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STROKE CARE SYSTEMS: CAN SIMULATION MODELING CATCH UP WITH THE RECENT ADVANCES IN STROKE TREATMENT?

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ABSTRACT

Stroke is one of the three most common causes of death and the sixth most common cause of disability worldwide. Building effective and efficient stroke care systems is critical for improving patient outcomes in the prevention, treatment, and rehabilitation of stroke. A systems approach is necessary to improve the way stroke is treated so that patients have access to the most appropriate treatment in centers that are best equipped to deal with their critical and time-sensitive needs. System simulation has much to contribute to the design and operation of effective and efficient stroke care systems. The success on this path depends, among other factors, upon common vision for problems to attack. The objective of this paper is to review existing contribution of simulation modeling to stroke care systems and to propose the ways for future contribution of system simulation to the effort of designing and operating effective stroke care systems.

1 INTRODUCTION

In 2010, stroke was ranked as the second most common cause of death and the third most common cause of reduced disability-adjusted life years around the world (World Health Organization 2014). In 2010, the total number of people with first stroke was 16.9 million worldwide (Feigin et al. 2014).

Developing effective treatment strategies for ischaemic stroke, when a blood clot or plaque blocks a blood vessel – these account for 80% of all strokes (Donnan et al. 2008), has become a focal point for the effort of the stroke research and practitioners' community. These, in particular, include hyper-acute treatment aimed at the speediest possible unblocking of the blood vessel, acute and rehabilitation treatment, as well as primary and secondary prevention. Up until very recently, together with decompressive surgery for ischaemic stroke, aspirin for secondary prevention, and specialized stroke unit care, the main evidence-based intervention for ischaemic stroke was intravenous thrombolysis within 4.5 hours from stroke symptom onset (Lees et al. 2010; Wahlgren 2008); with each minute of onset-to-treatment time saved granted on average 1.8 days of extra healthy life for the stroke patients (Meretoja et al. 2014).

The most recent results from a new generation of acute stroke trials became available in late 2014 and early 2015. These trials demonstrate that intra-arterial clot removal can be successfully used to further improve the outcomes in patients with ischemic stroke (Campbell et al. 2015; Goyal et al. 2015; Hacke 2015; Jovin et al. 2015; Saver et al. 2015). Now that the benefit of the intra-arterial therapy has been convincingly proven, stroke care systems worldwide face a serious challenge of incorporating the intra-arterial treatment into the existing care processes by providing and optimizing the necessary resources for such a change.

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These developments in the field of stroke care together with the accompanying systemic challenges present an exciting opportunity for simulation modeling to contribute to the design and evaluation of different interventions within the stroke care system with the aim of improving the patients’ outcomes in the prevention, treatment, and rehabilitation of stroke. It has been argued that this opportunity to contribute to effective and efficient design and operations of stroke care systems has not been fully realized, calling for further research studies to address different problem areas within the stroke care system (Churilov & Donnan 2012).

The objective of this paper is to review existing contribution of simulation modeling to stroke care systems and to propose the ways for future contribution of system simulation to the effort of designing and operating effective stroke care systems.

The paper is organized as follows. The next section provides a background of the Operational Research (OR) applications in stroke care. Section 3 reports on the literature search methodology and results. Section 4 is dedicated to classification of simulation studies, and summary and conclusions are presented in Section 5.

2 THE BACKGROUND OF THE OR APPLICATIONS IN STROKE CARE

In this paper, we adopt the conceptual framework proposed by Churilov and Donnan (2012) to position the systems simulation studies reported in literature in relation to both the specific part of the stroke care system (problem area) being addressed and the nature and purpose of the simulation modeling intervention. This framework resulted from the comprehensive analysis of the four key public policy documents for stroke services published in USA, UK, Canada, and Australia. The framework identified the following problem areas in the stroke care systems worldwide as having the highest need for a concentrated systems modeling effort (Churilov & Donnan 2012):

1. Stroke prevention (SP): effective evaluation and management of risk factors and increasing the public awareness on lifestyle and available treatment options;
2. Pre-hospital stroke care (PH): increasing the number of eligible patients to receive tPA treatment by reducing the stroke-to-hospital delay times;
3. Improving Information support for stroke patients (IS);
4. Appropriate and timely management of TIAs (TIA);
5. Stroke unit care (SU): patients suffering from stroke should have immediate access to required facilities and services within the stroke unit care;
6. Rehabilitation (REH): patients should have access to post-stroke rehabilitation services for as long as they need;
7. Social and community care (SOC): to support the long-term needs of the stroke patients and their families;
8. Stroke networks (NET): to connect the key stakeholders across the stroke care system;
9. Appropriate stroke care expertise (EXP): to facilitate the implementation of new therapeutic strategies;
10. Financial viability (FIN): Cost-effectiveness analysis of different stroke care models to financially support people affected by stroke.

In addition to the ten areas identified above, the potential modeling interventions could be classified according to their nature and purpose.

1. Simulation modeling for Stroke care operations improvement: (1.1) processes design and performance, risk, and quality measurement; (1.2) scheduling and workforce planning; (1.3) stroke specialist workload models; (1.4) stroke services utilization models; (1.5) social and

support care services planning and utilization models; (1.6) ambulance service models; (1.7) equipment planning; (1.8) stroke units and thrombolysis facility location and layout; and (1.9) clinical and management decision support systems.

2. Simulation modeling for Economic analysis: (2.1) imaging and surgical equipment evaluation and selection models; (2.2) optimal pricing and costing models; (2.3) stroke demand forecasting and planning models; (2.4) impact of prevention and knowledge dissemination policies on stroke care demand; and (2.5) long term evaluation of stroke burden and implications of various intervention strategies.
3. Simulation modeling for Public policy: (3.1) stroke national and regional planning and network models; (3.2) stroke unit treatment access and availability population models; (3.3) stroke prevention and risk factors management models; and (3.4) risk screening subsequent to TIAs.
4. Simulation modeling for Clinical applications: (4.1) stroke risk assessment and analysis; (4.2) stroke clinical decision support; (4.3) disease modeling at individual level; (4.4) drug selection and interaction models for stroke prevention; and (4.5) optimal therapy dose selection models

This adopted framework will be used as a tool to classify the simulation modeling studies reported in literature in Section 4.

3 LITERATURE SEARCH METHODOLOGY AND RESULTS

The simulation modeling studies in stroke care selected for this review were identified from the following sources (Table 1):

1. PubMed – the most comprehensive database for biomedical literature;
2. Proceedings of the Winter Simulation Conference (WSC) and available proceedings of the Association of European Operational Research Societies (EURO) conferences;
3. A compiled list of high impact Operations Research, Management Science, and Decision Science journals as well as the journals specifically mentioned in the review of healthcare simulation literature by Mustafee, Katsaliaki, and Taylor (2010);

Table 1: List of different sources used for the selection of stroke simulation modeling studies.

Database	
PubMed (no specific starting date before 2014 was fixed for this database)	
Conference Proceedings	
WSC (1971–2014)	
EURO (2007–2011)	
Journal Title	
Operations Research (1957–2014)	Antimicrobial Agents and Chemotherapy (1963–2014)
Management Science (1929–2014)	Journal of Operations Management (1980–2014)
European Journal of Operational Research (1978–2014)	Omega (1973–2014)
Computers and Operations Research (1978–2014)	Annals of Operations Research (1996–2014)
Operations Research for Health Care (2012–2014)	Decision Support System (1989–2014)
The Journal of the Operational Research Society (1978–2014)	Chemosphere (1933–2014)
International Journal of Simulation and Process Modeling (2005–2014)	Preventive Veterinary Medicine (1982–2014)
Pharmacoeconomics (1992–2014)	Vaccine (1929–2014)
Applied Health Economics and Health Policy (2002–2014)	Simulation: Transactions of The Society for Modeling and Simulation International (1963–2014)

Medical Decision Making (1981–2014)	Health Policy (1984–2014)
Current Medical Research and Opinion (1972–2014)	American Journal of Public Health (1954–2014)
Journal of Simulation (2006–2014)	Clinical Pharmacokinetics (1976–2015)
Risk Analysis (1981–2014)	IIE Transactions (1982–2015)
Health Economics (1988–2014)	International Journal of Nursing Studies (1965–2014)
Human and Ecological Risk Assessment (1998–2014)	Decision Analysis (1977–2014)

The search was conducted in two stages. At the first stage, we used different combinations of the terms "stroke", "simulation", and "simulation model*" as string search criteria in the article's title, abstract or keywords. As a result, we found 117 articles which titles and abstracts were further screened to exclude both duplicates (n=4) and irrelevant studies (n=49). In the second stage, we screened the full text of the 64 remaining articles to include those which specifically addressed the stroke care system as a focus of the study or as a full illustrative example, as opposed to the studies not specifically focusing on stroke. This stage resulted in 30 studies being identified for the subsequent in-depth analysis. The summary of the search process is graphically presented in Figure 1.

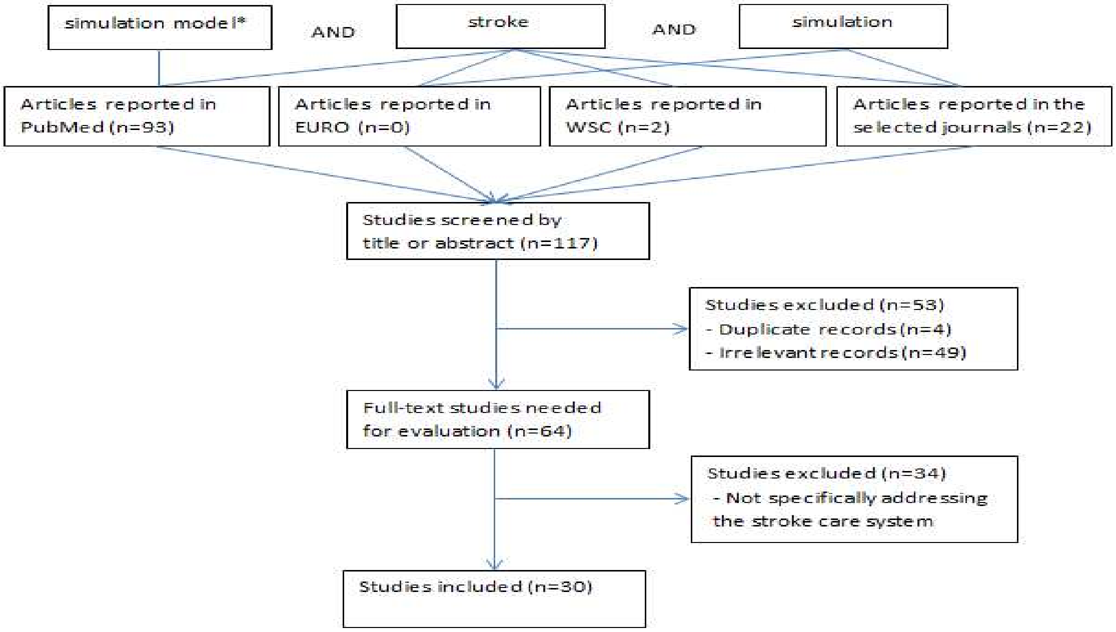

Figure 1: Flow diagram for selection of the simulation modeling studies in stroke care from literature.

Below we present a brief summary of the identified simulation studies, broadly grouping them according to the simulation techniques Monte Carlo Simulation (MCS), Discrete-Event Simulation (DES), System Dynamics (SD), Agent-Based Simulation (ABS), hybrid simulation (where more than one technique is used) and other simulation techniques. Overall, of the 30 studies analyzed, 11 studies reported on using MCS, 12 articles used DES, one study employed SD, two studies reported on hybrid use of SD and ABS, and three articles utilized other simulation models (two cases of physiological simulation, and one study using pharmacokinetics simulation). In addition, one study used the case of a mental simulation for conducting a hypothetical scenario analysis. We provide a reference number (in square brackets) for every study discussed to facilitate the future discussion in Section 4.

Simulation studies reporting the use of MCS: Pitt et al. (2012) [1] used MCS to investigate the effect of extended time window for thrombolysis treatment on stroke patients data form UK. The results of the study showed that, despite the benefits of the increased number of the treated patients due to the extended time window, the absolute benefit from thrombolysis were reduced by delayed treatments.

Yang et al. (2014) [2] used a Markov simulation model to compare the long-term effect of three medications (aspirin, clopidogrel, and clopidogrel plus aspirin) used for prevention of stroke or transient ischemic attack (TIA) in patients with intracranial artery stenosis, demonstrating that an increased benefit of treatment with clopidogrel plus aspirin.

Davidson et al. (2013) [3] reported on using a Markov-based simulation model to compare the cost-effectiveness of dabigatran compared to warfarin used for stroke prevention. Data for swedish patients were obtained to investigate the outcomes on the number of strokes prevented, life years gained, and quality-adjusted life years (QALYs) gained. The study concluded that dabigatran is a cost-effective treatment in Sweden.

Matchar, Samsa, and Liu (2005) [4] and Matchar et al. (1997) [5] used a Duke Stroke Policy Model, a continuous-time simulation model, to investigate the cost-effectiveness of the alternative therapies compared with placebo for secondary prevention of recurrent ischemic stroke patients. A dataset for male patients with nondisabling stroke was used to measure the QALYs, costs, and costs per QALYs for the patients.

Matchar and Samsa (1999) [6] used a Stroke Prevention Policy Model, a semi-Markov simulation model, to identify the best treatment alternative for the prevention of stroke. This model factors the viewpoints of different stakeholders, incorporates the best evidences from multiple sources, and performs sensitivity analysis to assess the effect of uncertainty in the model parameters on the model outcomes.

Samsa et al. (1999) [7] described a simulation model used to perform the cost-effectiveness analysis of randomized controlled trials to provide a link between the short-term and long-term effects of different treatment alternatives for the acute ischemic stroke patients. The authors concluded that treatment alternatives with moderate improvements in the health benefits for patients are more likely to be cost-effective.

Sullivan et al. (2006) [8] reported on using a semi-Markov Monte Carlo simulation model to investigate the cost-effectiveness of a medication used to prevent stroke, specifically in old patients with high risk of stroke. The model was built based on an Artrial Fibrillation (AF) trial and a Medical Expenditure Panel Survey over 10-year time horizon to estimate the cost and QALYs for the patients.

Ghijben, Lancsar, and Zavarsek (2014) [9] used a Discrete Choice Experiment to investigate the patients preferences with different medications used for stroke prevention in patients with AF. The study used data for seventy-six participants, who completed the study followed up by an interview to check whether patients had moderate-to-high risk of stroke. Following the simulation-based sensitivity analysis, the study concluded that new medications are more cost-effective when compared to the currently most used medications.

Rivero-Arias et al. (2010) [10] reported on using both Ordinary least squares regression method and multinomial logistic regression with a Monte Carlo simulation approach to map the Modified Rankin Scale Measurement into a Generic Health Outcome.The study compared the performance of each of the mentioned models based on the magnitude of their predicted-to-actual mean health outcome tariff difference, their mean absolute and mean squared errors, and associated 95% confidence intervals.

Parmigiani et al. (1997) [11] used both the Bayesian inference and resampling methods to quantify the cost uncertainty, effectiveness measures, and marginal cost-effectiveness ratios for a complex stroke-prevention policy model.

Simulation studies reporting the use of DES: Lahr et al. (2013) [12] reported on using a DES to re-organize the pre- and in-hospital pathways in community hospitals adopted from the organizational model performance achieved by centralized stroke care centers. The study investigated the number of patients treated with thrombolysis, and patient outcome at 90 days for stroke onset to treatment time.

Monks et al. (2012) [13] used DES to investigate the stroke patients benefits from both reducing the in-hospital delays and extending the treatment time window from 3 to 4.5 hours. The study concluded that the patients benefits can be maximized when the two mentioned interventiones are used to gether in the hospitals.

Lahr et al. (2013) [14] used a three-step simulation-based approach to improve utilization of tissue plasminogen activator (tPA) therapy for patients with acute brain infarction. Having identified the barriers and solutions to those barriers from literature and expert consultation, the authors used DES to test the solutions identified for Dutch acute stroke pathway. The results of this study showed that the tPA treatment rates and efficacy of thrombolysis can be increased by using a scoop-and-run protocol for ambulance personnel and point-of-care diagnostic device instead of laboratory technician.

Barton et al. (2012) [15] used Irish data to investigate the benefits of investing on thrombolysis provision for the eligible stroke patients. The study used the results of survival analysis based on the length of stay and discharge destinations for stroke patients to create different groups of patients to form the basis of a DES model used to explore both the benefits on patient's quality of life and the cost-efficitveness of increasing thrombolysis provision in the hospital, community rehabilitation and social services.

Mar, Arrospide, and Comas (2010) [16] reported on using a DES model to estimate the budget impact of thrombolysis on the prevalence rate of stroke-related disability in Spain and its consequent hospital and social costs. The results of this study suggest a decreased rate of dependent patients and financial savings on social communities' budgets after 6 years.

Stahl et al. (2003) [17] presented the results of the cost-effectiveness analysis of implementing a protocol compliant with National Institute of Neurological Disorders and Stroke (NINDS) recommendations for ischemic stroke patients. The authors use DES to model the stroke care pathways from onset-to-treatment time. Having obtained data for process times, performance of computed tomography, health outcomes, and cost estimates from literature, a "base-case" strategy was developed and compared with that of NINDS-compliant strategy based on the cost-effectiveness analysis of the outcomes followed up by a sensitivity analysis. The authors conclude that applying NINDS-compliant strategy is cost-effective.

Quaglini et al. (2001) [18] described a simulation model used to represent the careflow system for treating patients with ischemic stroke in a Stroke Unit (SU), adopted from both the process and organisational model. The simulation model was developed based on a database for 100 patients and was applied for identifying the bottlenecks in the workflow processes to optimize the recourse utilization within the stroke unit.

Heinrichs, Beekman, and Limburg (1999) [19] used data from The Netherlands to model a patient flow in a SU. Due to the high variability of admission rates for stroke patients, the model was used as a decision support tool to assist with the capacity planning and optimization in the SU.

Churilov et al. (2013) [20] used a DES model to show how multi-factorial interventions in pre-hospital acute care system will impact the eligibility of acute stroke patients to receive thrombolysis treatment.

Vasilakis and Marshall (2005) [21] used different analytical and simulation modeling techniques to analyse the length of stay for stroke patients who were discharged from English hospitals over a 1-year period. The authors then provide a summary of the alternative methods and their similarity in terms of the parameters used to estimate the patient flow as calculated by the phase-type distribution and compartmental modeling techniques.

Kongnakorn et al. (2009) [22] used DES to investigate the cost-effectiveness of a medication used for prevention of stroke based on a trial. The simulation model generates two groups of patients one for those who only receive the usual care and one for those that also receive the medication under study. The simulation model was used to estimate the cost within a 5-year period and QALYs for the patient's lifetime.

Bayer et al. (2010) [23] described a prototype model to support integrative planning for local stroke services by using DES to map the pathways for stroke patients. The authors concluded that simulation modeling provides a systematic approach to further understand the impact of service change and improvements within the system.

Simulation studies reporting the use of SD: Lich et al. (2014) [24] described a SD model to investigate the effect of different scenarios of prevention and rehabilitation interventions on reducing the burden of disease for stroke patients using the US Veteran population data. Different outcomes reported in this study were QALYs, stroke prevented, stroke fatilities prevented, and the number-needed-to-treat per QALY gained.

Simulation studies reporting the use of hybrid simulation: Djanatliev et al. (2012) [25] and Gantner-Bär et al. (2011) [26] used a technology assessment approach developed in Germany to assess the effects of using Mobile Stroke Units within the stroke care system in the metropolitan Berlin. The authors used both the SD and the ABS to investigate the effect of using this new technology from perspective of different stakeholders before its implementation. The paper concludes that stroke patients benefit about 18% more from thrombolysis therapy by using the MSU technology.

Simulation studies reporting other simulation techniques: AlMuhanna et al. (2012) [27] used a linear circuit simulation model to represent the anatomical mechanisms associated with the occurrence of ischemic stroke. Bredno, Olszewski, and Wintermark (2010) [28] used a brain perfusion simulation model to represent the physiological mechanisms associated with secondary stroke prevention. Clemens et al. (2012) [29] used a pharmacokinetic model to investigate the effect of a medication dose on prevention of stroke in patients with AF, and finally Jørgensen et al. (1999) [30] reported on using a mental simulation model to predict the impact of tPA on prognosis of general population of stroke patients.

4 CLASSIFICATION OF SIMULATION STUDIES

Table 2 summarizes the positioning of the systems simulation studies reviewed above in relation to both the specific part of the stroke care system (problem area) being addressed and the nature and purpose of the simulation modeling intervention as per Churilov and Donnan (2012).

Table 2: Simulation modeling studies in stroke care by problem areas and the purpose of the modeling.

Interventions		**Problem areas**									
		SP	PH	IS	TIA	SU	REH	SOC	NET	EXP	FIN
Operations improvement	1.1	[12],[14], [17],[20], [25],[26]			[1],[12], [13],[14], [17],[18], [19],[21], [24]	[17],[23]	[17],[23]	[23]			
	1.2		[12],[17], [23],[25], [26]			[12],[17], [18],[19], [23]	[17],[23]	[17],[23]	[23]		
	1.3					[17],[18], [19]	[17]	[17]			
	1.4		[12],[14], [25],[26]			[1],[5], [6],[12], [13],[14], [15],[16], [17],[18], [19],[21]	[5],[6], [15],[16], [17]	[5],[6], [15],[16], [17]			
	1.5	[24]	[23]			[23]	[23],[24]	[23],[24]	[23]		
	1.6		[12],[14], [20],[23], [25],[26]			[12],[17], [23]	[17],[23]	[17],[23]	[23]		
	1.7		[12],[23], [25],[26],			[12],[17], [18],[23]	[17],[23]	[17],[23]	[23]		
	1.8										

	1.9		[12],[14],[20],[23],[25],[26]			[1],[12],[14],[17],[18],[19],[21],[23]	[17],[23]	[17],[23]	[23]		
Economic analysis	2.1										
	2.2		[25],[26]								
	2.3		[23]			[18],[23]	[23]	[23]	[23]		
	2.4										
	2.5	[3],[5],[6],[7],[8],[9],[11],[22],[24],[29]				[4],[5],[6],[7],[8],[9],[11],[15],[16],[17],[22]	[4],[5],[6],[7],[8],[9],[11],[15],[16],[17],[22],[24]	[4],[5], [6],[7],[8],[9],[11],[15],[16],[17],[22],[24]		[4]	[10]
	3.1	[24]	[12],[23]			[12],[23],[24]	[23],[24]	[23],[24]	[23]		
Public policy	3.2		[20],[23],[25],[26]			[12],[23]	[23]	[23]	[23]		
	3.3	[2],[3],[4],[5],[6],[7],[8],[9],[11],[22],[24],[29]			[2]	[4],[5],[6],[7],[8],[9],[11],[22]	[4],[5],[6],[7],[8],[9],[11],[22],[24]	[4],[5],[6],[7],[8],[9],[11],[22],[24],[31]			
	3.4										
Clinical application	4.1										
	4.2		[25],[26]			[1],[13],[15],[16],[17],[30],	[15],[16],[17]	[15],[16],[17]			
	4.3	[6],[7],[11],[27],[28]				[5],[6],[11]	[5],[6],[11]	[5],[6],[7],[11]			
	4.4	[2],[3],[4],[8],[9],[22]			[2]	[4],[8],[9],[22]	[4],[8],[9],[22]	[4],[8],[9],[22]			
	4.5	[29]									

5 SUMMARY AND CONCLUSIONS

We reviewed the simulation modeling studies in stroke care domain reported in the literature to identify the articles that were specifically addressing a problem area within the stroke care system as the main focus of the study. We further classified the studies in relation to both the specific problem area of the stroke care system being addressed and the nature and purpose of the simulation modeling intervention. As the result, we found that the following interventions have been addressed more actively than others: stroke care process design and performance, stroke team scheduling and workforce planning, stroke services planning and utilization models, long term evaluation of stroke burden, stroke prevention and risk factors management models, and stroke clinical and management decision support models. On the other hand, there was a lack of attention to interventions such as stroke units and thrombolysis facility location and layout, imaging and surgical equipment evaluation and selection models, optimal pricing and costing models for stroke care and insurance, impact of prevention and knowledge dissemination policies on stroke care demand, risk screening subsequent to TIAs, stroke risk assessment and analysis, and optimal therapy dose selection models.

With regard to different problem areas, stroke prevention, pre-hospital, stroke unit care, rehabilitation and social and community care parts were identified as the most addressed areas; while information and support for stroke patients, appropriate management of TIAs, appropriate stroke care expertise, and financial viability were addressed least in the literature.

New interventions in stroke care are likely to stretch the existing capacity of the stroke care centers capable of providing neuro-interventional services, thus placing extra demand on the existing stroke care processes and systems. It is easy to envisage that operational issues of hyper acute and acute stroke care will require a particularly concentrated simulation modeling effort, not to the exclusion of the other problem areas discussed in the paper. In summary, although it is clear that the existing system simulation effort in the stroke care domain has been successful and productive, there is a major scope for detailed high quality system simulation studies that rely on integrated effort of simulation modelers, stroke clinicians, and health systems experts and utilize a variety of different simulation techniques.

REFRENCES

AlMuhanna, K., L. Zhao, G. Kowalewski, K. W. Beach, B. K. Lal, and S. Sikdar. 2012. Investigation of Cerebral Hemodynamics and Collateralization in Asymptomatic Carotid Stenoses. Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE.

Barton, M., S. McClean, J. Gillespie, L. Garg, D. Wilson, and K. Fullerton. 2012. "Is It Beneficial to Increase the Provision of Thrombolysis?—a Discrete-Event Simulation Model." QJM: An International Journal of Medicine 105 (7):665-673.

Bayer, S., C. Petsoulas, B. Cox, A. Honeyman, and J. Barlow. 2010. "Facilitating Stroke Care Planning through Simulation Modelling." Health informatics journal 16 (2):129-143.

Bredno, J., M. E. Olszewski, and M. Wintermark. 2010. "Simulation Model for Contrast Agent Dynamics in Brain Perfusion Scans." Magnetic Resonance in Medicine 64 (1):280-290.

Campbell, B. C., P. J. Mitchell, T. J. Kleinig, H. M. Dewey, L. Churilov, N. Yassi, B. Yan, R. J. Dowling, M. W. Parsons, and T. J. Oxley. 2015. "Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection." New England Journal of Medicine 372 (11):1009-1018.

Churilov, L., and G. A. Donnan. 2012. "Operations Research for Stroke Care Systems: An Opportunity for the Science of Better to Do Much Better." Operations Research for Health Care 1 (1):6-15.

Churilov, L., A. Fridriksdottir, M. Keshtkaran, I. Mosley, A. Flitman, and H. M. Dewey. 2013. "Decision Support in Pre-Hospital Stroke Care Operations: A Case of Using Simulation to Improve Eligibility of Acute Stroke Patients for Thrombolysis Treatment." Computers & Operations Research 40 (9):2208-2218.

Clemens, A., S. Haertter, J. Friedman, M. Brueckmann, J. Stangier, J. van Ryn, and T. Lehr. 2012. "Twice Daily Dosing of Dabigatran for Stroke Prevention in Atrial Fibrillation: A Pharmacokinetic Justification." Current Medical Research & Opinion 28 (2):195-201.

Davidson, T., M. Husberg, M. Janzon, J. Oldgren, and L.-Å. Levin. 2013. "Cost-Effectiveness of Dabigatran Compared with Warfarin for Patients with Atrial Fibrillation in Sweden." European heart journal 34 (3):177-183.

Djanatliev, A., R. German, P. Kolominsky-Rabas, and B. M. Hofmann. 2012. Hybrid Simulation with Loosely Coupled System Dynamics and Agent-Based Models for Prospective Health Technology Assessments. Proceedings of the Winter Simulation Conference.

Donnan, G. A., M. Fisher, M. Macleod, and S. M. Davis. 2008. "Stroke." Lancet 371 (9624):1612-1623.

Feigin, V. L., M. H. Forouzanfar, R. Krishnamurthi, G. A. Mensah, M. Connor, D. A. Bennett, A. E. Moran, R. L. Sacco, L. Anderson, and T. Truelsen. 2014. "Global and Regional Burden of Stroke During 1990–2010: Findings from the Global Burden of Disease Study 2010." The Lancet 383 (9913):245-255.

Gantner-Bär, M., A. Djanatliev, H.-U. Prokosch, and M. Sedlmayr. 2011. "Conceptual Modeling for Prospective Health Technology Assessment." Studies in health technology and informatics 180:33-37.

Ghijben, P., E. Lancsar, and S. Zavarsek. 2014. "Preferences for Oral Anticoagulants in Atrial Fibrillation: A Best–Best Discrete Choice Experiment." Pharmacoeconomics 32 (11):1115-1127.

Goyal, M., A. M. Demchuk, B. K. Menon, M. Eesa, J. L. Rempel, J. Thornton, D. Roy, T. G. Jovin, R. A. Willinsky, and B. L. Sapkota. 2015. "Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke." New England Journal of Medicine 372 (11):1019-1030.

Hacke, W. 2015. "Interventional Thrombectomy for Major Stroke—a Step in the Right Direction." New England Journal of Medicine 372 (1):76-77.

Heinrichs, M., R. Beekman, and M. Limburg. 1999. "Simulation to Estimate the Capacity of a Stroke Unit." Studies in health technology and informatics 77:47-50.

Jørgensen, H. S., H. Nakayama, L. P. Kammersgaard, H. O. Raaschou, and T. S. Olsen. 1999. "Predicted Impact of Intravenous Thrombolysis on Prognosis of General Population of Stroke Patients: Simulation Model." BMJ 319 (7205):288-289.

Jovin, T. G., A. Chamorro, E. Cobo, M. A. de Miquel, C. A. Molina, A. Rovira, L. S. Román, J. Serena, S. Abilleira, and M. Ribó. 2015. "Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke." New England Journal of Medicine.

Kongnakorn, T., A. Ward, C. S. Roberts, J. A. O'Brien, I. Proskorovsky, and J. J. Caro. 2009. "Economic Evaluation of Atorvastatin for Prevention of Recurrent Stroke Based on the Sparcl Trial." Value in Health 12 (6):880-887.

Lahr, M. M., D.-J. van der Zee, G.-J. Luijckx, P. C. Vroomen, and E. Buskens. 2013. "A Simulation-Based Approach for Improving Utilization of Thrombolysis in Acute Brain Infarction." Medical care 51 (12):1101-1105.

Lahr, M. M., D.-J. van der Zee, P. C. Vroomen, G.-J. Luijckx, and E. Buskens. 2013. "Thrombolysis in Acute Ischemic Stroke: A Simulation Study to Improve Pre-and in-Hospital Delays in Community Hospitals." PloS one 8 (11):e79049.

Lees, K. R., E. Bluhmki, R. Von Kummer, T. G. Brott, D. Toni, J. C. Grotta, G. W. Albers, M. Kaste, J. R. Marler, and S. A. Hamilton. 2010. "Time to Treatment with Intravenous Alteplase and Outcome in Stroke: An Updated Pooled Analysis of Ecass, Atlantis, Ninds, and Epithet Trials." The Lancet 375 (9727):1695-1703.

Lich, K. H., Y. Tian, C. A. Beadles, L. S. Williams, D. M. Bravata, E. M. Cheng, H. B. Bosworth, J. B. Homer, and D. B. Matchar. 2014. "Strategic Planning to Reduce the Burden of Stroke among Veterans Using Simulation Modeling to Inform Decision Making." Stroke 45 (7):2078-2084.

Mar, J., A. Arrospide, and M. Comas. 2010. "Budget Impact Analysis of Thrombolysis for Stroke in Spain: A Discrete Event Simulation Model." Value in Health 13 (1):69-76.

Matchar, D., and G. P. Samsa. 1999. "Using Outcomes Data to Identify Best Medical Practice: The Role of Policy Models." Hepatology (Baltimore, Md.) 29 (6 Suppl):36S-39S.

Matchar, D. B., G. P. Samsa, and S. Liu. 2005. "Cost-Effectiveness of Antiplatelet Agents in Secondary Stroke Prevention: The Limits of Certainty." Value in Health 8 (5):572-580.

Matchar, D. B., G. P. Samsa, J. R. Matthews, M. Ancukiewicz, G. Parmigiani, V. Hasselblad, P. A. Wolf, R. B. D'Agostino, and J. Lipscomb. 1997. "The Stroke Prevention Policy Model: Linking Evidence and Clinical Decisions." Annals of internal medicine 127 (8_Part_2):704-711.

Meretoja, A., M. Keshtkaran, J. Saver, T. Tatlisumak, M. Parsons, M. Kaste, S. Davis, G. Donnan, and L. Churilov. 2014. "Stroke Thrombolysis Save a Minute, Save a Day." Stroke 45 (4):1053-1058.

Monks, T., M. Pitt, K. Stein, and M. James. 2012. "Maximizing the Population Benefit from Thrombolysis in Acute Ischemic Stroke a Modeling Study of in-Hospital Delays." Stroke 43 (10):2706-2711.

Mustafee, N., K. Katsaliaki, and S. J. Taylor. 2010. "Profiling Literature in Healthcare Simulation." Simulation.

Parmigiani, G., G. P. Samsa, M. Ancukiewicz, J. Lipscomb, V. Hasselblad, and D. B. Matchar. 1997. "Assessing Uncertainty in Cost-Effectiveness Analyses Application to a Complex Decision Model." Medical decision making 17 (4):390-401.

Pitt, M., T. Monks, P. Agarwal, D. Worthington, G. A. Ford, K. R. Lees, K. Stein, and M. A. James. 2012. "Will Delays in Treatment Jeopardize the Population Benefit from Extending the Time Window for Stroke Thrombolysis?" Stroke 43 (11):2992-2997.

Quaglini, S., E. Caffi, A. Cavallini, G. Micieli, and M. Stefanelli. 2001. "Simulation of a Stroke Unit Careflow." Studies in health technology and informatics (2):1190-1194.

Rivero-Arias, O., M. Ouellet, A. Gray, J. Wolstenholme, P. M. Rothwell, and R. Luengo-Fernandez. 2010. "Mapping the Modified Rankin Scale (Mrs) Measurement into the Generic Euroqol (Eq-5d) Health Outcome." Medical decision making 30 (3):341-354.

Samsa, G. P., R. A. Reutter, G. Parmigiani, M. Ancukiewicz, P. Abrahamse, J. Lipscomb, and D. B. Matchar. 1999. "Performing Cost-Effectiveness Analysis by Integrating Randomized Trial Data with a Comprehensive Decision Model: Application to Treatment of Acute Ischemic Stroke." Journal of clinical epidemiology 52 (3):259-271.

Saver, J. L., M. Goyal, A. Bonafe, H.-C. Diener, E. I. Levy, V. M. Pereira, G. W. Albers, C. Cognard, D. J. Cohen, and W. Hacke. 2015. "Stent-Retriever Thrombectomy after Intravenous T-Pa Vs. T-Pa Alone in Stroke." New England Journal of Medicine.

Stahl, J. E., K. L. Furie, S. Gleason, and G. S. Gazelle. 2003. "Stroke: Effect of Implementing an Evaluation and Treatment Protocol Compliant with Ninds Recommendations 1." Radiology 228 (3):659-668.

Sullivan, P. W., T. W. Arant, S. L. Ellis, and H. Ulrich. 2006. "The Cost Effectiveness of Anticoagulation Management Services for Patients with Atrial Fibrillation and at High Risk of Stroke in the Us." Pharmacoeconomics 24 (10):1021-1033.

Vasilakis, C., and A. H. Marshall. 2005. "Modelling Nationwide Hospital Length of Stay: Opening the Black Box**." Journal of the Operational Research Society 56 (7):862-869.

Wahlgren N, A. N., Davalos A, Hacke W, Millan M, Muir K, et al. 2008. "Thrombolysis with Alteplase 3-4.5 H after Acute Ischaemic Stroke (Sits-Istr): An Observational Study." Lancet 372 (9646):1303-1309.

World Health Organization. 2014. "Global Status Report on Noncommunicable Diseases 2014." Accessed April 29. http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf?ua=1.

Yang, J., L. Chen, N. Chitkara, and Q. Xu. 2014. "A Markov Model to Compare the Long-Term Effect of Aspirin, Clopidogrel and Clopidogrel Plus Aspirin on Prevention of Recurrent Ischemic Stroke Due to Intracranial Artery Stenosis." Neurology India 62 (1):48.

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