occlusion.
5. Sensitivity analysis with utility weights as defined in the study of Chaisinanunkul et al.<sup>7</sup>



## References

1. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: Pooled analysis of atlantis, ecass, and ninds rt-pa stroke trials. *Lancet*. 2004;363:768-774
2. Tsivgoulis G, Katsanos AH, Schellinger PD, Köhrmann M, Varelas P, Magoufis G, et al. Successful Reperfusion With Intravenous Thrombolysis Preceding Mechanical Thrombectomy in Large-Vessel Occlusions. *Stroke*. 2018;49:232-235.
3. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *JAMA*. 2016;316:1279-1288
4. Dijkland SA, Voormolen DC, Venema E, Roozenbeek B, Polinder S, Haagsma JA, et al. Utility-weighted modified rankin scale as primary outcome in stroke trials: A simulation study. *Stroke*. 2018;49:965-971
5. Samsa GP, Reutter RA, Parmigiani G, Ancukiewicz M, Abrahamse P, Lipscomb J, et al. Performing cost-effectiveness analysis by integrating randomized trial data with a comprehensive decision model: Application to treatment of acute ischemic stroke. *J Clin Epidemiol*. 1999;52:259-271
6. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723-1731
7. Chaisinanunkul N, Adeoye O, Lewis RJ, Grotta JC, Broderick J, Jovin TG, et al. Adopting a patient-centered approach to primary outcome analysis of acute stroke trials using a utility-weighted modified rankin scale. *Stroke*. 2015;46:2238-2243