Original Contribution

Mortality Reduction for Fever, Hyperglycemia, and Swallowing Nurse-Initiated Stroke Intervention

QASC Trial (Quality in Acute Stroke Care) Follow-Up

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Background and Purpose—Implementation of nurse-initiated protocols to manage fever, hyperglycemia, and swallowing dysfunction decreased death and disability 90 days poststroke in the QASC trial (Quality in Acute Stroke Care) conducted in 19 Australian acute stroke units (2005–2010). We now examine long-term all-cause mortality.

Methods—Mortality was ascertained using Australia's National Death Index. Cox proportional hazards regression compared time to death adjusting for correlation within stroke units using the cluster sandwich (Huber–White estimator) method. Primary analyses included treatment group only unadjusted for covariates. Secondary analysis adjusted for age, sex, marital status, education, and stroke severity using multiple imputation for missing covariates.

Results—One thousand and seventy-six participants (intervention n=600; control n=476) were followed for a median of 4.1 years (minimum 0.3 to maximum 70 months), of whom 264 (24.5%) had died. Baseline demographic and clinical characteristics were generally well balanced by group. The QASC intervention group had improved long-term survival (>20%), but this was only statistically significant in adjusted analyses (unadjusted hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.58–1.07; P=0.13; adjusted HR, 0.77; 95% CI, 0.59–0.99; P=0.045). Older age (75–84 years; HR, 4.9; 95% CI, 2.8–8.7; P<0.001) and increasing stroke severity (HR, 1.5; 95% CI, 1.3–1.9; P<0.001) were associated with increased mortality, while being married (HR, 0.70; 95% CI, 0.49–0.99; P=0.042) was associated with increased likelihood of survival. Cardiovascular disease (including stroke) was listed either as the primary or secondary cause of death in 80% (211/264) of all deaths.

Conclusions—Our results demonstrate the potential long-term and sustained benefit of nurse-initiated multidisciplinary protocols for management of fever, hyperglycemia, and swallowing dysfunction. These protocols should be a routine part of acute stroke care.

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Key Words: fever ■ hyperglycemia ■ implementation ■ mortality ■ stroke ■ swallowing

Despite the global decline in stroke mortality rates, the burden of stroke (absolute numbers of people who have a stroke every year and live with the consequences of stroke or die from their stroke) is increasing,[1] highlighting this leading cause of death and disability as a major public health issue. Populations now live longer, and impressive advances in modern stroke medicine, such as the introduction of stroke care units, thrombolysis, and improved use of effective secondary prevention therapies,[2] has resulted in increased numbers of stroke survivors.[3,4]

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However, the impact of these treatments on the overall reduction in long-term mortality in Australia is unclear because the most recently available population data use premillennia cohorts,[5,6] which predate the systematic introduction of these treatments. In the absence of current national stroke incidence data, regional population studies have been used as a relative measure of stroke incidence rates.[7,8] While the decline in these rates is in keeping with that reported for developed countries internationally,[9] they only report mortality ≤12 months.[7] More recent population data with long-term follow-up are required to better inform contemporary healthcare delivery.

In Australia, the inception of the Australian Stroke Clinical Registry, routinely collecting prospective continuous data on stroke and transient ischemic attack hospital presentations with linkage to the National Death Index (NDI), should soon be able to provide substantial information related to long-term stroke mortality.[10,11] As we await Australian Stroke Clinical Registry outputs, the unique QASC trial (Quality in Acute Stroke Care) cohort not only affords an interim snapshot into current long-term stroke mortality but also on the additional effect of a nurse-initiated intervention implemented in stroke units.[12]

The QASC trial conducted in 19 acute stroke care units throughout New South Wales from 2005 to 2010 demonstrated that use of an evidence-based implementation strategy to introduce 3 clinical protocols for the management of fever, hyperglycemia (sugar), and swallowing dysfunction (Table 1 FeSS intervention elements) in the first 72 hours after stroke unit admission delivered significant reductions in death and disability 90 days poststroke (adjusted absolute difference 15.7%). Four years after completion of the QASC trial, this cohort of patients was available to examine long-term survival and cause of death by treatment group.

In Australia, the Australian Bureau of Statistics compile and code national mortality data.[13] All deaths are registered with the Registrars of Births, Deaths, and Marriages in each state and territory. Coroner-certified death data are maintained by the National Coronial Information System. The NDI is a catalogue of these death records from both sources available from 1980, whereby the records can be securely and reliably merged with other data sets.[14] Through data linkage with the NDI, we aimed to assess the impact of the QASC intervention on long-term all-cause mortality for patients in the postintervention patient cohorts.

Methods

Of the 1126 participants (626 intervention and 500 control) in the QASC postintervention cohorts, 21 withdrew during the trial. We also excluded those who lived overseas (n=5) or who requested to have no

Table 1. FeSS Intervention Elements

Clinical treatment protocols for FeSS management by nurses for first 72 h of ASU care: key elements
Fever
Temperature monitored and charted every 4 h after admission to ASU for first 72 h
Temperature ≥37.5°C treated with paracetamol (intravenous, per rectum, or oral), unless clinically contraindicated
Sugar (hyperglycemia)
Formal glucose measured (venous blood not finger prick) on admission to hospital or admission to the ASU
Finger-prick blood glucose on admission to ASU
Finger-prick glucose every 1–6 h for first 72 h after ASU admission depending on previous blood glucose value
On admission, if blood glucose level between 8 and 11 mmol/L and patient is diabetic or between 8 and 16 mmol/L and patient is not diabetic, start saline infusion for 6 h
If, at any time in first 48 h after admission, blood glucose level is ≥11 mmol/L and patient is diabetic or blood glucose is ≥16 mmol/L and patient is not diabetic, start insulin infusion
Swallowing
Nurses underwent an education program about dysphagia screening, which consisted of all nurses attending an in-service administered by the speech pathologist using a DVD prepared specifically for this study
Nurses underwent a competency assessment before being able to screen patients, consisting of a pre-education and posteducation written knowledge test, and a clinical competency test, completed on 3 patients and assessed by a speech pathologist
Patients were screened with the ASSIST tool by either a nurse who passed the competency test or a speech pathologist within 24 h of admission to ASU; the result of the screening was clearly documented in the patient's medical record by use of a sticker
Patients who failed the swallowing screening were referred to a speech pathologist for a swallowing assessment
Site-based education and support
Two multidisciplinary team-building workshops to identify local barriers and enablers to implement the FeSS nurse-initiated treatment protocols
Two site-based educational outreach meetings consisting of a standardized education program about the FeSS treatment protocols delivered by the Project Officer (SD); Microsoft Powerpoint slides were left with the ASU nurse educator to be delivered to those who did not attend the meetings
Engagement of local stroke unit co-ordinators through support and feedback. The Project Officer (SD) visited each intervention ASU every 6 wk, sent 3 monthly proactive emails to each site, and also instigated scheduled telephone follow-up every 3 mo; all acted as reminders. She also responded to any site-based request for support if needed. Newsletters were sent out yearly

ASSIST indicates Acute Screening of Swallow in Stroke/TIA; ASU, acute stroke unit; FeSS, fever, sugar, swallowing; and TIA, transient ischemic attack.

further involvement in the study (n=24), leaving 1076 patients eligible for data linkage with the NDI. Trial participants who were lost to follow-up (n=96) or reported as deceased during the trial period (n=45) were included for linkage (the latter group was included to obtain cause and time of death, as fact of death previously had been ascertained). Variables submitted to the NDI for matching were first name, second name (if available), surname, sex, date of birth, and date of last contact (QASC 90-day follow-up date). Date and cause of death information was requested up until the time of application (October 31, 2013).

The NDI receives fact of death from all the state and territory Registries of Births, Deaths, and Marriages, and data are uploaded monthly. Underlying (primary) and other (secondary) causes of death as documented on the death certificates are sent to the Australian Bureau of Statistics for coding according to the *International Classification of Diseases*, 10th Revision.[15] The Australian Institute of Health and Welfare is responsible for performing data linkage and provide results of a probabilistic data linkage method with a weighting attached (0–100) that requires manual clerical review by the researchers before accepting or rejecting as a true link/match. This weighting is meant to reflect the quality of the match and is derived from sophisticated computer algorithms based predominantly on name, date of birth, and sex (in order of contribution).[16] The data linkage results may also be returned with a warning flag to indicate if there has been a significant mismatch on variables (eg, sex, date of birth, or if date of death precedes the date of last contact).

Some commonly accepted industry rules were established for the process of clerical review based on advice received from the Australian Institute of Health and Welfare and in conjunction with the study's senior epidemiologist (G. Mnatzaganian). These were (1) the setting of a lower limit of ≤13 weighting for exclusion as true matches and an upper limit of those with weighting ≥90 for automatic inclusion as true matches; (2) exclusion of any matches if there was >1 discrepancy in the date of birth; (3) exclusion of any matches with a warning flag to indicate that the date of death preceded date of last contact; and (4) special consideration to be taken before excluding any matches with rare surnames even if a warning flag (to indicate mismatch on any variable) was attached. The clerical review was performed independently by 2 researchers, with adjudication on any conflicting or difficult cases provided by the consulting epidemiologist.

Ethical approvals were received from Australian Catholic University Human Research Ethics Committee and the Australian Institute of Health and Welfare Ethics Committee.

Statistical Methods

Descriptive statistics are presented for characteristics of the sample and cause of death. Four cause of death variables were generated based on *International Classification of Diseases*, 10th Revision codes: Cardiovascular (cardiovascular disease, including stroke) as the primary cause of death (*International Classification of Diseases*, 10th Revision codes starting with the letter I versus other); stroke as the primary cause of death (*International Classification of Diseases*, 10th Revision codes I60-I65, I67.8, and I69 versus other); cardiovascular disease as either primary or secondary cause of death; and stroke as either primary or secondary cause of death.

Preliminary analysis involved generating Kaplan–Meier curves to estimate the probability of survival and the log-rank test to compare crude survival by treatment group. Survival analysis was performed using Cox proportional hazard regression to compare time from hospital admission because of stroke to time of death between intervention and control groups. All eligible patients were followed from admission until they died or were right censored at the end of follow-up (October 31, 2013). Two a priori analyses were specified: (1) primary analysis: unadjusted for covariates and (2) secondary analysis: adjusted for variables collected during QASC trial and known to be associated with increased mortality after stroke[17,18]: age, sex, marital status, education, and stroke severity (Los Angeles Motor Scale). The proportional hazard assumption of the Cox model was tested using Schoenfeld residuals. Standard errors were adjusted for correlation within hospitals using the cluster sandwich (Huber–White) estimator.

Approximately 1% (n=11), 11% (n=120), and 12% (n=127) of the patients had a missing value on Los Angeles Motor Scale, marital status, and education, respectively. We used multiple imputation by chained equations to generate the missing data using the *mi* Stata command in Stata,[19] with 50 imputed data sets and final estimates obtained using Rubin's rules.[20]

Statistical analyses were undertaken in SPSS version 22.0 and Stata (Version 13; StataCorp, College Stations, TX).

Results

Data were received from the Australian Institute of Health and Welfare for 1076 QASC Trial participants (intervention n=600 and control n=476). Mean (SD) age was 70 (14.2) years for the intervention group and 71 (13.6) years for the control group. Demographic and clinical characteristics for both groups were well balanced, with the possible difference that intervention group participants had a higher level of education compared with the control group (Table 2).

Median time for follow-up was 4.1 years (minimum 0.3 to maximum 70 months). Of the 1076 participants, 264 (24.5%) died during study follow-up (intervention n=134 [22.3%] and control n=130 [27.3%]). Of these, 16 deaths were registered outside of New South Wales.

More than 3 quarters of the overall cohort (80% [211/264]) had cardiovascular disease (including stroke) listed either as the primary or secondary cause of death. Stroke was identified specifically as a primary or secondary cause of death in over half of all deaths (52%; n=138/264; Table 3).

Figure shows crude Kaplan–Meier survival estimates by treatment groups. There was a small but clear divergence in survival curves by treatment group in the immediate

Table 2. Baseline Demographic and Clinical Characteristics by Treatment Group

	Intervention (n=600), n (%)*	Control (n=476), n (%)*
Age, mean (SD)	70 (14.2)	71 (13.6)
<65 y	192 (32%)	133 (28%)
65–74 y	141 (23%)	125 (26%)
75–84 y	174 (29%)	151 (32%)
>85 y	93(15%)	66 (14%)
Female	239 (40%)	193 (40%)
Married or cohabitating	319 (60%)	267 (63%)
Education		
Primary or less	42 (8%)	41 (9.7%)
Intermediate	271 (52%)	280 (66%)
Leaving or HSC	92 (17%)	43 (10%)
University/College	119 (23%)	58 (13%)
LAMS		
0 (mild stroke)	248 (41%)	198 (42%)
1 (more severe stroke)	348 (58%)	271 (58%)

HSC indicates Higher School Certificate (the highest educational award in New South Wales, Australian schools after successful completion of years 11 and 12); and LAMS, Los Angeles Motor Scale (which measures stroke severity).

*Percentages do not add up to total sample size due to missing values.

Table 3. Cause of Death by Treatment Group

	Intervention (n=134)	Control (n=130)	Total (n=264)
CVD as primary cause of death*	67 (50%)	66 (51%)	133 (50%)
Stroke as primary cause of death	37 (28%)	35 (27%)	72 (27%
CVD as primary or secondary cause of death*	108 (81%)	103 (79%)	211 (80%)
Stroke as primary or secondary cause of death	68 (51%)	70 (54%)	138 (52%)

CVD indicates cardiovascular disease.
*Including stroke.

post-trial period, which persisted over time (*P* value for log-rank test=0.05). The regression analyses showed that those in the QASC intervention group, relative to control group, had improved survival of >20%. While unadjusted and adjusted hazard ratio benefits were similar, the difference was only statistically significant in the adjusted analyses (unadjusted hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.58–1.07; *P*=0.13; adjusted HR, 0.77; 95% CI, 0.59–0.99; *P*=0.045).

Older age (HR, 2.0; 95% CI, 1.2–3.2; *P*=0.004; HR, 4.9; 95% CI, 2.8–8.7; *P*<0.001; and HR, 9.6; 95% CI, 6.1–15.2; *P*<0.001 for 65–74, 75–84, and 85+ years age groups, respectively) and increasing stroke severity of Los Angeles Motor Scale ≥1 (HR, 1.5; 95% CI, 1.3–1.9; *P*<0.001) were associated with poorer survival, while being married was associated with improved survival (HR, 0.70; 95% CI, 0.49–0.99; *P*=0.042; Table 4). Assessment of the Schoenfeld residuals showed that the proportional hazards assumption was valid.

Table 4. Risk of Death by Treatment Group, Age, Stroke Severity and Marital Status: Cox Multivariable Regression

	HR	95% CI	*P* Value
Treatment vs control group	0.77	0.59–0.99	0.045
Sex			
Male*			
Female	1.01	0.77–1.3	0.94
Age			
≤64 y*			
65–74 y	2.0	1.2–3.2	0.004
75–84 y	4.9	2.8–8.7	<0.001
85+ years	9.6	6.1–15.2	<0.001
LAMS			
0*			
≥1	1.5	1.3–1.9	<0.001
Marital status			
Never married/widowed/divorced or separated*			
Married or cohabitating	0.70	0.49–0.99	0.042
Education			
Did not complete primary school*			
Primary school, but did not complete intermediate school certificate	1.2	0.81–1.7	0.39
Leaving or higher school certificate	0.97	0.55–1.7	0.92
University or college degree	0.95	0.59–1.5	0.84

Standard errors adjusted for correlation within hospitals using the cluster sandwich (Huber–White) estimator. LAMS indicates Los Angeles Motor Scale (which measures stroke severity).
*Reference category.

Discussion

This follow-up analysis of the QASC cohort using linked death data demonstrates the potential for long-term benefit in addition to the short-term (90-day) benefit generated from the original trial data,[12] of our rigorous implementation of protocols for fever, hyperglycemia, and swallowing dysfunction in the acute stroke setting. The primary outcome in the original QASC trial was combined death and dependency (modified Rankin scale score ≤1), with the percentage of patients alive and independent in the intervention group 15.7% higher than those in the control group. Although there was no statistical difference in mortality alone at 90 days between treatment groups (intervention 21 [4%], control 24 [5%]; *P*=0.36),[12] our new data clearly demonstrate the divergence in survival curves in the immediate post-trial period, which was maintained throughout the follow-up period, further demonstrating the treatment benefit of this intervention.

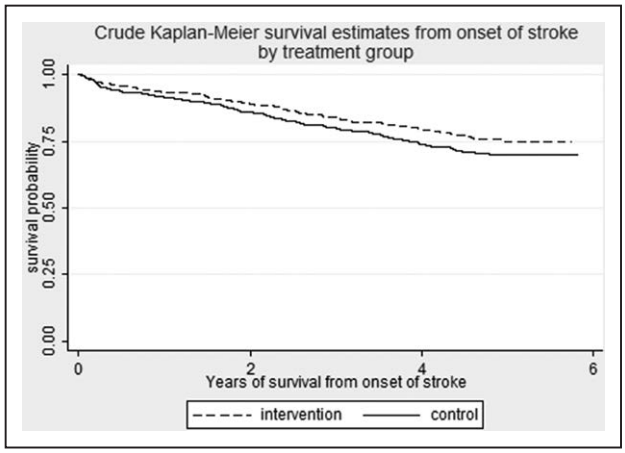

Figure. Kaplan–Meier survival estimates by treatment group.

The difference in hazard ratio adjusted and unadjusted for covariates, although minimal and of marginal statistical significance in adjusted analyses, are persuasive in terms of their clinical importance and resulting impact on patient outcomes. The rigorous implementation of our protocols in an organized stroke services setting[21] and within 48 hours enabling salvageable tissue preservation (penumbra) potentially explains our treatment benefits.

The crude mortality rates reported in both the original QASC trial (4.5% at 90 days) and in this follow-up study (24.5% at 3–5 years) are significantly lower than those reported in previous Australian population studies.[5–7] The

QASC cohort deliberately excluded patients who were deemed for palliation on admission or who died before recruitment and only included those who were admitted to a stroke unit within 48 hours of symptom onset. Both factors may have resulted in the under-representation of more severe strokes (although they were similarly distributed between treatment groups) and lower mortality rates in our cohort. However, mortality rates reported by these previous population studies may have decreased over time because of the improved use of therapeutic medicines for modifiable stroke risk factors,[4] raised community awareness about stroke as a medical emergency,[22] improved access to stroke unit care[23]; and the use of thrombolysis.[23]

Methodologically, our mortality data are subject to the limitations of use of the NDI; however, the validity of this resource for ascertaining mortality has been established in many different populations.[24–29] The problems inherent to use of death certificate information in general, related to incorrect clinical diagnoses and coding miss-classification, are well known, and the significant costs and time delays associated with application to these organizations are not unique to this country.[30] The alternative of using the local state-based death registry (given all participants were recruited within New South Wales) would not have captured 6% (16/264) of deaths registered outside of New South Wales, making the use of the NDI the gold standard for obtaining mortality data in this instance.

While organized stroke unit care programs, including the introduction of stroke unit co-ordinators,[31] have been shown to improve adherence to important clinical processes of care and result in decreased disability,[32] there is a dearth of international literature explicating the precise role of nurse-initiated care within stroke. The QASC trial provided important data to address this evidence gap,[12,33] the value of which is further enhanced by findings from this follow-up study of sustained mortality reduction. Future follow-up with additional events would provide increased statistical power for assessing the long-term benefit of the QASC intervention on all-cause and cardiovascular disease mortality.

Conclusions

We provide persuasive evidence that the benefits of nurse-initiated multidisciplinary protocols for management of fever, hyperglycemia, and swallowing dysfunction when rigorously implemented has a sustained effect in reducing long-term mortality after discharge from stroke units. Longer follow-up will be important to track these benefits still further over time. Long-term survival benefits of implementation of these protocols have wide-reaching clinical implications for health professionals working with acute stroke patients internationally.

Acknowledgments

Dr Middleton as lead investigator conceived, designed, obtained funding, supervised the study, assisted with data interpretation, and wrote the first draft of the article. Dr Low Choy helped conceive, design, and obtain funding for the study. Dr Hiller helped conceive, design, and obtained funding for the study. S. Dale coordinated the study and supervised data collection. A. Jammali-Blasi assisted with data collection and analysis. K. Coughlan assisted with data collection, analysis, and preparing first draft of the article. Drs D'Este and Mnatzaganian assisted with design of statistical plans, data analysis, and interpretation of first draft. Dr Middleton, Dr D'Este, Dr Mnatzaganian, Dr Low Choy, S. Dale, and K. Coughlan assisted with data interpretation. C. Levi, Dr Cadilhac, Dr Ward, Dr Grimshaw, Dr McElduff, S. Dale, Dr D'Este as original QASC study coauthors approved follow-up study design and contributed to subsequent versions of the article. All authors contributed to draft versions of the article and approved the final article.

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Disclosures

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