Supplementary material; Expediting workflow in the acute stroke pathway for endovascular thrombectomy in the northern Netherlands: A simulation model.

Introduction

The main text of the manuscript provides the most important findings of the study. This supplementary material provides details of the research setting (Figure S1) and on the simulation modeling methodology and the estimation of each of the 7 scales belonging to the modified Rankin Scale (mRS) score, ranging from 0 (no symptoms) to 6 (death).

Setting

Fig. S1. Regional organization of PSCs and CSCs.

CSC, Comprehensive Stroke Centre; PSC, Primary Stroke Centre

Simulation modeling methodology

Monte Carlo simulation modeling

Within the Monte Carlo simulation methodology random variables are used for solving stochastic or deterministic problems. The passage of time plays no substantial role, as there is no competition between patients.[1] Variety in patient diagnostics, characteristics, time delays towards endovascular thrombectomy (EVT) and routing patterns are incorporated into the model by probability distributions derived from real patient data. The Monte Carlo simulation modeling is to test 'what if' scenarios for workflow changes in the acute stroke pathway.

Distribution fitting

Activity durations and diagnostics are modeled by probability distributions, using data on individual patients. ExpertFit™ is used for distribution fitting, supporting the selection of statistical distributions, determining their parameters and testing candidate distributions for their goodness-of-fit.[2] Main steps in distribution fitting concerned:

- Importing of patient data into ExpertFit™.
- Fitting theoretical distributions.
- Seeking further evidence in case goodness of fit tests are indeterminate, in an attempt to underpin the choice of a specific theoretical distribution.[3] Evidence considered includes conceptual usage of the candidate distribution(s), commonalities between highest ranked distributions, and consultation of domain experts. If such evidence is not found an empirical distribution was chosen.

Set-up of experiments

All experiments concern observations on 100.000 hypothetical patients. The number of patients is chosen such that the relative 95% confidence interval half width for the likelihood mRS 0-2 score is below 1%.

Software

Plant Simulation™ was used to model the acute stroke pathway and perform experiments.[4] Expertfit™[,2] was used to find the probability distributions and their parameters.

Models

In the main text the conceptual models, the set-up for both the mothership model (MS) and drip-and-ship model (DS), are visualized (figure 2). After stroke onset patients either enter the hospital from outside by ambulance transportation or are already hospitalized. This applies for both models. 10% of the DS patients were already hospitalized and 12% of the MS patients. After distinguishing these patient routes (Table S1 and Table S2), the following time variable was modeled for hospitalized patients; 'time from stroke onset to CT. For patients with a stroke onset outside the hospital the following time variables were modeled; 'time from stroke onset to 911 call', i.e. call for help, 'EMS response', 'EMS on scene', 'EMS transport', 'time from hospital arrival to CT'. The distributions of these time variables are presented in Table S1 (DS model) and Table S2 (MS model).

After the time variables 'time from stroke onset to CT' (hospitalized patients) and 'time from hospital arrival to CT' (patients outside the hospital) patients are modeled according to the same routes in the emergency department (ED). Within the ED patients are routed according to 3 routes; route 1 = CT to IVT to CTA, route 2 = CT to CTA to IVT and route 3 = CT to CTA (in case of a contraindication for IVT). This applies for both models. For the DS model also the 'time from last examination ED to transfer call' is modeled according to these routes. For the DS model the following percentages per routes are used; 37.7% of the patients are routed according to route 1, 41.7% according to route 2 and 20.5 % according to route 3. For the MS model the percentages are; 28.0%, 36.6% and 35.4 %, respectively.

After ED routing the following time variables are modeled in the DS model; EMS response for transfer to a comprehensive stroke center (CSC), EMS handover for transfer, EMS transfer. After CSC arrival there are 2 routes for DS patients; patients with additional diagnostics (10.9%) and patients without additional diagnostics. The following time variables are modeled for patients receiving additional diagnostics; 'time from hospital arrival to last additional diagnostics' and 'time from additional diagnostics to angiography suite'. For the other patients, without additional diagnostics, 'time from hospital arrival to angiography suite' is modeled. For all patients the same 'time from angiography suite to groin puncture' is modeled. For all distributions of the DS model see Table S1.

For the MS patients the following time variables are modeled after the different routes in the ED; 'time from last examination ED to angiography suite' and 'time from angiography suite to groin puncture'. For all distributions of the MS model see Table S2.

In addition, patients age and diagnostics (National Institutes of Health Stroke Scale (NIHSS) and collaterals) are modeled to estimate the 7 scales of the mRS at 90 days. Collaterals are divided in 4 categories:

absent of collaterals, less than 50% filling of occluded area, more than 50% filling but less than 100% filling of occluded area or 100% filling of occluded area, and NIHSS score and age are both continuous variables. Mean (SD) in the DS model are for NIHSS 15.3 (5.3) and for age 70.2 (12.9) years. Collateral categories were divided in 7.2%, 52.9%, 31.4% and 8.5%, respectively. For the MS model the mean (SD) is 14.9 (5.5) for NIHSS and 65.2 (14.5) years for age. Collateral categories were divided in 10.1%, 35.4%, 36.7% and 17.7%, respectively.

Table S1. Distributions of the DS simulation model.

Activity duration	Distribution	Parameters		
Hospitalized vs. patients outside hospital	Discrete empirical	Value		Frequency
		Hospitalized		15
		Outside hospital		150
Time from stroke onset to CT (hospitalized patients)	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	30	7
		30	60	5
		227	227	1
Time from stroke onset to 911 call (patients outside hospital)	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	1	26
		1	5	22
		5	10	17
		10	15	10
		15	20	10
		20	30	11
		30	40	8
		40	50	7
		50	75	10
		75	100	6
		100	150	6
		150	200	3
EMS Response	Beta	Lower endpoint = 2.29; Upper endpoint = 30.53; α1 = 2.56; α2 = 7.15		
EMS on Scene	Gamma	Location = 1.70; α = 5.43; β = 2.73		
EMS Transport	Weibull	Location = 0.00 α = 2.11; β = 13.14		
Time from hospital arrival to CT	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	5	8
		5	10	21
		10	15	39
		15	20	28
		20	25	14
		25	35	12
		35	55	3
ED routing (3Catergories)	Discrete empirical	Value		Frequency

		Route 1: CT to IVT to CTA		57
		Route 2: CT to CTA to IVT		63
		Route 3: CT to CTA		31
Time from CT to IVT (route 1)	Erlang	Location = 0.00; α = 1; β = 13.70		
Time from IVT to CTA (route 1)	Erlang	Location = 0.85; α = 1; β = 13.69		
Time from last examination ED to transfer call (route 1)	Gamma	Location = 0.00; α = 2.63; β = 13.66		
Time from CT to CTA (route 2)	Gamma	Location = 0.00; α = 2.63; β = 3.53		
Time from CTA to IVT (route 2)	Erlang	Location = 0.00; α = 1; β = 12.57		
Time from last examination ED to transfer call (route 2)	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	5	12
		5	15	10
		15	25	14
		25	35	13
		35	60	9
		60	90	3
Time from CT to CTA (route 3)	Lognormal	μ = 23.06; σ = 21.72		
Time from last examination ED to transfer call (route 3)	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	15	6
		15	30	5
		30	45	8
		45	60	9
		60	95	3
EMS response for transfer	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	2	12
		2	4	17
		4	6	18
		6	8	29
		8	10	39
		10	15	17
		15	30	8
EMS handover for transfer	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	5	5
		5	10	31
		10	15	59
		15	20	31
		20	30	11
		30	40	2
EMS transfer	Beta	Lower endpoint = 0.00; Upper endpoint = 50.06; α1 = 2.17; α2 = 2.29		
Additional diagnostics vs. no additional diagnostics	Discrete empirical	Value		Frequency
		Additional diagnostics		18

		No additional diagnostics	147
Time from hospital arrival to last additional diagnostics	Gamma	Location = 10.39; α = 1.11; β = 17.41	
Time from additional diagnostics to angiography suite	Beta	Lower endpoint = 4.82; Upper endpoint = 124.31; α1 = 0.67; α2 = 1.60	
Time from hospital arrival to angiography suite	Gamma	Location = 4.25; α = 2.23; β = 10.19	
Time from angiography suite to groin puncture	Beta	Lower endpoint = 4.72; Upper endpoint = 65.69; α1 = 4.55; α2 = 6.55	
NIHSS(continuous)	Discrete empirical	Value	Frequency
		3	1
		4	5
		5	3
		6	3
		7	10
		8	7
		9	3
		10	2
		11	2
		12	7
		13	5
		14	10
		15	12
		16	10
		17	19
		18	17
		19	14
		20	9
		21	8
		22	7
		23	6
		24	3
		28	1
Age(Continuous)	Discrete empirical	Value	Frequency
		25	1
		34	1
		38	1
		40	1
		42	1
		45	2
		46	1
		48	1
		51	2
		52	2
		53	3
		54	2
		55	4
		56	1
		57	3
		58	2
		59	4
		60	4
		61	4

		62	4
		63	3
		64	4
		65	6
		66	5
		67	5
		68	5
		69	4
		70	5
		71	4
		72	5
		73	7
		74	5
		75	3
		76	2
		77	6
		78	5
		79	6
		80	5
		82	3
		83	7
		84	2
		85	4
		86	7
		87	1
		88	2
		89	2
		90	3
		91	1
		92	1
		93	1
		97	1
		99	1
Collaterals(2Categories), NIHSS ≤ 15*	Discrete empirical	Value	Frequency
		Absent (0)	11
		less than 50 % filling (1)	81
		> 50% or < 100% filling (2)	48
		100% filling (3)	13

DS, 'drip-and-ship' model; CT, Computed Tomography; EMS, Emergency Medical Services; SD, Standard deviation; IVT, intravenous thrombolysis; CTA, Computed Tomography angiography; ED, Emergency department; NIHSS, National Institutes of Health Stroke Scale.

Table S2. Distributions of the MS simulation model.

Activity duration	Distribution	Parameters		
Hospitalized vs. patients outside hospital	Discrete empirical	Value		Frequency
		Hospitalized		10
		Outside hospital		73
Time from stroke onset in hospital to CT (hospitalized patients)	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	20	3
		20	90	4
		90	130	2

Time from stroke onset to 911 call (patients outside hospital)	Continuous empirical	Lower Bound	Upper Bound	Frequency
		0	1	10
		1	5	6
		5	10	9
		10	20	10
		20	30	5
		30	50	7
		50	100	11
		100	240	8
EMS Response	Lognormal	μ = 9.77; σ = 3.61		
EMS on Scene	Lognormal	μ = 21.55; σ = 8.16		
EMS Transport	Weibull	Location = 0.00; α = 2.16; β = 20.03		
Time from hospital arrival to CT	Log-logistic	Location = 6.47; α = 6.29; β = 2.57		
ED routing (3Catergories)	Discrete empirical	Value		Frequency
		Route 1: CT to IVT to CTA		23
		Route 2: CT to CTA to IVT		30
		Route 3: CT to CTA		29
Time from CT to IVT (route 1)	Log-logistic	Location = 1.79; α = 8.58; β = 2.86		
Time from IVT to CTA (route 1)	Lognormal	μ = 15.74; σ = 17.43		
Time from CT to CTA (route 2)	Beta	Lower endpoint = 0.47; Upper endpoint = 30.69; α1 = 1.96; α2 = 6.53		
Time from CTA to IVT (route 2)	Gamma	Location = 0.00; α = 1.44; β = 8.93		
Time from CT to CTA (route 3)	Lognormal	μ = 10.96, σ = 11.45		
Time from last examination ED to angiography suite	Gamma	Location = 0.00; α = 3.49; β = 18.63		
Time from angiography suite to groin puncture	Log-logistic	Location = 0.00; α = 28.36; β = 4.89		
NIHSS(continuous)	Discrete empirical	Value		Frequency
		2		1
		3		2
		4		2
		5		2
		6		1
		7		2
		8		3
		9		2
		10		4
		11		5
		12		2
		13		3
		14		3
		15		4
		16		7
		17		9
		18		6
		19		4
		20		12

		21	2
		22	3
		23	2
		27	1
Age(Continuous)	Discrete empirical	Value	Frequency
		19	1
		24	1
		27	1
		36	1
		42	1
		46	2
		48	1
		49	1
		50	1
		51	1
		52	2
		53	1
		54	1
		55	2
		56	3
		57	2
		58	2
		59	2
		60	1
		61	2
		62	2
		63	1
		64	3
		65	2
		66	3
		68	1
		69	2
		70	6
		71	6
		72	3
		73	3
		74	1
		77	1
		78	3
		79	4
		82	2
		83	1
		85	1
		87	1
		88	2
		89	1
		91	2
Collaterals(2Categories), NIHSS ≤ 15*	Discrete empirical	Value	Frequency
		Absent (0)	8
		less than 50 % filling (1)	28
		> 50% or < 100% filling (2)	29
		100% filling (3)	14

MS, 'mothership' model; CT, Computed Tomography; EMS, Emergency Medical Services; SD, Standard deviation; IVT, intravenous thrombolysis; CTA, Computed Tomography angiography; ED, Emergency department; NIHSS, National Institutes of Health Stroke Scale.

Table S3. Scenarios DS model and MS model.

	Baseline	Input parameters	Source
DS model			
1. PSC workflow, reduce DIDO times			
a. Route 1 = route 2 to reduce time from PSC arrival to departure to CSC.	85*	Choice of routing through ED	Analyses of patient data, UMCG
b. Reduce ambulance response time to 0 minutes, pre-alert for transfer from PSC to CSC	8*	Response time of ambulance	Sablot et al., 2016[5]
c. Reduce handover time to 11 minutes	14*	Handover time of patient from PSC to ambulance	Analyses of patient data, UMCG
d. Combine PSC workflow improvements; 1a + 1b + 1c		See scenarios 1a, 1b and 1c	
2. CSC Workflow			
a. Reduce time from CSC arrival to angiography suite to a maximum of 5 minutes	26*	Time from CSC arrival to angiography suite	Expert opinion
b. Reduce time from angiography suite arrival to groin puncture to a maximum of 10 minutes	30*	Time from angiography suite arrival to groin puncture	Expert opinion, analysis of the MR CLEAN Registry (NL), Aghaebrahim et al., 2017[6]
c. Combine CSC workflow improvement; 2a + 2b		See scenarios 2a and 2b	
3. Combine PSC workflow and CSC workflow; 1d + 2c		See scenarios 1d and 2c	
MS model			
4. CSC workflow			
a. Route 1 = route 2 to reduce time from CSC arrival to angiography suite arrival.	98*	Choice of routing through ED	Analyses of patient data, UMCG
b. Reduce time from last examination at the ED (IVT/CTA) to arrival at angiography suite to a maximum of 30 minutes	58*	Time from last examination at ED (IVT/CTA)	Expert opinion, Analysis of the MR CLEAN Registry (NL), Saver et al., 2016[7] Mehta et al., 2014[8]
c. Reduce time from angiography suite arrival to groin puncture to a maximum of 10 minutes	28*	Time from angiography suite arrival to groin puncture	Expert opinion, Analysis of the MR CLEAN Registry (NL), Saver et al., 2016[7]
d. Combine CSC workflow improvement; 1a + 1b + 1c		See scenarios 1a, 1b and 1c	

*Median times. DS, drip-and-ship; MS, mothership; PSC, primary stroke center; DIDO, door in door out; ED, emergency department; CSC, comprehensive stroke center; IVT, intravenous thrombolysis; CTA, computed tomography angiography.

Estimating patient outcomes

The efficacy of EVT is time dependent. For the simulation model the likelihood of each of the 7 scales belonging to the modified Rankin Scale (mRS) score, ranging from 0 (no symptoms) to 6 (death) is approximated by a ordinal logistic regression model. Regression models are developed for the DS [1] and MS model [2]:

Regression models account for patient characteristics using the following variables;

- Stroke onset-to-groin puncture time (Total delay in minutes), continuous variable
- Age, continuous variable
- NIHSS score, continuous variable
- Collaterals in 4 categories, with dummy variables for absent of collaterals (yes or no, dummy 0), < 50 filling (yes or no, dummy 1), >50% filling, <100% filling (yes or no, dummy 2), 100% filling (yes or no, dummy 3).

[1] For the DS model the following formulas were used (n=154):

Likelihood mRS6 = 1/(1+exp(6.975-(Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017)))

Likelihood mRS5 = (1/(1+exp(6.841- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))-(1/(1+exp(6.975- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

Likelihood mRS4 = (1/(1+exp(6.359- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))-

(1/(1+exp(6.841- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

Likelihood mRS3 = (1/(1+exp(5.549- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))-(1/(1+exp(6.359- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

Likelihood mRS2 = (1/(1+exp(4.131- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))-(1/(1+exp(5.549- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

Likelihood mRS1 = (1/(1+exp(2.366- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))-(1/(1+exp(4.131- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

Likelihood mRS0 = 1-(1/(1+exp(2.366- (Collaterals_dummy_0 * 0.712)-(Collaterals_dummy_1 * 0.455)-(Collaterals_dummy_2 * -0.148)-(TotalDelay * 0.006)-(NIHSS * 0.165)-(Age * 0.017))))

[2] For the MS model the following formula was used (n=80):

Likelihood mRS6 = 1/(1+exp(3.886-(Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025)))

Likelihood mRS5 = (1/(1+exp(3.808- (Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))-

(1/(1+exp(3.886- Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))

Likelihood mRS4 = (1/(1+exp(3.444- (Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))-(1/(1+exp(3.808- Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))

Likelihood mRS3 = (1/(1+exp(2.720- (Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))-(1/(1+exp(3.444- Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))

Likelihood mRS2 = (1/(1+exp(1.722-(Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))-(1/(1+exp(2.720- (Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))

Likelihood mRS1 = (1/(1+exp(-0.588- (Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))-(1/(1+exp(1.722- (Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))

Likelihood mRS0 = 1-(1/(1+exp(-0.588- (Collaterals_dummy_0 * 0.853)-(Collaterals_dummy_1 * 1.262)-(Collaterals_dummy_2 * -0.534)-(TotalDelay * 0.003)-(NIHSS * 0.010)-(Age * 0.025))))

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