BMJ Open

Expediting workflow in the acute stroke pathway for endovascular thrombectomy; a simulation modeling approach.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-056415
Article Type:	Original research
Date Submitted by the Author:	19-Aug-2021
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Keywords:	Stroke < NEUROLOGY, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Organisational development < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Expediting workflow in the acute stroke pathway for endovascular thrombectomy; a simulation modelling approach.

On behalf of the CONTRAST investigators.

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Word Count, 3268;

Number of figures/tables, 5

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Abstract

Objective The aim of this study is to identify barriers for timely endovascular thrombectomy (EVT) delivery and to study the effects of potential workflow improvements in the acute stroke pathway.

Design Hospital data prospectively collected in the MR CLEAN Registry was linked to emergency medical services data for each EVT patient and used to build two Monte Carlo simulation model. Two archetypical models reflecting patients arrived directly at the comprehensive stroke centre (CSC), i.e. 'mothership' model, and patients transferred from primary stroke centres (PSCs) to the CSC, i.e. 'drip-and-ship' model.

Setting North of the Netherlands. One CSC provides EVT and its catchment area includes eight PSCs.

Participants Simulation modelling using data from 248 patients that were treated with EVT between July 2014 and November 2017. Eighty-three patients were routed according to the 'mothership' model and 165 patients according to the 'drip-and-ship' model.

Primary outcome measures The main outcome measures were total delay from stroke onset until groin puncture, functional independence at 90 days (modified Rankin Scale 0-2) and mortality.

Results Barriers identified included fast-track emergency department routing, pre-alert for transfer to the CSC, reduced handover time between PSC and ambulance, direct transfer from CSC arrival to angiography suite entry and reducing time to groin puncture. Workflow improvements may reduce onset to groin time by approximately 1 hour. Thus more patients, i.e., 7.4% ('drip-and-ship') and 3.7% ('mothership') might regain functional independence after 90 days and mortality would decrease by 5.0% and 3.0%, respectively.

Conclusions In our region proposed workflow improvements might reduce time to treatment by about 1 hour, and an additional 6% of patients would regain functional independence. Simulation modelling is a useful tool to assess potential effects of interventions reducing the onset to EVT time.

Article Summary

Strengths and limitations of this study

- Time delays along the acute stroke pathway for patients treated with endovascular thrombectomy are collected, allowing barriers from onset to treatment to be identified, analysed and simulated.
- An extensive set of workflow improvements is suggested based on data-analysis, expert opinion and literature.
- A simulation model of the acute stroke pathway is developed enabling effective and efficient assessment of workflow improvements, relying on realistic in-silico modelling.
- The simulation model only includes patients treated with endovascular thrombectomy, but could be extended to all suspected stroke patients, allowing a more comprehensive assessment of stroke care.

Introduction

Acute ischemic stroke places a large burden on society and the overall incidence has increased by 78% since 1990.[1] The main reperfusion treatments for acute ischemic stroke due to large vessel occlusion are intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT). For both treatments the adagio "time is brain" holds. For EVT, the probability of regaining functional independence at 90 days after stroke declines by 5% to 6% per additional hour delay from onset to groin puncture (OTG).[2,3]

Successful and timely EVT largely depends on the regional organization of acute stroke care delivery. During both pre- and intra-hospital processes and along each step in the acute stroke pathway delays may occur, which might worsen patient outcomes or even render them ineligible for acute treatment. Identified pathway elements known to potentially cause treatment delays are prehospital stroke management, in-hospital patient transfer, anaesthetic management, teamwork and inter-hospital patient transfer.[4]

Most interventions aimed at improving workflow processes have primarily been studied discretely, examining bits and pieces of the acute stroke pathway separately. Actual improvements might be identified through analyses that assess several improvements conjointly. To support such comprehensive analyses, simulation modelling has been suggested and performed with different organizational models for IVT.[5,6]

The aim of this study is to (1) assess delays in the workflow of acute stroke care, using patient-level data, and 2) to estimate the impact of reducing delays throughout the work-up towards EVT treatment using simulation modelling.

Methods

Setting

This study is based on prospective data collected in the MR CLEAN registry[7] from patients treated with EVT in our comprehensive stroke centre (CSC). Our CSC provides EVT for eligible patients in the northern part of the Netherlands (1.7 million inhabitants). Its catchment area includes eight primary stroke centres (PSCs), at distances between 6 and 84 kilometres shown in Figure 1.

Fig. 1. Regional organization of PSCs and CSCs.

Figure 1

Participants and data collection

Between July 2014 and November 2017, 285 patients were included. According to the emergency medical services (EMS) protocol,[8] patients suspected of acute stroke were routed to the nearest IVT capable hospital being either a CSC (mothership (MS) model) or presented at a PSC after which patients were subsequently transferred to the CSC for EVT (drip and ship (DS) model). In the eastern part of the province of Groningen patients were directly routed towards the CSC, reflecting a centralized organizational model.[9]

Patient data on clinical characteristics, diagnostics processes, time delays and ambulance routing patterns served as input for simulation modelling. In-hospital time delays included: onset or time last seen well, computed tomography (CT), IVT initiation, computed tomography angiogram (CTA), arrival at angiography suite and time of groin puncture. In-hospital (PSC or CSC) patients were routed through the Emergency Department (ED) according to three routes: 1) CT to IVT to CTA, 2) CT to CTA to IVT, or 3) CT to CTA (patients ineligible for IVT). Following secondary transfer of DS patients arriving at the CSC, they could undergo additional diagnostics (e.g. CT and/or CTA).

Prehospital data from three EMS organizations was retrospectively collected and linked to MR CLEAN registry data, per patient. Time delay items collected included: 911 notification, EMS arrival at the stroke onset location, departure to hospital and hospital arrival. In addition, for DS patients the timestamps for EMS transfer notification, arrival at PSC, departure to CSC, and CSC arrival were collected.

Patients were excluded from analyses in case of a prior modified Rankin Scale (mRS) >2, and when OTG exceeded 390 minutes, as perfusion CT based EVT beyond 6 hours was not indicated at that time. Missing values were excluded from analyses.

Informed consent

The MR CLEAN registry data collection has been approved for the Netherlands by the central medical ethics committee and research board (MEC-2014-235). The need for individual patient consent was waived.[10] In order to link hospital patient data with the corresponding EMS data, a Data Transfer Agreement was drafted and implemented.[11]

Patient and public involvement

No patients involved.

Simulation

For both the MS - and DS organization models separate Monte Carlo simulation models were developed.[12] Prior to model building, conceptual modelling was performed for abstracting real-world acute stroke pathways, shown in Figure 2. Conceptual models were validated using expert opinion (MU), combined with literature observations and input of stroke experts participating in the nation-wide collaboration for new treatments of acute stroke (CONTRAST) consortium.[13]

Both simulation models were developed using Plant Simulation™.[14] Distributions for each individual time delay variable were based on patient data and obtained using ExpertFit™.[15] Details are presented as Supplementary material. Simulation models were numerically validated by comparing mean, median, standard deviation, minimum and maximum time values of real-world patient data and observations with model data and outputs.

Within the simulation model ordinal regression was used for estimating the likelihood of each of the 7 scales belonging to the mRS score, ranging from 0 (no symptoms) to 6 (death). Known prognostic variables were: OTG (continuous), age (continuous), National Institutes of Health Stroke Scale score (continuous), and CTA collateral grading score 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). The likelihood of functional independence (mRS 0-2) was calculated from the formulas obtained by ordinal regression. Details are presented as Supplementary material.

Fig. 2. Conceptual models of the acute stroke pathway, 'Mothership' and 'Drip-and-ship'.

**** Figure 2****

Modelling scenarios

We identified barriers along the acute stroke pathway by analysing patient data, relevant literature and expert opinion (MU) and tested these hypothetical scenarios 'in silico' using the developed simulation model.

Outcome measures

Outcome measures include the OTG, the likelihood of functional independence (mRS 0-2) and mortality (mRS 6) at 90 days.

Analysis

For each scenario, we calculated the clinical benefits in terms of reduction in OTG and the likelihood of regaining functional independence and reducing mortality.

Results

Two-hundred-forty-eight patients met the inclusion criteria. Twenty-seven patients were excluded because of a pre-stroke mRS > 2 and/or 12 patients had an unknown OTG or > 390 minutes. Patients' characteristics, diagnostics and median time delays per model are shown in Table 1. 51.8% of the 83 MS patients and 52.1% of the 165 DS patients regained functional independence after 90 days.

Table 1. Characteristics, diagnostics and time delays of the MS and DS models.

	MS model	*n*	DS model	*n*
Patient characteristics				
Age in years (SD)	65 (14)	*83*	70 (13)	*165*
Male (%)	39 (47)	*83*	99 (60)	*165*
IVT rate (%)	53 (64)	*83*	132 (80)	*165*
Patient diagnostics				
Baseline NIHSS score 1-15 (%)	36 (44)	*82*	71 (43)	*165*
Collaterals absent or less than 50 % filling (%)	36 (45)	*80*	92 (60)	*155*
Process times EMS				
Symptom onset to 911 call	20 (6-63)	*66*	11 (3-33)	*139*
Response time	9 (7-12)	*65*	9 (7-12)	*132*
On scene time	20 (16-26)	*62*	16 (12-20)	*126*
Transport time	17 (12-23)	*61*	12 (7-15)	*122*
Process times inhospital, PSC or CSC				
Hospital arrival to CT	13 (11-17)	*63*	15 (11-20)	*125*
Route 1				
CT to IVT	10 (8-16)	*23*	8 (4-19)	*56*
IVT to CTA	10 (6-22)	*23*	11 (5-19)	*57*
Route 2				

CT to CTA	6 (5-10)	*30*	9 (5-11)	*62*
CTA to IVT	11 (7-18)	*30*	9 (4-15)	*63*
Route 3				
CT to CTA	7 (4-14)	*29*	14 (9-30)	*31*
Process times EMS for transfer from PSC to CSC				
Last examination ED (IVT or CTA) to 911 transfer call	NA		28 (15-44)	*148*
Response time	NA		8 (5-10)	*140*
Handover time	NA		14 (10-16)	*139*
Transport time	NA		27 (19-32)	*150*
Process times inhospital CSC				
Route additional diagnostics				
CSC arrival to additional diagnostics	NA		23 (17-45)	*17*
Additional diagnostics to angiography suite	NA		29 (14-70)	*18*
Last examination ED to angiography suite	58 (44-82)	*76*	NA	
CSC arrival to angiography suite	107 (74-133)	*60*	26 (16-38)	*151*
Arrival angiography suite to groin puncture	28 (25-35)	*77*	30 (24-35)	*163*
Overall time				
OTG	205 (160-260)	*83*	230 (198-275)	*165*

Time variables are in minutes, median (IQR). MS, mothership model; DS, drip-and-ship model; SD, Standard deviation; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; EMS, Emergency Medical Services; CSC, Comprehensive Stroke Centre; PSC, Primary Stroke Centre; CT, computed tomography; CTA, computed tomography angiogram; ED, Emergency department; NA, not applicable; OTG, time from stroke onset to groin puncture.

Identified delays

We identified multiple opportunities for improving workflow for both the DS and MS models.

DS model, PSC workflow Door In Door Out time (DIDO) was used to estimate the entire PSC workflow, defined as time from PSC arrival until departure to the CSC. Patients routed through the ED according to route 2 (CT to CTA to IVT) had a reduced DIDO compared to patients routed according to route 1 (CT to IVT to CTA), i.e., a mean (SD) of 82 (25) minutes vs. 100 (37) minutes, respectively.

Furthermore, we assessed the handover time, from PSC to ambulance for transfer to the CSC. The lowest median (IQR) handover time in one of the PSC was 11 (8-14) minutes compared with an overall median time of 14 (10-16) minutes.

DS model, CSC Workflow DS patients that arrive at the CSC should be transferred directly to the angiography suite, if no additional diagnostics are required.[16] The observed median (IQR) transfer time from CSC arrival to angiography suite was 26 (16-38) minutes, and from angiography suite arrival to groin puncture 30 (24-35) minutes.

MS model, CSC Workflow We assessed the time from CSC presentation to angiography suite arrival per route through the ED. Patients routed according to route 2 (CT to CTA to IVT) had shorter delays compared to patients routed according to route 1 (CT to IVT to CTA); with a mean (SD) of 103 (46) minutes compared to 113 (42) minutes, respectively. The observed median (IQR) time from last examination at the ED to angiography suite arrival was 58 (44-82) minutes, and between angiography suite arrival and groin puncture 28 (25-35) minutes.

Modelling scenarios

Based on the identified barriers for the DS model the following scenarios were defined (Supplementary material Table S3): all patients without contraindication for IVT are routed through the ED according to route 2 (CT-CTA-IVT) (scenario 1a), by using EMS pre-alert the ambulance response time is reduced to 0 minutes (scenario 1b), the handover time from PSC to ambulance is reduced to 11 minutes (scenario 1c) and combining all three experiments (scenario 1d).

For the CSC optimized workflow improvements (DS model) the following scenarios were considered: direct transfer from CSC arrival to angiography suite (maximum of 5 minutes, scenario 2a), reducing the time from angiography suite arrival to groin puncture to 10 minutes based on expert opinion, analysis of the MR CLEAN Registry dataset of all hospitals in the Netherlands and a previously published study[17] (scenario 2b). Scenario 2c combines both

experiments. In addition, PSC and CSC workflow improvements were combined in one experiment (scenario 3).

Furthermore, the scenarios for the MS model were: all patients without contraindication for IVT are routed through the ED according to route 2 (CT to CTA to IVT) (scenario 4a), time from last examination at the ED to angiography suite arrival is reduced to a maximum of 30 minutes (scenario 4b) and the time from angiography suite arrival to groin puncture is reduced to a maximum time of 10 minutes (scenario 4c). Scenario 4a and 4b are based on expert opinion, analysis of the MR CLEAN Registry dataset of all hospitals in the Netherlands and a previously published paper[2]. In scenario 4d all experiments were combined.

Simulation results

DS workflow Implementing all workflow improvements in a PSC (scenario 1d), would imply an absolute increase of 2.2% patients regaining functional independence after 90 days, a reduced mortality of 1,5% and a reduction in OTG of 18 minutes (Table 2). Realising workflow improvements within the CSC (scenario 2c) would increase the proportion of patients reaching functional independence at 90 days with 5.3%, a reduced mortality of 3.6% and OTG reduced by 43 minutes. Combining all workflow improvements in both PSC and CSC (scenario 3) would reduce OTG by 61 minutes, increase the proportion of patients reaching functional independence by 7.4% and mortality would decrease by 5.0%.

MS Workflow Implementing all workflow improvements (scenario 4d) would result in an additional 3.7% of patients regaining functional independence at 90 days, reducing OTG by 59 minutes and mortality would decrease by 3.0%.

Figure 3. shows the shift in likelihood per mRS score when all workflow improvements are executed in the DS model and MS Model.

Table 2. Simulation results

Scenarios	DIDO (DS)	Time from CSC arrival to angiography suite (MS)	OTG	Likelihood Functional Independence (95% CI)	Likelihood Mortality (95% CI)
0. (DS)	92.6 (92.4 - 92.8)	NA	240.7 (240.2 - 241.1)	52.4 (52.3 - 52.5)	21.4 (21.3 -21.5)
1a.	85.7 (85.5 - 85.8)	NA	233.8 (233.4 - 234.1)	53.3 (53.1 - 53.4)	20.8 (20.7 - 20.9)
1b.	84.7 (84.6 - 84.9)	NA	232.8 (232.5 - 233.2)	53.4 (53.2 - 53.5)	20.7 (20.6 - 20.8)
1c.	89.7 (89.6 - 89.9)	NA	237.8 (237.4 - 238.2)	52.8 (52.6 - 52.9)	21.1 (21.1 - 21.2)
1d.	74.9 (74.8 - 75.0)	NA	223.0 (222.6 - 223.4)	54.6 (54.5 - 54.7)	19.9 (19.8 -19.9)
2a.	92.6 (92.4 - 92.8)	NA	217.4 (217.1 - 217.7)	55.3 (55.1- 55.4)	19.4 (19.3 - 19.5)
2b.	92.6 (92.4 - 92.8)	NA	221.0 (220.6 - 221.4)	54.8 (54.7 - 55.0)	19.7 (19.6 - 19.8)
2c.	92.6 (92.4 - 92.8)	NA	197.7 (197.4 - 198.0)	57.7 (57.6 - 57.8)	17.8 (17.7 - 17.9)
3.	74.9 (74.8 - 75.0)	NA	180.0 (179.7 - 180.3)	59.8 (59.7 - 59.9)	16.4 (16.3 - 16.5)
0. (MS)	NA	96.9 (96.7 - 97.2)	214.5 (214.1 - 215.0)	49.2 (49.1 - 49.4)	27.7 (27.6 - 27.8)
4a.	NA	95.0 (94.9 - 95.3)	212.7 (212.3 - 213.1)	49.4 (49.2 - 49.5)	27.6 (27.5 - 27.7)
4b.	NA	60.7 (60.6 - 60.9)	178.4 (178.0 - 178.7)	51.5 (51.4 - 51.6)	25.8 (25.7 - 25.9)
4c.	NA	96.9 (96.7 - 97.2)	194.1 (193.7 - 194.6)	50.5 (50.4 - 50.7)	26.7 (26.6 - 26.8)
4d.	NA	58.9 (58.8 – 69.0)	156.1 (155.7 - 156.5)	52.9 (52.8 - 53.0)	24.7 (24.6 - 24.8)

Time variables are in minutes, mean (95% CI). MS, mothership model; DS, drip-and-ship model : CSC, Comprehensive Stroke Centre; PSC, Primary Stroke Centre; ED, Emergency department; OTG, time from stroke onset to groin puncture; DIDO, Door In Door Out, IVT, intravenous thrombolysis; CT, computed tomography; CTA, computed tomography angiogram; SA, Sensitivity Analysis.

Scenario 0., Baseline model, DS or MS model

Scenario 1., PSC workflow improvements for DS patients; 1a., all patients are routed according to ED route 2 (CT, CTA, IVT); 1b., Pre-alert to EMS, EMS response time 0 minutes; 1c., EMS handover time reduced to 11 minutes; 1d., 1a + 1b + 1c.

Scenario 2., CSC workflow improvements for DS patients; 2a., expedite CSC door to angiography suite by 5 minutes; 2b., expedite angiography suite to groin by 10 minutes, SA1; 2c., 2a + 2b.

Scenario 3., Total workflow improvements DS patients; 3., 1d + 2c.

Scenario 4., Total workflow improvement MS patients; 4a., all patients are routed according to ED route 2 (CT, CTA, IVT); 3b., expedite time from last examination ED (IVT/CTA) to angiography suite by 30 minutes; 3c., expedite angiography suite to groin by 10 minutes; 3d., 3a + 3b + 3c.

Fig. 3. Likelihood shift per mRS, baseline model vs. all workflow improvements

*** Figure 3 ***

Discussion

This study demonstrated that simulation modelling can be used to identify barriers for timely EVT and to assess the impact of workflow improvements in regional acute stroke care systems.

Workflow improvements such as ED routing of CT to CTA to IVT, a pre-alert to the ambulance, reducing handover time between PSC and EMS and reducing CSC workflow from hospital arrival to groin puncture could possibly reduce the time to EVT by approximately 1 hour. For DS patients, we estimated that with suggested workflow improvements the OTG could be reduced by 61 minutes ultimately resulting in a decreased mortality of 5.0% and an additional 7.4% of patients that may regain functional independence at 90 days. With the implementation of all hypothetical PSC workflow improvements for DS patients the DIDO target time value of 75 minutes,[2,17] could be reached. For MS patients, proposed interventions could lead to a reduction of OTG by 59 minutes, mortality would decrease by 3.0% and an additional 3.7% of patients regaining functional independence at 90 days.

For the above mentioned improvements, we specifically considered the acute stroke pathway of our region and the potential improvements which we have implemented 'in silico' step by step. However, by analysing the MR CLEAN Registry[10] of all hospitals in the Netherlands, some are already at the level of our proposed improvements while others are not. This suggests that even greater improvements than those presented here might be achieved when implemented, and that the selection of policies and improvements will depend on regional set-up and characteristics of existing acute stroke care systems.

Improvements found in the DS model are slightly higher, and in the MS model slightly lower than previously reported, with an additional 5-6% of patients regaining functional independence for each hour of reduction in OTG.[2,3] Possible explanations of the difference between our region and other regions might be that data in other studies was collected at the time EVT was newly introduced and because of region specific differences, such as the hospital infrastructure. Furthermore, using ordinal regression we observed more fluctuations in estimating the likelihood of mRS in the DS model compared to the MS model. Possible explanations include that we performed a separate ordinal regression per model, that the data

had a small sample size, i.e. n=154 (DS model) and n=80 (MS model), and earlier studies did not analyse the data in separate routing groups, i.e. DS model or MS model.[2,3]

The benefit of the proposed simulation modelling study is that potential improvements can be tested and their impact estimated for a specific region. As guidelines suggest taking regional and patients characteristics into account,[18] simulation modelling may serve as a useful tool by repopulating our generic model. i.e., using conceptual models and patient data from other regions. Also, in terms of efficiency, simulation modelling might be an attractive option, as it starts with hypothetical improvements without requiring investments and associated costs in 'hardware' and organization yet. Still, simulation modelling will not entirely replace RCTs, but can be useful as a precursor for clinical studies, as a tool for organizational learning and as a design approach such as for acute stroke care.[19,20]

Limitations

Our study has limitations. Within our simulation model we only modelled the acute stroke pathway for patients with large vessel occlusion. Ideally, a simulation model would take all suspected stroke patients into account, allowing a more comprehensive assessment of stroke care.

In addition, by identifying the optimal ED routing for timely EVT, we did not take additional delays for administering IVT into account. For large vessel occlusion patients a rapid IVT administration is associated with less disability at 90 days.[21] Furthermore, the question regarding the most beneficial treatment for large vessel occlusion patients, faster IVT and fast EVT, faster EVT with increased delay for IVT or direct EVT without IVT remains unanswered. Currently, direct EVT is being studied in the MR CLEAN NO-IV (ISRCTN80619088)[22] and the SWIFT DIRECT (NCT03192332)[23] trials. The recently published DIRECT-MT study

demonstrated that direct EVT was non-inferior compared to IVT and EVT.[24] Until this question is answered, balancing the benefit of both treatments is necessary.

Conclusions

The use of simulation is very useful to assess the potential effects of reducing regional specific delays from OTG. In our region potential workflow improvements would reduce the time to treatment by 1 hour, and as a result an additional 8% (DS model) and 4% (MS model) of patients would regain functional independence after 90 days and mortality would be decreased by 5% (DS model) and 3% (MS model).

Acknowledgement

We acknowledge the support of the Cardiovascular Research Initiative, part of the Dutch Heart Foundation (CVON2015-01: CONTRAST), the Brain Foundation Netherlands (HA2015.01.06), Health~Holland, Top Sector Life Sciences & Health (LSHM17016), Medtronic and Cerenovus. Furthermore, we acknowledge the UMCG Emergency Medical Services, Kijlstra Emergency Medical Services and Emergency Medical Services Groningen.

Author Contributions All authors designed the study. WM, ML, MU gathered data. WM and DJZ analysed the data and made the simulation models. WM wrote the draft of the manuscript and ML, MU, EB, and DJZ revised the manuscript for important intellectual content.

Funding The CONTRAST consortium is supported by Netherlands Cardiovascular Research Initiative, an initiative of the Dutch Heart Foundation (CVON2015-01: CONTRAST), by the Brain Foundation Netherlands and powered by Health~Holland, Top Sector Life Sciences and receives unrestricted funding from Medtronic and Cerenovus. The collaboration project is

additionally financed by the Ministry of Economic Affairs by means of the PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public-private partnerships.

Competing interests None declared.

Patient consent for publication

Not required.

Ethics approval

The MR CLEAN registry data collection has been approved for the Netherlands by the central medical ethics committee and research board of Erasmus University Medical Centre (MEC-2014-235). The need for individual patient consent was waived.[10] In order to link hospital patient data with the corresponding EMS data, a Data Transfer Agreement was drafted and implemented.[11]

Data availability statement

The data of this sub study from the MR CLEAN Registry and the data of the EMS are not publicly available because individual centres can be identified. Sharing this data is in conflict with the privacy regulations in the Netherlands.

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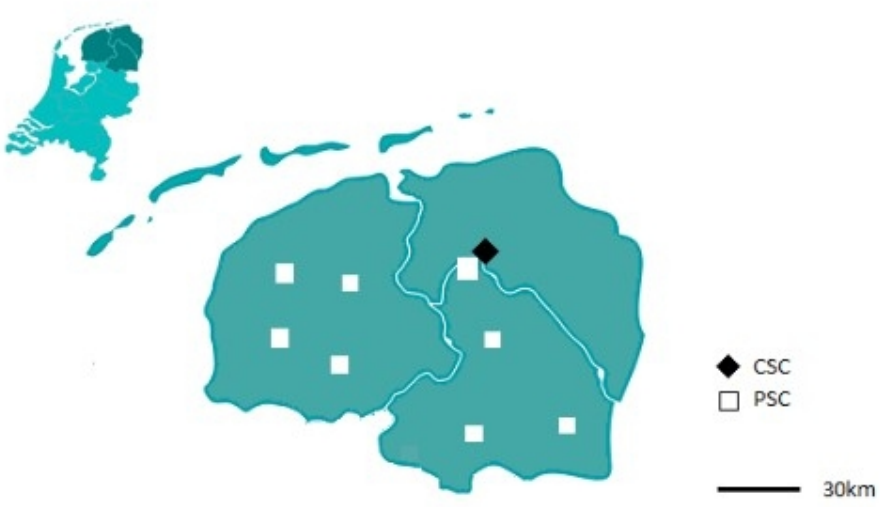
Figure Legends

Fig. 1. CSC, Comprehensive Stroke Centre; PSC, Primary Stroke Centre

Fig. 2. EMS, emergency medical services; POC, point of care; CT, computed tomography; IVT, intravenous thrombolysis; CTA, computed tomography angiography; EVT, endovascular thrombectomy.

Fig. 3. DS indicates 'drip-and-ship' model; MS, 'mothership' model; mRS, modified Rankin Scale



CSC, Comprehensive Stroke Centre; PSC, Primary Stroke Centre

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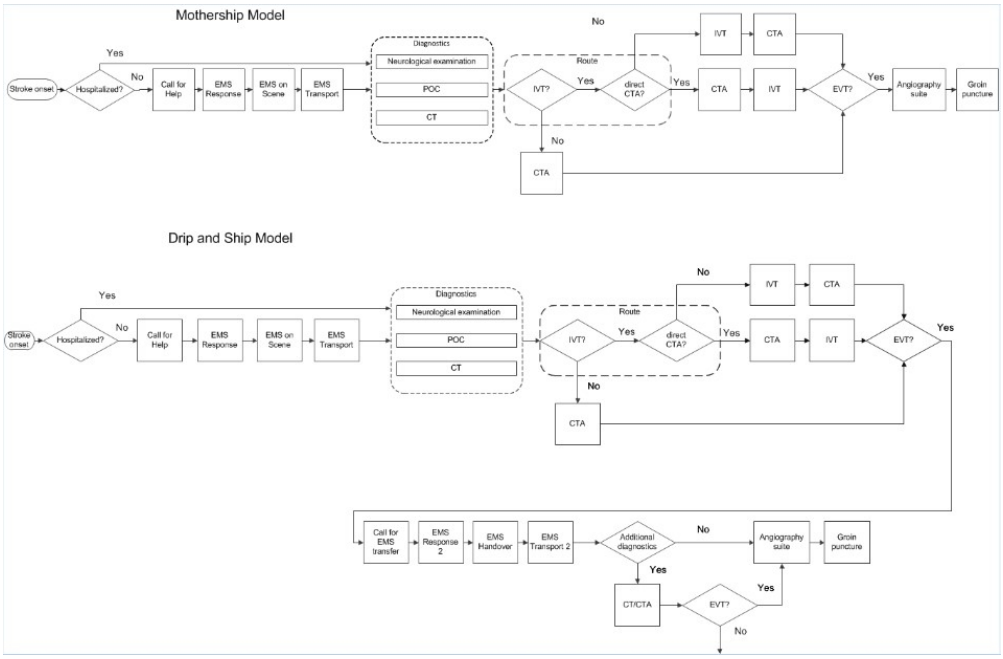

EMS, emergency medical services; POC, point of care; CT, computed tomography; IVT, intravenous thrombolysis; CTA, computed tomography angiography; EVT, endovascular thrombectomy.

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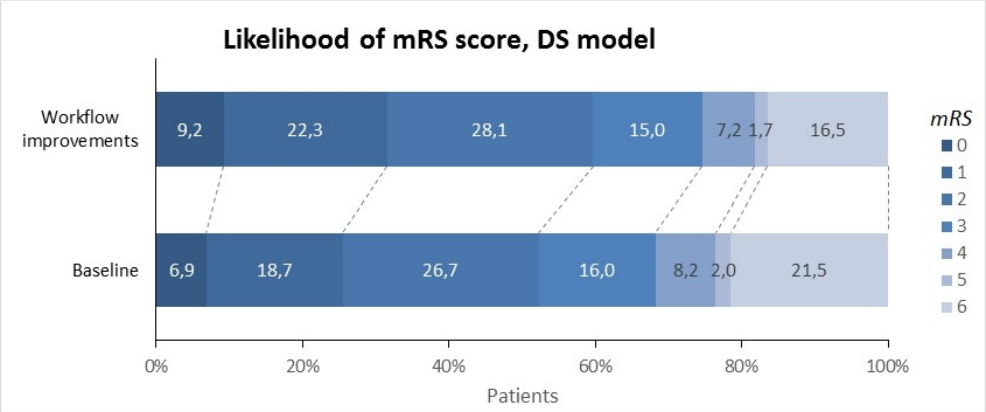

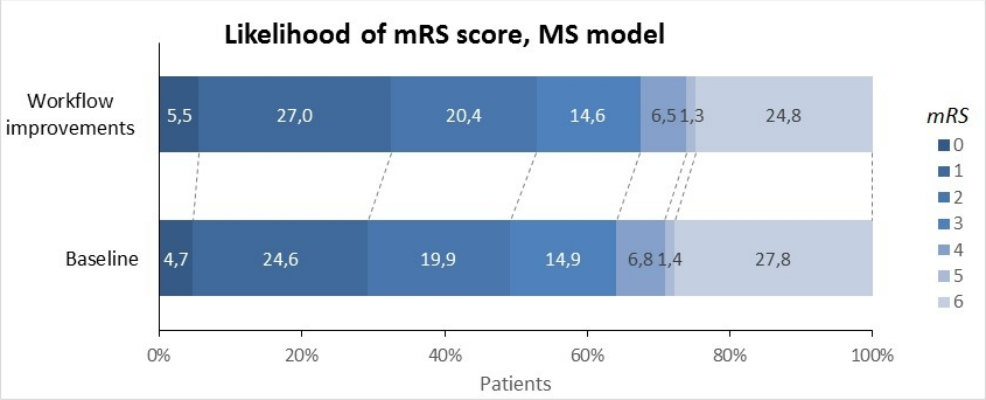

DS indicates 'drip-and-ship' model; MS, 'mothership' model; mRS, modified Rankin Scale

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Supplementary material; Expediting workflow in the acute stroke pathway for endovascular thrombectomy; a simulation modeling approach.

Introduction

The main text of the manuscript provides the most important findings of the study. This supplementary material provides details 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).

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 95% confidence interval half width for the mRS 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 as 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; $\alpha1 = 2.56$; $\alpha2 = 7.15$		
EMS on Scene	Gamma	Location = 1.70; $\alpha = 5.43$; $\beta = 2.73$		
EMS Transport	Weibull	Location = 0.00 $\alpha = 2.11$; $\beta = 13.14$		
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	$\mu = 13.70$; $\sigma = 17.09$		
Time from IVT to CTA (route 1)	Erlang	$\mu = 14.54$; $\sigma = 13.73$		
Time from last examination ED to transfer call (route 1)	Gamma	Location = 0.00; $\alpha = 2.63$; $\beta = 13.66$		
Time from CT to CTA (route 2)	Gamma	Location = 0.00; $\alpha = 2.63$; $\beta = 3.53$		
Time from CTA to IVT (route 2)	Erlang	$\mu = 12.57$; $\sigma = 13.05$		
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	$\mu = 23.06$; $\sigma = 21.72$		
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; $\alpha1 = 2.17$; $\alpha2 = 2.29$		
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; $\alpha = 1.11$; $\beta = 17.41$		
Time from additional diagnostics to angiography suite	Beta	Lower endpoint = 4.82; Upper endpoint = 124.31; $\alpha1 = 0.67$; $\alpha2 = 1.60$		
Time from hospital arrival to angiography suite	Gamma	Location = 4.25; $\alpha = 2.23$; $\beta = 10.19$		
Time from angiography suite to groin puncture	Beta	Lower endpoint = 4.72; Upper endpoint = 65.69; $\alpha1 = 4.55$; $\alpha2 = 6.55$		
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
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		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 I. 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	$\mu = 9.77$; $\sigma = 3.61$		
EMS on Scene	Lognormal	$\mu = 21.55$; $\sigma = 8.16$		
EMS Transport	Weibull	Location = 0.00; $\alpha = 2.16$; $\beta = 20.03$		
Time from hospital arrival to CT	Log-logistic	Location = 6.47; $\alpha = 6.29$; $\beta = 2.57$		
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; $\alpha = 8.58$; $\beta = 2.86$		
Time from IVT to CTA (route 1)	Lognormal	$\mu = 15.74$; $\sigma = 17.43$		
Time from CT to CTA (route 2)	Beta	Lower endpoint = 0.47; Upper endpoint = 30.69; $\alpha 1 = 1.96$; $\alpha 2 = 6.53$		
Time from CTA to IVT (route 2)	Gamma	Location = 0.00; $\alpha = 1.44$; $\beta = 8.93$		
Time from CT to CTA (route	Lognormal	$\mu = 10.96$, $\sigma = 11.45$		

3)			
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 II. 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 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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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5,6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	13

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,9
		(b) Indicate number of participants with missing data for each variable of interest	7,8,9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11,12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	11,12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11,12
		(*b*) Report category boundaries when continuous variables were categorized	11,12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10,11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Expediting workflow in the acute stroke pathway for endovascular thrombectomy in the northern Netherlands: a simulation model

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-056415.R1
Article Type:	Original research
Date Submitted by the Author:	21-Feb-2022
Complete List of Authors:	Maas, Willemijn; University Medical Centre Groningen, Department of Neurology; University Medical Centre Groningen, Health Technology Assessment, Department of Epidemiology Lahr, Maarten ; University Medical Centre Groningen, Health Technology Assessment, Department of Epidemiology Uyttenboogaart, Maarten; University Medical Centre Groningen, Department of Neurology; University Medical Centre Groningen, Department of Radiology, Medical Imaging Centre Buskens, Erik; University Medical Centre Groningen, Health Technology Assessment, Department of Epidemiology; University of Groningen, Department of Operations, Faculty of Economics & Business van der Zee, Durk-Jouke; University of Groningen, Department of Operations, Faculty of Economics & Business
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Health services research, Epidemiology
Keywords:	Stroke < NEUROLOGY, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Organisational development < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Expediting workflow in the acute stroke pathway for endovascular thrombectomy in the northern Netherlands: a simulation model

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Word Count: 3713

Number of figures/tables: 4

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Abstract

Objective: The objective of this study is to identify barriers for the timely delivery of endovascular thrombectomy (EVT) and to investigate the effects of potential workflow improvements in the acute stroke pathway.

Design: Hospital data prospectively collected in the MR CLEAN Registry were linked to emergency medical services data for each EVT patient and used to build two Monte Carlo simulation models. The 'mothership model', reflecting patients who arrived directly at the comprehensive stroke centre (CSC); and the 'drip and ship' model, reflecting patients who were transferred to the CSC from primary stroke centres (PSCs).

Setting: Northern region of the Netherlands. One CSC provides EVT, and its catchment area includes eight PSCs.

Participants: 248 patients who were treated with EVT between July 2014 and November 2017.

Outcome measures: The main outcome measures were total delay from stroke onset until groin puncture, functional independence at 90 days (modified Rankin Scale 0–2), and mortality.

Results: Barriers identified included fast-track emergency department routing, pre-alert for transfer to the CSC, reduced handover time between PSC and ambulance, direct transfer from CSC arrival to angiography suite entry, and reducing time to groin puncture. Taken together, all workflow improvements could potentially reduce the time from onset to groin puncture by 59 minutes for the 'mothership' model and 61 minutes for the 'drip and ship' model. These improvements could thus result in more patients—3.7% 'mothership' and 7.4% 'drip and ship'—regaining functional independence after 90 days, in addition to decreasing mortality by 3.0% and 5.0%, respectively.

Conclusions: In our region, the proposed workflow improvements might reduce time to treatment by about one hour and increase the number of patients regaining functional independence by 6%. Simulation modelling is useful for assessing the potential effects of interventions aimed at reducing time from onset to EVT.

Strengths and limitations of this study

- Data were collected on time delays along the acute stroke pathway for patients treated with endovascular thrombectomy, thereby allowing the identification, analysis, and simulation of barriers from onset to treatment.
- An extensive set of workflow improvements is suggested based on data analysis, expert opinion, and literature.
- A simulation model of the acute stroke pathway is developed, enabling the effective and efficient assessment of workflow improvements, relying on realistic in-silico modelling.
- The simulation model includes only patients treated with endovascular thrombectomy in a region with one comprehensive stroke center, but it could be extended to all suspected stroke patients, thereby allowing a more comprehensive assessment of stroke care.

Introduction

Acute ischemic stroke places a large burden on society, and the overall incidence has increased by 78% since 1990.[1] The main reperfusion treatments for acute ischemic stroke due to large vessel occlusion are intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT). The phrase 'time is brain' applies to both treatments. For EVT, the probability of regaining functional independence at 90 days after stroke declines by 5% to 6% for each additional hour delay from onset to groin puncture (OTG).[2,3]

Successful and timely EVT largely depends on the regional organization of acute stroke care delivery. Delays that can occur during pre-hospital and intra-hospital processes, as well as along each step in the acute stroke pathway, have the potential to worsen patient outcomes or even rule out the possibility of acute treatment. Pathway elements that have been identified as having the potential to cause treatment delays include pre-hospital stroke management, in-hospital patient transfer, anaesthetic management, teamwork, and inter-hospital patient transfer.[4]

Most studies of interventions aimed at improving workflow processes have focused on specific interventions, examining bits and pieces of the acute stroke pathway separately. The joint analysis of several improvements might lead to the identification of actual improvements. Simulation modelling has been suggested as a means of supporting such comprehensive analyses, and it has been performed within the context of IVT based on a variety of organizational models.[5,6]

The objectives of this study are (1) to assess delays in the workflow of acute stroke care, based on patient-level data; and (2) to estimate the impact of reducing delays throughout the process, from work-up to EVT treatment, based on simulation modelling.

Methods

Setting

This study is based on prospective data collected in the MR CLEAN Registry[7] from patients treated with EVT in one comprehensive stroke centre (CSC), which provides EVT for eligible patients in the northern part of the Netherlands (1.7 million inhabitants). Its catchment area includes eight primary stroke centres (PSCs), spaced at distances of six to 84 kilometres, as shown in Figure S1 of the supplemental material.

Participants and data collection

Between July 2014 and November 2017, 285 patients were included. According to the emergency medical services (EMS) protocol,[8] patients suspected of acute stroke were routed to the nearest IVT-capable hospital. The patients were either sent directly to a CSC (mothership [MS] model) or first presented at a PSC and subsequently transferred to the CSC for EVT (drip and ship [DS] model). In the eastern part of the province of Groningen, patients were routed directly to the CSC, reflecting a centralized organizational model.[9]

Patient data on clinical characteristics, diagnostic processes, time delays, and ambulance routing patterns were used as input for simulation modelling. In-hospital time delays included onset or time last seen well, computed tomography (CT), IVT initiation, computed tomography angiogram (CTA), arrival at the angiography suite, and the time of groin puncture. In-hospital (PSC or CSC) patients were routed through the emergency department (ED) according to three routes: 1) CT to IVT to CTA; 2) CT to CTA to IVT; and 3) CT to CTA (patients ineligible for IVT). Following secondary transfer, DS patients arriving at the CSC could undergo additional diagnostics (e.g. CT and/or CTA).

Pre-hospital data from three EMS organizations were collected retrospectively and linked to the MR CLEAN Registry data for each patient. Time-delay items collected included

911 notification, EMS arrival at the stroke-onset location, departure to hospital, and arrival at hospital. Additional data collected for DS patients included the timestamps for EMS transfer notification, arrival at PSC, departure to CSC, and arrival at CSC.

Patients were excluded from analyses in case of a prior modified Rankin Scale (mRS) > 2 and when OTG exceeded 390 minutes, as EVT based on perfusion CT beyond six hours was not indicated at that time. Missing values were excluded from analyses.

Informed consent

The MR CLEAN Registry data collection has been approved for the Netherlands by the central medical ethics committee and research board (MEC-2014-235). The need for individual patient consent was waived.[10] A Data Transfer Agreement was drafted and implemented for purposes of linking hospital patient data to the corresponding EMS data.[11]

Patient and public involvement

No patients involved.

Simulation

Separate Monte Carlo simulation models were developed for the MS and DS organization models.[12] Prior to model building, conceptual modelling was performed in order to abstract real-world acute stroke pathways, as shown in Figure 1. Conceptual models were validated using expert opinion (MU), combined with literature observations and input from stroke experts participating in the national collaboration for new treatments of acute stroke (CONTRAST) consortium.[13]

Both simulation models were developed using Plant Simulation™.[14] Distributions for the individual time-delay variables were based on patient data and obtained using ExpertFit™.[15] Details are presented as supplementary material, Table S1 and S2.

Fig. 1. Conceptual models of the acute stroke pathway: 'Mothership' and 'Drip and ship'.

**** Figure 1****

Modelling scenarios

We identified barriers along the acute stroke pathway by analysing patient data, relevant literature, and expert opinion (MU). These barriers were used to create hypothetical scenarios, which we tested 'in silico' using the simulation model developed for this purpose.

Outcome measures

Outcome measures include OTG, likelihood of functional independence (mRS 0-2), and mortality (mRS 6) at 90 days.

Analysis

The simulation models were validated numerically by comparing mean, median, standard deviation, minimum, and maximum time values of real-world patient data and observations to model data and outputs.

Within the simulation model, ordinal logistic regression was used to estimate the likelihood of each of the seven scales belonging to the mRS score, ranging from 0 (no symptoms) to 6 (death). Known prognostic variables were OTG (continuous), age (continuous), National Institutes of Health Stroke Scale score (continuous), and CTA

collateral grading score in four categories (absence of collaterals, less than 50% filling of the occluded area, more than 50% filling but less than 100% filling of the occluded area, and 100% filling of the occluded area). The likelihood of functional independence (mRS 0–2) was calculated from the formulas obtained by ordinal logistic regression, using IBM SPSS Statistics 23 software. Details are presented as supplementary material.

For each scenario, we calculated the clinical benefits in terms of reduction in OTG and the likelihood of regaining functional independence and reducing mortality. Significance testing was inappropriate, as the goal was to assess the potential gain expected based on 100,000 hypothetical patients, rather than to test a hypothesis as in an actual experiment.

Results

In all, 248 patients met the inclusion criteria. Of these patients, 27 were excluded because of a pre-stroke mRS > 2, and/or an unknown OTG of > 390 minutes (12 patients). Patient characteristics, diagnostics, and median time delays for each model are presented in Table 1. For MS patients (n=83), the median (IQR) OTG was 205 (160–260) minutes; 51.8% regained functional independence after 90 days, and mortality was 26.5%. For DS patients (n=165), the respective figures were 230 (198–275) minutes, 52.1%, and 22.4%. To obtain the likelihood formulas for each of the seven mRS scales, data from 80 MS patients and 154 DS patients were used. Despite faster OTG, the MS patients had a lower likelihood of functional independence and a higher likelihood of mortality after 90 days compared to DS patients.

Table 1. Characteristics, diagnostics, and time delays of the MS and DS models.

	MS model	*n*	DS model	*n*
Patient characteristics				
Age in years (SD)	65 (14)	*83*	70 (13)	*165*
Male (%)	39 (47)	*83*	99 (60)	*165*
IVT rate (%)	53 (64)	*83*	132 (80)	*165*
Patient diagnostics				
Baseline NIHSS score (IQR)	16 (11-19)	*82*	17 (12-19)	*165*

Collaterals absent or filling of less than 50% (%)	36 (45)	*80*	92 (60)	*155*
Process times EMS				
Symptom onset to 911 call	20 (6-63)	*66*	11 (3-33)	*139*
Response time	9 (7-12)	*65*	9 (7-12)	*132*
On-scene time	20 (16-26)	*62*	16 (12-20)	*126*
Transport time	17 (12-23)	*61*	12 (7-15)	*122*
Process times in-hospital, PSC or CSC				
Hospital arrival to CT	13 (11-17)	*63*	15 (11-20)	*125*
Route 1				
CT to IVT	10 (8-16)	*23*	8 (4-19)	*56*
IVT to CTA	10 (6-22)	*23*	11 (5-19)	*57*
Route 2				
CT to CTA	6 (5-10)	*30*	9 (5-11)	*62*
CTA to IVT	11 (7-18)	*30*	9 (4-15)	*63*
Route 3				
CT to CTA	7 (4-14)	*29*	14 (9-30)	*31*
Process times EMS for transfer from PSC to CSC				
Last examination ED (IVT or CTA) to 911 transfer call	NA		28 (15-44)	*148*
Response time	NA		8 (5-10)	*140*
Handover time	NA		14 (10-16)	*139*
Transport time	NA		27 (19-32)	*150*
Process times in-hospital CSC				
Route additional diagnostics				
CSC arrival to additional diagnostics	NA		23 (17-45)	*17*
Additional diagnostics to angiography suite	NA		29 (14-70)	*18*
Last examination ED to angiography suite	58 (44-82)	*76*	NA	
CSC arrival to angiography suite	107 (74-133)	*60*	26 (16-38)	*151*
Arrival angiography suite to groin puncture	28 (25-35)	*77*	30 (24-35)	*163*
Overall time				
OTG	205 (160-260)	*83*	230 (198-275)	*165*
mRS after 90days		*83*		*165*
0 (%)	4 (5)		12 (7)	
1 (%)	22 (27)		32 (19)	
2 (%)	17 (21)		42 (26)	
3 (%)	12 (15)		26 (16)	
4 (%)	5 (6)		13 (8)	
5 (%)	1 (1)		3 (2)	
6 (%)	22 (27)		37 (22)	

Time variables are in minutes, median (IQR). MS, mothership model; DS, drip-and-ship model; SD, standard deviation; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; EMS, Emergency Medical Services; CSC, Comprehensive Stroke Centre; PSC, Primary Stroke Centre; CT, computed tomography;

CTA, computed tomography angiogram; ED, emergency department; NA, not applicable; OTG, time from stroke onset to groin puncture; mRS, modified Rankin Scale.

Identified delays

We identified multiple opportunities for improving workflow for both the DS and MS models.

DS model, PSC workflow: The door-in-door-out (DIDO) time was used to estimate the entire PSC workflow, defined as time from PSC arrival until departure to the CSC. The DIDO time of patients routed through the ED according to Route 2 (CT to CTA to IVT) was less than that of patients routed according to route 1 (CT to IVT to CTA), with a mean (SD) of 82 (25) minutes vs 100 (37) minutes, respectively.

We also assessed the handover time from PSC to ambulance for transfer to the CSC. The lowest median (IQR) handover time in one of the PSCs was 11 (8–14) minutes, as compared to an overall median time of 14 (10–16) minutes.

DS model, CSC Workflow: If no additional diagnostics are required, DS patients arriving at the CSC should be transferred directly to the angiography suite.[16] The observed median (IQR) transfer time from CSC arrival to angiography suite was 26 (16–38) minutes, and from angiography suite arrival to groin puncture 30 (24–35) minutes.

MS model, CSC Workflow: We assessed the time from CSC presentation to arrival at the angiography suite for each route through the ED. Patients who were routed according to Route 2 (CT to CTA to IVT) had shorter delays compared to those who were routed according to Route 1 (CT to IVT to CTA); with a mean (SD) of 103 (46) minutes compared to 113 (42) minutes, respectively. The observed median (IQR) time from last examination at the

ED to angiography suite arrival was 58 (44–82) minutes, and between angiography suite arrival and groin puncture 28 (25–35) minutes.

Modelling scenarios

The following scenarios were defined, based on the barriers identified for the DS model (Supplementary material, Table S3): routing all patients without contraindication for IVT through the ED according to Route 2 (CT to CTA to IVT) (Scenario 1a); EMS pre-alert is used, thus reducing the ambulance response time to 0 minutes (Scenario 1b); reducing the handover time from PSC to ambulance to 11 minutes (Scenario 1c); and combining all three experiments (Scenario 1d).

The following scenarios were considered for the CSC optimized workflow improvements (DS model): direct transfer from CSC arrival to the angiography suite (maximum of five minutes, Scenario 2a); reducing the time from angiography suite arrival to groin puncture to 10 minutes, based on expert opinion, analysis of the MR CLEAN Registry dataset for all hospitals in the Netherlands, and a previously published study[17] (Scenario 2b); and combining the two experiments (Scenario 2c). In addition, the PSC and CSC workflow improvements were combined into one experiment (Scenario 3).

The scenarios for the MS model were as follows: routing all patients without contraindication for IVT through the ED according to Route 2 (CT to CTA to IVT; Scenario 4a); reducing time from last examination at the ED to angiography suite arrival to a maximum of 30 minutes (Scenario 4b); and reducing the time from angiography suite arrival to groin puncture to a maximum of 10 minutes (Scenario 4c). Scenarios 4a and 4b are based on expert opinion, analysis of the MR CLEAN Registry dataset on all hospitals in the Netherlands, and a previously published paper.[2] In Scenario 4d, all experiments were combined.

Simulation results

DS workflow: Implementing all workflow improvements in a PSC (Scenario 1d) would imply an absolute increase of 2.2% in the number of patients regaining functional independence after 90 days, a mortality reduction of 1.5%, and a reduction in OTG of 18 minutes (Table 2). Realizing workflow improvements within the CSC (Scenario 2c) would reduce OTG by 43 minutes, increase the proportion of patients reaching functional independence at 90 days by 5.3% and reduce mortality by 3.6%. Combining all workflow improvements in both PSC and CSC (Scenario 3) would reduce OTG by 61 minutes, increase the proportion of patients reaching functional independence by 7.4%, and decrease mortality by 5.0%.

MS Workflow: Implementing all workflow improvements (Scenario 4d) would reduce OTG by 59 minutes increase the number of patients regaining functional independence at 90 days by 3.7%, and decrease mortality by 3.0%.

The shifts in likelihood for each mRS score when all workflow improvements are executed in the DS and MS models are displayed in Figure 2.

Table 2. Simulation results

Scenarios	DIDO (DS)	Time from CSC arrival to angiography suite (MS)	OTG	Likelihood of Functional Independence (95% CI)	Likelihood of Mortality (95% CI)
0. (DS)	92.6 (92.4 - 92.8)	NA	240.7 (240.2 - 241.1)	52.4 (52.3 - 52.5)	21.4 (21.3 -21.5)
1a.	85.7 (85.5 - 85.8)	NA	233.8 (233.4 - 234.1)	53.3 (53.1 - 53.4)	20.8 (20.7 - 20.9)
1b.	84.7 (84.6 - 84.9)	NA	232.8 (232.5 - 233.2)	53.4 (53.2 - 53.5)	20.7 (20.6 - 20.8)
1c.	89.7 (89.6 - 89.9)	NA	237.8 (237.4 - 238.2)	52.8 (52.6 - 52.9)	21.1 (21.1 - 21.2)
1d.	74.9 (74.8 - 75.0)	NA	223.0 (222.6 - 223.4)	54.6 (54.5 - 54.7)	19.9 (19.8 -19.9)
2a.	92.6 (92.4 - 92.8)	NA	217.4 (217.1 - 217.7)	55.3 (55.1- 55.4)	19.4 (19.3 - 19.5)
2b.	92.6 (92.4 - 92.8)	NA	221.0 (220.6 - 221.4)	54.8 (54.7 - 55.0)	19.7 (19.6 - 19.8)
2c.	92.6 (92.4 - 92.8)	NA	197.7 (197.4 - 198.0)	57.7 (57.6 - 57.8)	17.8 (17.7 - 17.9)
3.	74.9 (74.8 - 75.0)	NA	180.0 (179.7 - 180.3)	59.8 (59.7 - 59.9)	16.4 (16.3 - 16.5)
0. (MS)	NA	96.9 (96.7 - 97.2)	214.5 (214.1 - 215.0)	49.2 (49.1 - 49.4)	27.7 (27.6 - 27.8)
4a.	NA	95.0 (94.9 - 95.3)	212.7 (212.3 - 213.1)	49.4 (49.2 - 49.5)	27.6 (27.5 - 27.7)
4b.	NA	60.7 (60.6 - 60.9)	178.4 (178.0 - 178.7)	51.5 (51.4 - 51.6)	25.8 (25.7 - 25.9)
4c.	NA	96.9 (96.7 - 97.2)	194.1 (193.7 - 194.6)	50.5 (50.4 - 50.7)	26.7 (26.6 - 26.8)

4d.	NA	58.9 (58.8 – 69.0)	156.1 (155.7 - 156.5)	52.9 (52.8 - 53.0)	24.7 (24.6 - 24.8)

Time variables are in minutes, mean (95% CI). Likelihood of functional independence and mortality are in percentages (95% CI). MS, mothership model; DS, drip-and-ship model; CSC, Comprehensive Stroke Centre; PSC, Primary Stroke Centre; ED, emergency department; OTG, time from stroke onset to groin puncture; DIDO, door-in-door-out; IVT, intravenous thrombolysis; CT, computed tomography; CTA, computed tomography angiogram; SA, Sensitivity Analysis.

Scenario 0. Baseline model, DS or MS model.

Scenario 1. PSC workflow improvements for DS patients; 1a., all patients are routed according to ED route 2 (CT, CTA, IVT); 1b., Pre-alert to EMS, EMS response time 0 minutes; 1c., EMS handover time reduced to 11 minutes; 1d., 1a + 1b + 1c.

Scenario 2. CSC workflow improvements for DS patients; 2a., expedite CSC door to angiography suite by 5 minutes; 2b., expedite angiography suite to groin by 10 minutes, SA1; 2c., 2a + 2b.

Scenario 3. Total workflow improvements DS patients; 3., 1d + 2c.

Scenario 4. Total workflow improvement MS patients; 4a., all patients are routed according to ED route 2 (CT, CTA, IVT); 3b., expedite time from last examination ED (IVT/CTA) to angiography suite by 30 minutes; 3c., expedite angiography suite to groin by 10 minutes; 3d., 3a + 3b + 3c.

Fig. 2. Likelihood shift for each mRS; baseline model vs all workflow improvements

*** Figure 2 ***

Discussion

The results of this study demonstrate that simulation modelling can be used to identify barriers for timely EVT and to assess the impact of workflow improvements in regional acute stroke care systems. Workflow improvements (e.g. ED routing of CT to CTA to IVT, pre-alerting the ambulance, reducing handover time between PSC and EMS, and reducing CSC workflow from hospital arrival to groin puncture) could possibly reduce the time to EVT by approximately one hour. For DS patients, we estimate that the suggested workflow improvements could reduce OTG by 61 minutes, ultimately decreasing mortality by 5.0% and increasing the number of patients regaining functional independence at 90 days by 7.4%. The implementation of all hypothetical PSC workflow improvements for DS patients could make it possible to achieve the DIDO target time value of 75 minutes.[2,17] For MS patients, the proposed interventions could reduce OTG by 59 minutes, decrease mortality by 3.0% and increase the number of patients regaining functional independence at 90 days by 3.7%.

For the aforementioned improvements, we specifically considered the acute stroke pathway of our region and the potential improvements that we systematically implemented 'in silico'. Analysis of the MR CLEAN Registry[10] for all hospitals in the Netherlands nevertheless revealed that some hospitals have already attained the level of our proposed improvements, while others have not. This suggests that the implementation of the proposed improvements could result in even greater benefits and that the selection of policies and improvements will depend on regional set-up and characteristics of existing acute stroke care systems.

The findings for the DS model indicate slightly greater improvement than has been reported in previous studies, while those for the MS model indicate slightly less improvement, with the number of patients regaining functional independence increasing by between 5% and 6% for each hour reduction in OTG.[2,3] Possible explanations for the difference between our region and other regions might have to do with the fact that data in other studies were collected shortly after the introduction of EVT was newly introduced, as well as with region-specific differences (e.g. hospital infrastructure). Furthermore, the use of ordinal logistic regression revealed greater fluctuations in estimating the likelihood of mRS in the DS model, as compared to the MS model. Possible explanations include the fact that a separate ordinal logistic regression was performed for each model, the small sample size (i.e. n=154 for the DS model and n=80 for the MS model), and the fact that previous studies have not analysed data in separate routing groups (i.e. the DS model vs. the MS model).[2,3] Another striking result was the higher probability of death and poor functional outcome for MS patients, despite a decrease in OTG. One possible explanation could be that patients with highly complex comorbidity and ischemic stroke were more likely to be transferred directly to the CSC instead of to a PSC.

The results of our study can be generalized in part to other regions. Suggested improvements for the acute stroke pathway may be related to a generic conceptual model of care delivery that is consistent with many existing regional pathways and that faces similar challenges. While the impact of these improvements within specific regions will differ, they can jointly create a relevant starting point for optimizing stroke systems. The most important benefit of the proposed simulation modelling study is that it allows the testing of potential improvements and the estimation of their impact for specific regions. As suggested by guidelines, and taking regional and patient characteristics into account,[18] simulation modelling may be particularly useful for re-populating the generic model (i.e. using conceptual models and patient data from other regions). In addition, simulation modelling might be an attractive option in terms of efficiency, as it starts with hypothetical improvements without immediately requiring investments and costs associated with hardware and organization. Although it cannot completely replace RCTs, simulation modelling can be useful as a precursor to clinical studies, as a tool for organizational learning, and as a design approach (e.g. for acute stroke care).[19,20]

Limitations

Our study is subject to several limitations. The simulation model includes only the acute stroke pathway for patients with large vessel occlusion. Ideally, a simulation model should take all suspected stroke patients into account, thereby allowing a more comprehensive assessment of stroke care.

In addition, as a consequence of identifying the optimal ED routing for timely EVT, additional delays for administering IVT were not taken into account. For patients with large vessel occlusion, rapid IVT administration is associated with less disability at 90 days.[21] Furthermore, many questions remain unanswered with regard to the most beneficial treatment

for these occlusion patients: faster IVT and fast EVT; faster EVT with increased delay for IVT; or direct EVT without IVT. Direct EVT is currently being studied in the MR CLEAN NO-IV (ISRCTN80619088)[22] and the SWIFT DIRECT (NCT03192332)[23] trials. The recently published DIRECT-MT study reports that direct EVT was non-inferior compared to IVT and EVT.[24] Until this question is answered, it will be necessary to balance the relative benefits of both treatments.

Conclusions

Simulation is useful in assessing the potential effects of reducing region-specific delays from OTG. In our region, potential workflow improvements could reduce the time to treatment by one hour, thereby increasing the number of patients regaining functional independence after 90 days by 8% (DS model) and 4% (MS model), in addition to decreasing mortality by 5% (DS model) and 3% (MS model).

Acknowledgments

We acknowledge the support of the Cardiovascular Research Initiative, part of the Dutch Heart Foundation (CVON2015-01: CONTRAST), the Brain Foundation Netherlands (HA2015.01.06), Health~Holland, Top Sector Life Sciences & Health (LSHM17016), Medtronic and Cerenovus. We also acknowledge the UMCG Emergency Medical Services, Kijlstra Emergency Medical Services and Emergency Medical Services Groningen.

Contributors

All authors designed the study. WM, ML, MU gathered data. WM and DJZ analysed the data and made the simulation models. WM wrote the draft of the manuscript and ML, MU, EB, and DJZ revised the manuscript for important intellectual content.

Funding

The CONTRAST consortium is supported by Netherlands Cardiovascular Research Initiative, an initiative of the Dutch Heart Foundation (CVON2015-01: CONTRAST) and by the Brain Foundation Netherlands. It is powered by Health~Holland, Top Sector Life Sciences, and it receives unrestricted funding from Medtronic and Cerenovus. Additional funding for this collaborative project is provided by the Netherlands Ministry of Economic Affairs through a PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public-private partnerships.

Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

The MR CLEAN Registry data collection has been approved for the Netherlands by the central medical ethics committee and research board of Erasmus University Medical Centre (MEC-2014-235). The need for individual patient consent was waived.[10] A Data Transfer Agreement was drafted and implemented for purposes of linking hospital patient data to the corresponding EMS data.[11]

Data availability statement

The data for this sub-study from the MR CLEAN Registry and the data of the EMS are not publicly available, as they allow for the identification of individual centres. The sharing of such data is in conflict with the privacy regulations in the Netherlands.

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Figure titles and legends

Figure 1. Conceptual modelling

EMS, emergency medical services; POC, point of care; CT, computed tomography; IVT, intravenous thrombolysis; CTA, computed tomography angiography; EVT, endovascular thrombectomy.

Figure 2. Shifts in likelihood for each mRS score when all workflow improvements are executed in the DS and MS models

DS indicates the 'drip and ship' model; MS indicates the 'mothership' model; mRS indicates the modified Rankin Scale.

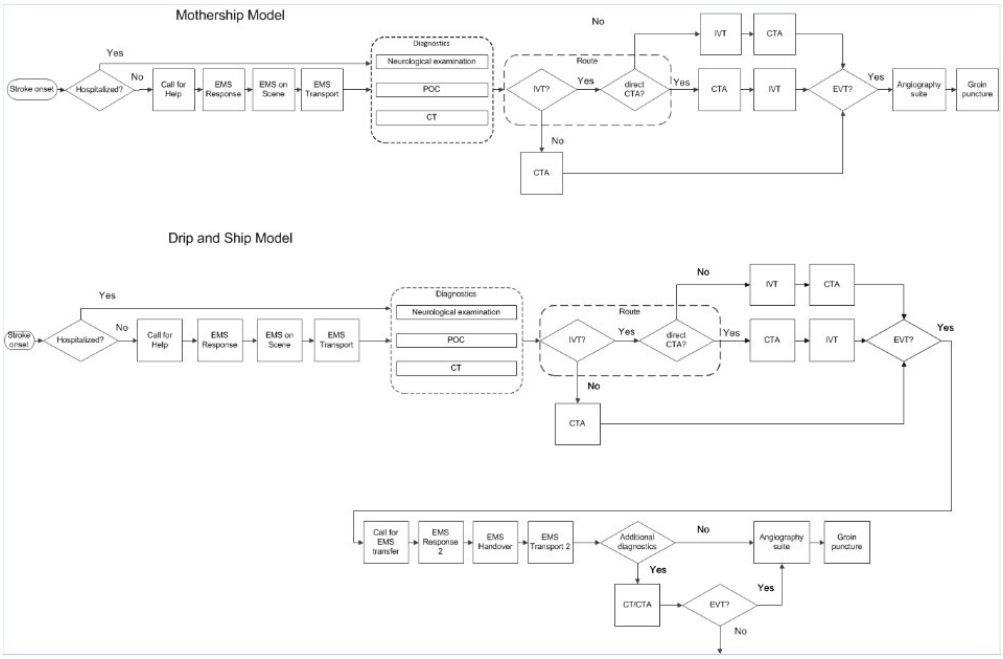

Fig. 1. EMS, emergency medical services; POC, point of care; CT, computed tomography; IVT, intravenous thrombolysis; CTA, computed tomography angiography; EVT, endovascular thrombectomy.

252x164mm (96 x 96 DPI)

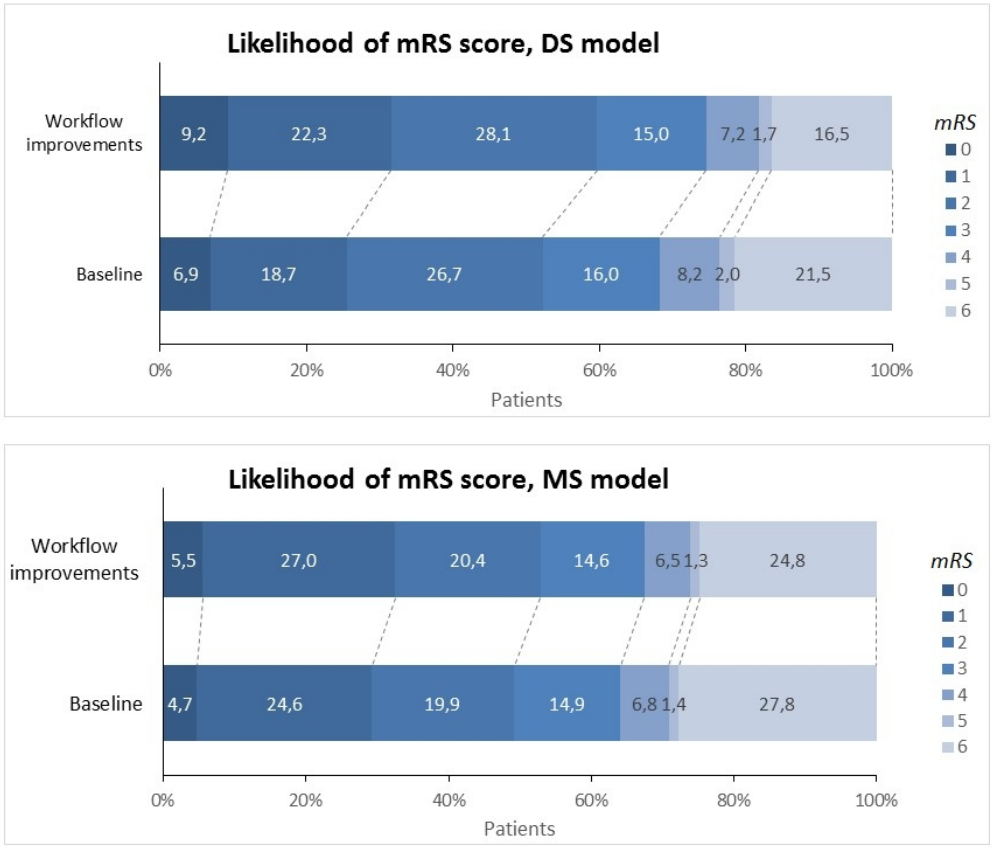

Fig. 2. DS indicates the 'drip and ship' model; MS indicates the 'mothership' model; mRS indicates the modified Rankin Scale

226x194mm (96 x 96 DPI)

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; $\alpha1 = 2.56$; $\alpha2 = 7.15$		
EMS on Scene	Gamma	Location = 1.70; $\alpha = 5.43$; $\beta = 2.73$		
EMS Transport	Weibull	Location = 0.00 $\alpha = 2.11$; $\beta = 13.14$		
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; $\alpha 1$ = 0.67; $\alpha 2$ = 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; $\alpha 1$ = 4.55; $\alpha 2$ = 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	$\mu = 9.77$; $\sigma = 3.61$		
EMS on Scene	Lognormal	$\mu = 21.55$; $\sigma = 8.16$		
EMS Transport	Weibull	Location = 0.00; $\alpha = 2.16$; $\beta = 20.03$		
Time from hospital arrival to CT	Log-logistic	Location = 6.47; $\alpha = 6.29$; $\beta = 2.57$		
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; $\alpha = 8.58$; $\beta = 2.86$		
Time from IVT to CTA (route 1)	Lognormal	$\mu = 15.74$; $\sigma = 17.43$		
Time from CT to CTA (route 2)	Beta	Lower endpoint = 0.47; Upper endpoint = 30.69; $\alpha 1 = 1.96$; $\alpha 2 = 6.53$		
Time from CTA to IVT (route 2)	Gamma	Location = 0.00; $\alpha = 1.44$; $\beta = 8.93$		
Time from CT to CTA (route 3)	Lognormal	$\mu = 10.96$, $\sigma = 11.45$		
Time from last examination ED to angiography suite	Gamma	Location = 0.00; $\alpha = 3.49$; $\beta = 18.63$		
Time from angiography suite to groin puncture	Log-logistic	Location = 0.00; $\alpha = 28.36$; $\beta = 4.89$		
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))))

References

1. Law AM. Simulation modeling and analysis. Vol McGrawHill: Boston, 5th edition. McGrawHill: Boston, 5th edition.; 2015.
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5. Sablot D, Farouil G, Laverdure A, Arquizan C, Bonafe A. Shortening time to reperfusion after transfer from a primary to a comprehensive stroke center. Neurol Clin Pract. 2019;9(5):417-423.
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7. Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. JAMA. 2016;316(12):1279-1288.
8. Mehta BP, Leslie-Mazwi TM, Chandra RV, Bell DL, Sun CHJ, Hirsch JA, Rabinov JD, Rost NS, Schwamm LH, Goldstein JN, et al. Reducing door-to-puncture times for intra-arterial stroke therapy: A pilot quality improvement project. J Am Heart Assoc. 2014;3(6):e000963.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5,6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	13

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,9
		(b) Indicate number of participants with missing data for each variable of interest	7,8,9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11,12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	11,12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11,12
		(*b*) Report category boundaries when continuous variables were categorized	11,12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10,11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.