


BMJ Open Door-to-needle time for thrombolysis: a secondary analysis of the TIPS cluster randomised controlled trial

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ABSTRACT

Objective The current study aimed to evaluate the effects of a multi-component in-hospital intervention on the door-to-needle time for intravenous thrombolysis in acute ischaemic stroke.

Design This study was a post hoc analysis of door-to-needle time data from a cluster-randomised controlled trial testing an intervention to boost intravenous thrombolysis implementation.

Setting The study was conducted among 20 hospitals from three Australian states.

Participant Eligible hospitals had a Stroke Care Unit or staffing equivalent to a stroke physician and a nurse, and were in the early stages of implementing thrombolysis.

Intervention The intervention was multifaceted and developed using the behaviour change wheel and informed by breakthrough collaborative methodology using components of the health behaviour change wheel.

Primary and secondary outcome measures The primary outcome for this analysis was door-to-needle time for thrombolysis and secondary outcome was the proportion of patients received thrombolysis within 60 min of hospital arrival.

Results The intervention versus control difference in the door-to-needle times was non-significant overall nor significant by hospital classification. To provide additional context for the findings, we also evaluated the results within intervention and control hospitals. During the active-intervention period, the intervention hospitals showed a significant decrease in the door-to-needle time of 9.25 min (95% CI: -16.93 to 1.57), but during the post-intervention period, the result was not significant. During the active intervention period, control hospitals also showed a significant decrease in the door-to-needle time of 5.26 min (95% CI: -8.37 to -2.14) and during the post-intervention period, this trend continued with a decrease of 12.13 min (95% CI: -17.44 to 6.81).

Conclusion Across these primary stroke care centres in Australia, a secular trend towards shorter door-to-needle times across both intervention and control hospitals was evident, however the TIPS (Thrombolysis Implementation in Stroke) intervention showed no overall effect on door-to-needle times in the randomised comparison.

Trial registration number Trial Registration-URL: <http://www.anzctr.org.au/> Unique Identifier: ACTRN 12613000939796.

Strengths and limitations of this study

- TIPS (Thrombolysis Implementation in Stroke) is the first in Australia to rigorously evaluate the effect of a comprehensive, multi-component and multidisciplinary collaborative approach on door-to-needle time for thrombolysis.
- This study was a post hoc analysis of door-to-needle time data. The data were obtained from a cluster randomised controlled trial which aimed to improve the rates of intravenous thrombolysis in acute ischaemic stroke.
- The study used data collected as part of routine hospital care rather than independent or objective data sources.
- The study was not controlled for any changes in policies, guidelines or process of care being rolled out during the intervention period.

BACKGROUND

When administered to eligible patients with acute ischaemic stroke, intravenous thrombolysis significantly improves patient disability.¹ However, the efficacy of this treatment is highly time-dependent, with earlier treatment being associated with lower rates of unfavourable outcome.²⁻³ Because of the time-dependent benefit, international guidelines have recommended the completion of all in-hospital processing and initiation of intravenous thrombolysis within 60 min of arrival at hospital.⁴ Unfortunately, despite the potential benefits of intravenous thrombolysis among eligible patients, achieving and sustaining optimal rates of intravenous thrombolysis has been challenging.⁵ In Australia, the rate of intravenous thrombolysis among all stroke patient is only 13% according to the 2017 Australian National Stroke Audit.⁶ The National Stroke Audit report also indicates that in Australia, only 30% of intravenous thrombolysis given within 60 min of hospital arrival.⁶ The time between hospital arrival and intravenous thrombolysis, the door-to-needle (DTN) time,



is an important surrogate for stroke service efficiency with shorter DTN times recognised to be associated with better patient outcomes.⁷ Therefore, internationally, system improvement strategies are focusing on both increasing the implementation of intravenous thrombolysis and reducing DTN times.⁸

Reducing DTN time can be a complicated clinical process requiring coordination across departments and disciplines.^{9 10} Successful interventions based on the redesign of modifiable hospital factors and multilevel multi-component hospital level changes have improved DTN times in some settings.¹⁰ A nationwide quality improvement initiative in the USA achieved a 40% success rate in attaining the recommended 60 min DTN time.¹¹ In contrast, in single large metropolitan comprehensive stroke centres (Helsinki and Melbourne), major reductions in DTN have been reported with multifaceted interventions.^{12 13} The Thrombolysis ImPlementation in Stroke (TIPS) study, a clustered randomised controlled trial, tested a combined multi-component and multidisciplinary in-hospital approach aimed at improving intravenous thrombolysis rates at multiple sites across Australia but particularly targeting primary stroke care centres.¹⁴ This intervention was based on the behaviour change wheel.¹⁴ The study achieved significant improvement of intravenous thrombolysis rates in the intervention hospitals during the active intervention phase, however, this improvement was no longer significant during the post-intervention phase.¹⁵ The TIPS outcome paper reported the intended primary and secondary outcomes of the trial as per protocol. However, DTN time is also an important indicator of stroke care. A reduced DNT can increase the proportion of patients eligible for intravenous thrombolysis because more patients can be treated before the 4.5 hour time limit.¹⁶ Moreover, the DNT is increasingly used by administrations as a performance measure to monitor quality of care and to compare performances between hospitals.¹⁷ Therefore, it is important to evaluate the effect of the TIPS intervention on DTN time. In this study, we will explore the effect of the TIPS intervention on DTN, as well as door-to-imaging (DTI), and imaging-to-needle (ITN) times. In addition, as the recommended DTN, DTI and ITN time is <60 min, <25 min and <35 min, respectively,¹⁸ therefore, we will also explore the proportion of patients with the recommended time frame. Moreover, the quality of hospital care for stroke may vary in non-metropolitan areas as non-metropolitan hospitals are less likely to offer coordinated and dedicated services for stroke care in comparison with metropolitan hospitals.¹⁹ Therefore, we will also undertake subgroup analysis to assess whether the effect is modified by metropolitan versus non-metropolitan hospital location. We hypothesised that the intervention hospitals would show a significant and sustained reduction in DTN times.

METHODS

Study design, location and duration

The study was a post hoc analysis of data from the TIPS study, a cluster-randomised controlled trial involving 20 hospitals from three Australian states: New South Wales, Queensland and Victoria.¹⁴ The study adheres to Consolidated Standards of Reporting Trials guidelines. The hospital was the unit of randomisation, with randomisation conducted using a computer-generated stratified scheme where 10 hospitals were assigned to the intervention group and 10 to the control group. The intervention hospitals received the TIPS intervention, a multilevel, multi-component, collaborative approach, whereas the control hospitals continued with standard care. Blinding was not possible because of the nature of the intervention. Study-related activities were divided into three periods:

- ▶ Pre-intervention: January 2011 to August 2013.
- ▶ Active-intervention: September 2013 to December 2014.
- ▶ Post-intervention: January 2015 to December 2015.

Hospital eligibility and recruitment

Eligible hospitals were identified from the Stroke Foundation's audit records and state-based stroke care networks. The participating hospital had a Stroke Care Unit or staffing equivalent to a stroke physician and a nurse, and were in the early stages of implementing thrombolysis. Clinical leaders were contacted by the research team, either in person or over the phone, to discuss possible participation in the study. Once agreed, a memorandum of understanding and consent agreement was co-signed by the hospital's authority and the study team. Those recruited included publicly and privately funded hospitals, as well as metropolitan and non-metropolitan hospitals. Hospitals were randomised within strata defined according to their baseline intravenous thrombolysis rates:

- ▶ Very Low: 0% to 4%.
- ▶ Low: >4% to 10%.
- ▶ Medium: >10%.

Patient data eligibility

De-identified case data from patients treated with stroke thrombolysis were included in the TIPS data set and, for the current study, only data from patients that had complete data were included and each patient was different at each time point.

Ethical approval

The committee approved both the primary and secondary analysis of the data. The trial was registered at Australian New Zealand Clinical Trial Registry prior to random allocation of each hospital to experimental condition. Retrospective patient data were extracted from existing administrative records prior to allocation of each hospital to condition. Therefore, the trial registration status appears as retrospective, despite allocation to condition being prospective.

Patient and public involvement

Patients or the public were not involved in the design of the study.

Process for data collection

The following details were recorded for each thrombolysed case: age, gender, date and time of stroke onset, date and time of hospital arrival, date and time of brain imaging examination, time of treatment and patient medical history. Additionally, for each hospital the following details were considered: location (metropolitan/non-metropolitan), baseline thrombolysis rate and the implementation of TIPS intervention activity (intervention/control). These details were entered into a secure TIPS-specific database that was hosted on the Stroke Foundation's website. The database was only accessible via a secure login system and only accessible to those approved to do so. All patient data were de-identified and entered by a study-specific delegate at each participating hospital.

Interventional activity and components

The TIPS intervention was informed by the breakthrough collaborative methodology and was developed using the behaviour change wheel framework.¹⁴ The intervention included activities and components which have been described previously¹⁴ and those are: situational analysis — clarifying the patient journey, change agents - educating, persuading and modelling, information-based target setting — persuasion and incentivisation, collaborative problem solving - education, modelling and enablement, professional development — education and training, performance feedback - persuasion, modelling.

figure 1 shows distribution of intervention activities according to the behaviour change wheel components.

Statistical analysis

Patient characteristics were summarised using descriptive statistics: frequency and percentages for dichotomous variables, and mean and SD for continuous variables. Mixed-effects regression modelling was used to assess the effectiveness of the TIPS intervention: linear regression for DTN, DTI and ITN times, and logistic regression for DTN time ≤ 60 min, DTI time ≤ 25 min and ITN time ≤ 35 min. Each model included a hospital-level random intercept to adjust for the correlation of outcomes within the hospital. Time period (with pre-intervention as the reference), intervention group (with control as the reference) and time by intervention group interaction were included as fixed effects; and the models also adjusted for baseline hospital thrombolysis rate category (the stratification variable). Adjustment for hospital level factors was considered the most appropriate approach given the cluster randomised controlled design of the main outcome. Robust SEs and an independent structure of the residual errors were used for all models.

Separate models were used to explore whether there was an observable intervention effect when the data for each location type were considered in isolation. Separate mixed-effects regression models were conducted for each location type (metropolitan and non-metropolitan). This was linear for the continuous outcome of mean DTN, DTI, ITN times and logistic for the dichotomous outcome of the proportion of patients having DTN ≤ 60 min, DTI ≤ 25 min, ITN ≤ 35 min. The same fixed effects and

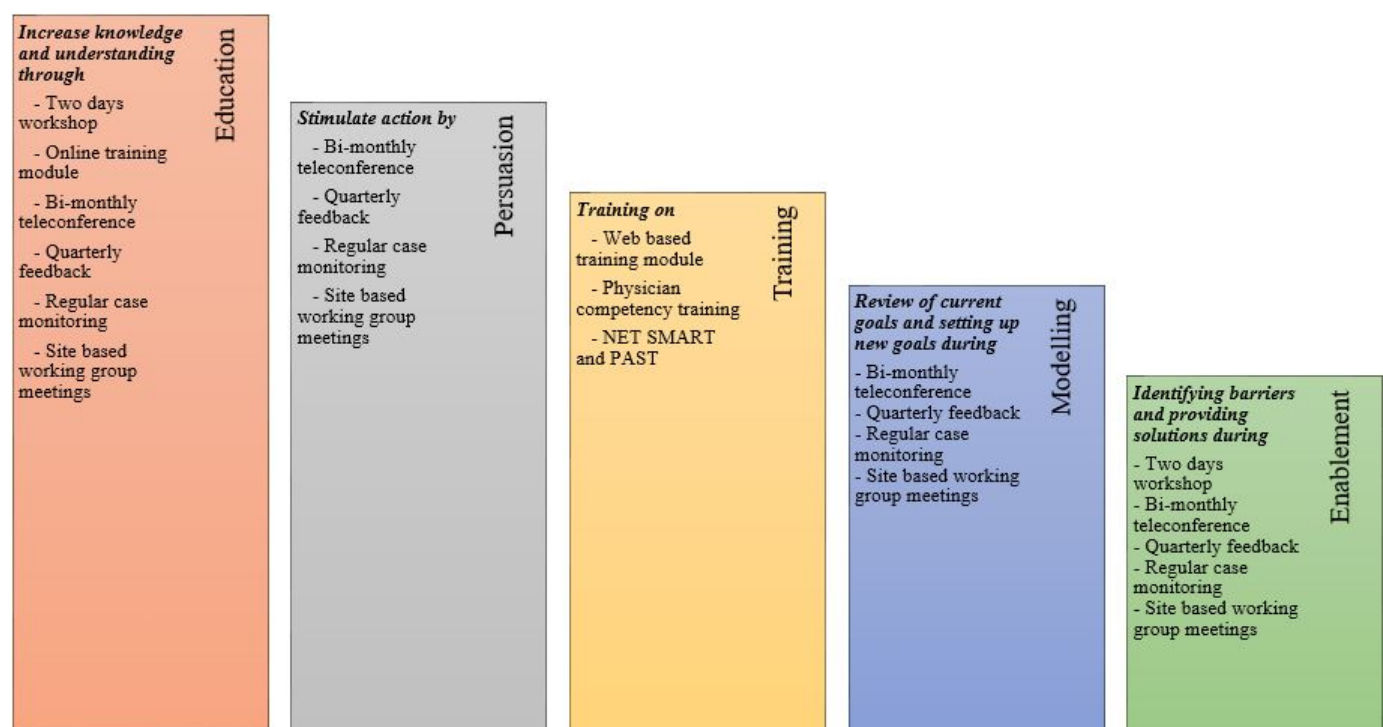


Figure 1 Distribution of intervention activities according to the behaviour change wheel components.

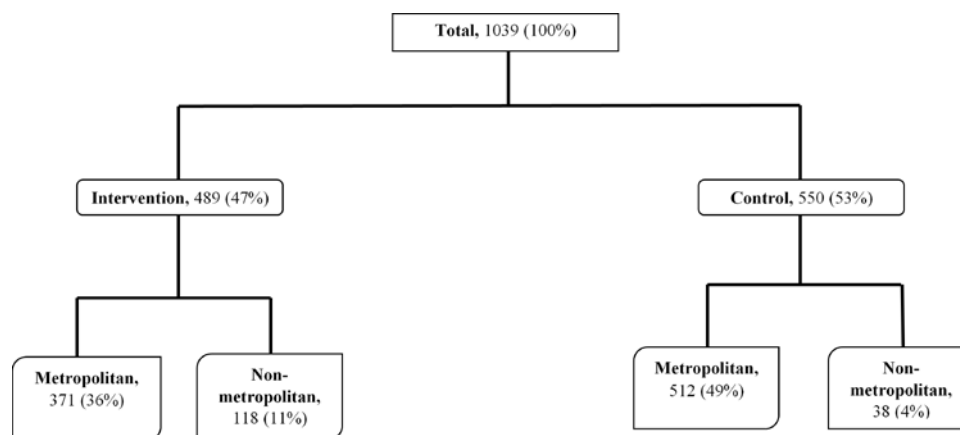


Figure 2 Distribution of patients between intervention and control hospitals across various hospital locations.

hospital-level random intercept included in the primary analysis were also included in these secondary analyses. All statistical analyses were performed using Stata V.14.0 (StataCorp, College Station, Texas).

RESULTS

From January 2011 to December 2015, 1535 patients with acute ischaemic stroke received thrombolysis at the 20 participating hospitals; of which 1039 (68%) had complete data regarding each time point and therefore included in this analysis. The rest were excluded as because of having missing value or not having compatibility. Of the included cases, 489 (47%) were treated in intervention hospitals and 550 (53%) were treated in control hospitals. The mean age of the patients was 72.07 (SD=13.84) years, and 499 (48%) were female. Across all hospitals, 421 (41%) patients were thrombolysed in the pre-intervention period, 364 (35%) in the active-intervention period and 254 (24%) in

the post-intervention period. Of the 20 hospitals, 12 were located in metropolitan areas and these hospitals admitted the majority of patients (n=883, 85%) (figure 2). Of the 20 hospitals, 12 had a baseline thrombolysis rate of 0% to 4% (n=320, 31%), six had a baseline rate of 4% to 10% (n=341, 33%) and two had a baseline rate of >10%. Across 12 Metropolitan hospitals, seven had a baseline rate of 0% to 4%, three had a baseline rate of 4% to 10% and the rest had a rate of more >10%. On the other hand, five out of eight non-metropolitan hospitals had a baseline rate of 0% to 4% and the rest had a baseline rate of 4% to 10%. Patient characteristics for the intervention and control hospitals over the three study periods are reported in table 1. The means and SD in DTN, DTI and ITN times for intravenous thrombolysis were 85.30 (29.88), 33.84 (19.56) and 52.00 (26.29) min, respectively. The proportions of patients with DTN time ≤60 min, DTI time ≤25 min and ITN time ≤35 min were 240 (23%), 410 (39%) and 322

Table 1 Patient characteristics between intervention and control hospitals over the three study periods (pre, active and post)

Characteristics	Pre-intervention, n=421		Active intervention, n=364		Post-intervention, n=254	
	Intervention n=202	Control n=219	Intervention n=177	Control n=187	Intervention n=110	Control n=144
Age in years						
Mean (SD)	72.46 (13.02)	70.87 (13.57)	73.42 (13.94)	73.30 (13.48)	74.57 (13.52)	70.78 (15.66)
Gender						
Female, n (%)	96 (48)	104 (47)	94 (53)	93 (50)	45 (41)	67 (47)
Pre-stroke modified Rankin Score, n (%)						
0	118 (64)	132 (66)	103 (62)	109 (63)	69 (66)	78 (65)
1	22 (12)	27 (13)	12 (7)	18 (10)	7 (7)	11 (9)
2	22 (12)	19 (9)	28 (17)	30 (17)	16 (15)	14 (12)
3	19 (10)	18 (9)	18 (11)	13 (7)	11 (11)	11 (9)
4	3 (2)	3 (2)	3 (2)	4 (2)	1 (1)	5 (4)
5	0 (0)	2 (1)	1 (1)	0 (0)	0 (0)	1 (1)
On admission National Institute of Health Stroke Scale						
Mean (SD)	10.51 (6.47)	11.32 (6.84)	10.4 (7.14)	11.19 (6.35)	11.72 (6.77)	10.52 (6.93)

(31%), respectively. The proportion of patients with DTN time ≤ 45 min was only 8% and none of them had DTN time ≤ 30 min.

Change in door-to-needle times

A ‘difference in differences’ approach was taken to explore the change in DTN times, to optimise the use of continuous data. The linear mixed model controlling for group based on baseline thrombolysis rate. There were no significant differences between the intervention and control hospitals in relation to the change in DTN times from the pre-intervention period to both the active and post-intervention periods (table 2). When comparing the pre-intervention period to the active-intervention period within experimental groups, all hospitals significantly decreased their DTN times. The intervention hospitals decreased the DTN time by 9.24 min (95% CI: -16.92 to 1.55) and the control hospitals decreased it by 5.59 min (95% CI: -9.00 to -2.19). When comparing the pre-intervention period to the post-intervention period within experimental groups, the difference in DTN time was significant for the control hospitals, with a mean decrease of 12.13 min (95% CI: -17.44 to 6.82), but this was not significant for the intervention hospitals (table 2). Online supplementary 1 shows predictive margins for DTN, DTI and ITN for both intervention and control hospitals.

When comparing hospitals based on their location, no metropolitan hospitals achieved significant reductions in DTN times from pre-intervention period to the active and post-intervention periods. However, during the active intervention period, metropolitan hospitals in the intervention group significantly decreased their DTN times by 10.19 min (95% CI: -18.48 to -1.89); while the metropolitan hospitals in the control group showed significant reductions in DTN times during both active and post-intervention period by 4.85 and 12.22 min, respectively (95% CI: -8.03 to -1.66% and 95% CI: -18.02 to -6.41). Almost similar results were found in the non-metropolitan hospitals and for the DTI and ITN times (table 2; online supplementary 2 and 3).

The proportion of patients with door-to-needle times ≤ 60 min

There were no significant differences between the intervention and control hospitals with regards to any change in the proportions of patients with DTN time ≤ 60 min from pre-intervention to either the active or post-intervention periods. However, across periods, there were significant changes from the pre-intervention phase to the post-intervention phase for both the intervention (OR: 1.90; 95% CI: 1.09 to 3.32) and control hospitals (OR: 1.87; 95% CI: 1.12 to 3.13); table 3. No within-group or between-group differences in the proportion of patients with DTN time ≤ 60 min was observed by the hospital’s location (table 3). Results with DTI time ≤ 25 min, and ITN time ≤ 35 min are shown in online supplementary 4 and 5.

Table 2 Effect of intervention on door-to-needle time for thrombolysis

	Intervention		Control		Intervention vs control	
	Number of events	Mean \pm SD	Number of events	Mean \pm SD	Difference in means from pre-intervention period (95% CI)	Difference in means from pre-intervention period (95% CI)
Pre-intervention period	202	87.70 \pm 30.31	219	92.30 \pm 29.13	Reference	Reference
Active intervention period	177	77.24 \pm 27.77	187	86.41 \pm 29.25	-9.24 (-16.92 to -1.55)*	-3.99 (-12.27 to 4.28)
Post-intervention period	110	84.83 \pm 32.63	144	80.08 \pm 28.81	-3.80 (-19.36 to 11.76)	8.33 (-8.10 to 24.76)
Metropolitan hospitals only						
Pre-intervention Period	157	88.28 \pm 31.04	205	91.73 \pm 28.91	Reference	Reference
Active intervention period	135	76.77 \pm 25.90	174	86.54 \pm 29.72	-10.19 (-18.48 to -1.89)*	-5.34 (-14.15 to 3.48)
Post-intervention period	79	86.42 \pm 31.64	133	79.39 \pm 28.72	-3.03 (-23.89 to 17.83)	9.19 (-12.37 to 30.74)
Non-metropolitan hospitals only						
Pre-intervention Period	45	85.69 \pm 27.83	14	100.6 \pm 32.27	Reference	Reference
Active intervention period	42	78.74 \pm 33.39	13	84.69 \pm 22.91	-6.28 (-24.49 to 11.92)	4.93 (-14.27 to 24.14)
Post-intervention Period	31	80.77 \pm 35.25	11	88.45 \pm 29.97	-5.44 (-22.52 to 11.63)	6.86 (-13.11 to 26.83)

*P value <0.05 considered as significant.

Table 3 Effect of intervention on the proportion of patients had DTN time ≤ 60 min

	Intervention			Control			Intervention vs control		
	Total number	Number of patients with DTN ≤ 60 min, n (%)	OR (95% CI)	Total number	Number of patients with DTN ≤ 60 min, n (%)	OR (95% CI)	Total number	Number of patients with DTN ≤ 60 min, n (%)	OR (95% CI)
Pre-intervention period	202	39 (19)	Reference	219	38 (17)	Reference	219	38 (17)	Reference
Active intervention period	177	47 (27)	1.42 (0.86 to 2.35)	187	43 (23)	1.43 (0.87 to 2.36)	187	43 (23)	0.99 (0.49 to 2.02)
Post-intervention period	110	33 (30)	1.90 (1.09 to 3.32)*	144	40 (28)	1.87 (1.12 to 3.13)*	144	40 (28)	1.01 (0.47 to 2.17)
Metropolitan hospitals only									
Pre-intervention Period	157	30 (19)	Reference	205	36 (18)	Reference	205	36 (18)	Reference
Active intervention period	135	34 (25)	1.31 (0.73 to 2.34)	174	42 (24)	1.50 (0.90 to 2.50)	174	42 (24)	0.87 (0.40 to 1.89)
Post-intervention period	79	21 (27)	1.60 (0.83 to 3.11)	133	38 (28)	1.91 (1.12 to 3.26)*	133	38 (28)	0.84 (0.36 to 1.96)
Non-metropolitan hospitals only									
Pre-intervention period	45	9 (20)	Reference	14	2 (14)	Reference	14	2 (14)	Reference
Active intervention period	42	13 (31)	1.78 (0.66 to 4.81)	13	1 (8)	0.51 (0.04 to 6.48)	13	1 (8)	3.51 (0.23 to 54.47)
Post-intervention period	31	12 (39)	2.80 (0.96 to 8.15)	11	2 (18)	1.35 (0.15 to 11.78)	11	2 (18)	2.08 (0.19 to 23.31)

*P value <0.05 considered as significant.
DTN, door-to-needle.

DISCUSSION

Here we reported the relative effect of the TIPS intervention in reducing the duration of within-hospital processes for intravenous thrombolysis. The intervention did not have a significant effect on any of the treatment times studied and there were no differences in treatment time associated with the non-metropolitan or metropolitan location. However, further within-group analyses did provide further information on the way in which practices at study sites were changing during the study period. During the active intervention period, intervention hospitals did show a significant decrease of DTN time but control hospitals also showed a significant decrease in DTN time at both active and post-intervention periods. Moreover, metro hospitals from the intervention arm showed a significant decrease in DTN time during the active intervention period but metro and non-metro hospitals from the control arm also showed a significant decrease in DTN time at both active and post-intervention periods. The primary outcome of the TIPS intervention, the difference in proportion of intravenous thrombolysis between groups, showed a small significant intervention versus control difference during active intervention phase (OR=1.6; 95% CI; 1.1 to 2.3) but a non-significant outcome during the post-interventional phase (rate difference=1.1%; 95% CI; -1.5 to 3.7).¹⁵ Therefore, the non-significant intervention versus control result of DTN time mirrored the primary outcome result reported previously, that is, intravenous thrombolysis rates.

Numerous studies have provided evidence for a variety of strategies to improve DTN time for intravenous thrombolysis. Previous single centre studies report DTN reductions of 8 to 47min from pre to post implementation of improvement strategies.²⁰ However, most of the single centre studies were limited to small numbers of patients (<500; except Helsinki Model) and varied across hospital types, layout and regional policies.⁷ On the other hand, multicentre studies evaluated their intervention effect over a long period of time, for example, US-Target: stroke from 2003 to 2009 and SITS-WATCH 2003 to 2011²¹. The changes described in TIPS occurred only over a 5 year period (2011 to 2015). TIPS was a multicentre study over a time period when intravenous thrombolysis was the focus of various national efforts to improve implementation rates. It is, therefore, possible that the intervention effects may have been partly associated with changes in national and state-level policies and events during the study period. From 2010, the Australian health system implemented several health policies to improve the management of stroke such as clinical guidelines for stroke management 2010, which provided a series of evidence-based recommendations relating to the management of stroke in Australia.²² The continuum of care covered by the guidelines includes pre-hospital and acute phases of care. In addition, the establishment of the Australian Stroke Coalition, a joint venture of the Stroke Foundation and the Stroke Society of Australasia, focussed attention on improvement in processes of care

and developed six areas of priority for action: acute stroke care including thrombolysis and stroke unit care, rehabilitation, community involvement, workforce, training and professional development, pooled data collection and quality development.²³ In 2015, the Stroke Foundation developed an innovative online resource that has information and support for clinicians and administrators working in stroke. It included the latest evidence, linked health professionals with their peers, provided monitoring data on current practice, shared success stories of sites that have improved care and offered tools and resources to maximise the quality of stroke care delivered.⁶ The secular trends seen in improvements in process of care may well have emerged, in part, due to these national systems-level factors.

Several improvement strategies have previously been implemented to reduce the DTN time for thrombolysis. Strategies which resulted in significant improvements in DTN time included pre-hospital notification by the emergency service, rapid triage and treatment protocol; prompt registration, laboratory testing and brain imaging and conducting intravenous thrombolysis in the imaging area.²⁴⁻²⁶ However, as the study authors have acknowledged, the prior studies involved hospitals with a large volume of stroke patients and experience in administering intravenous thrombolysis^{24 25 27} whereas the TIPS study primarily involved hospitals at the early stage of thrombolysis implementation. It is also possible that the null result in DTN times is a result of the modifications to Institute of Healthcare Improvement's breakthrough collaborative model,²⁶ such as two rather than three workshops and the timing of the second workshop. There were also difficulties at some sites with full implementation of the intended intervention. Therefore, the intervention might not be extensive enough to change DTN time in these hospitals. Interestingly, subgroup analysis based on metropolitan and non-metropolitan hospitals followed a similar pattern of overall DTN times, as did DTI and ITN times. Also, around a quarter (23%) of patients had DTN times ≤ 60 min and around one-third had DTI ≤ 25 min (39%) and ITN ≤ 35 min (31%) which are lower than other study results.²⁸ Even so, further research is needed to reduce in-hospital assessment processing times.

Finally, in this post hoc analysis we excluded 32% data as because of missing values or values that were not compatible with the data definitions. However, the problem of missing emphasises the challenges conducting health services research where clinical care teams are the primary vehicle for data collection. Finally, capturing precise timings of the onset of an event like stroke is often difficult.²⁹

CONCLUSION

The neutral overall result highlights that the components of the intervention were not sufficiently robust to modify the processes of care. The reasons behind this non-significant result may be the changes in acute stroke

care that were already occurring at the time, structural barriers to change in complex health systems, workforce capability and capacity to drive change and/or a lack of focus on change enablement among clinical and managerial leadership. Future TIPS analyses will investigate quantitative and qualitative data to identify whether intervention components impacted change in process of care with the aim of informing potential future implementation strategies.

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Contributors MGH, CLP and CRL designed and prepared the study concept. MGH and AH analysed the data with advice from CRL, JRA and CD'E. MGH drafted the manuscript with advice from CRL, JRA, AR, EK, CD'E, AH, AHM, IJH and CRL on method of data analysis, presentation of results. CRL, JRA, AR, EK, CD'E, AH, AHM, IJH and CRL were involved in critical revision of the manuscript. All authors read and approved the final manuscript.

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Patient consent for publication Not required.

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Data availability statement Data are available upon reasonable request. No data are available.

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