An Intracerebral Hemorrhage Care Bundle Is Associated with Lower Case Fatality

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Objective: Anticoagulation reversal, intensive blood pressure lowering, neurosurgery, and access to critical care might all be beneficial in acute intracerebral hemorrhage (ICH). We combined and implemented these as the "ABC" hyperacute care bundle and sought to determine whether the implementation was associated with lower case fatality.
Methods: The ABC bundle was implemented from June 1, 2015 to May 31, 2016. Key process targets were set, and a registry captured consecutive patients. We compared 30-day case fatality before, during, and after bundle implementation with multivariate logistic regression and used mediation analysis to determine which care process measures mediated any association. Difference-in-difference analysis compared 30-day case fatality with 32,295 patients with ICH from 214 other hospitals in England and Wales using Sentinel Stroke National Audit Programme data.
Results: A total of 973 ICH patients were admitted in the study period. Compared to before implementation, the adjusted odds of death by 30 days were lower in the implementation period (odds ratio [OR] = 0.62, 95% confidence interval [CI] = 0.38–0.97, $p = 0.03$), and this was sustained after implementation (OR = 0.40, 95% CI = 0.24–0.61, $p < 0.0001$). Implementation of the bundle was associated with a 10.8 percentage point (95% CI = −17.9 to −3.7, $p = 0.003$) reduction in 30-day case fatality in difference-in-difference analysis. The total effect of the care bundle was mediated by a reduction in do-not-resuscitate orders within 24 hours (52.8%) and increased admission to critical care (11.1%).
Interpretation: Implementation of the ABC care bundle was significantly associated with lower 30-day case fatality after ICH.

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Intracerebral hemorrhage (ICH) has the worst outcomes of all stroke subtypes, with a case fatality at 1 month of 30 to 40% and only 20% regaining independence.[1] Globally, hemorrhagic stroke accounts for 49% of 6.5 million annual stroke deaths and 58% of disability-adjusted life years lost to stroke.[2] Despite this substantial health burden, there are few effective treatments, and this may lead to pessimism among clinicians when managing ICH patients.[3]

Improving the implementation of existing evidence-based and guideline-recommended interventions might lead to improved outcomes. Ten to 20% of acute ICH occurs in patients taking oral anticoagulants, and this is associated with a high risk of early hematoma expansion.[4,5] Rapid treatment to normalize coagulation reduces this risk and might improve outcomes.[5,6] Intensive blood pressure (BP) lowering within 6 hours of onset to a target systolic BP (SBP) of 130 to 140mmHg was shown to reduce disability and improve quality of life at 90 days in a prespecified secondary analysis of the INTERACT2 trial, but this intervention can be challenging to implement.[7] Neurosurgery to evacuate the hematoma or treat hydrocephalus might improve outcome, but no single

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randomized controlled trial has been positive and who to operate on and when remains uncertain. An individual patient data meta-analysis of trials of early hematoma evacuation for supratentorial ICH shows patients with larger hematomas (20–50ml) and with reduced consciousness but who are not comatose (Glasgow Coma Scale [GCS] score = 9–12) might benefit from hematoma evacuation.[8] Surgery for cerebellar ICH is widely recommended and associated with lower mortality[9] but has not been tested in a randomized controlled trial.

Whether effective delivery of these interventions together improves survival is unknown. We aimed to evaluate the implementation of a care bundle combining these interventions (the “ABC” care bundle) on case fatality rates for patients with acute ICH. We considered individual patient randomization to be unethical and not feasible and so conducted the study in the setting of a quality improvement program at a large comprehensive stroke center in the United Kingdom. Using data from detailed local and national clinical registries, including data from all stroke centers in England and Wales, we sought to use quasiexperimental methods to evaluate the impact of the care bundle on 30-day case fatality in patients with ICH and to determine the contribution of individual bundle components to any overall treatment effects.

Patients and Methods

Intervention

The Acute Bundle of Care for Intracerebral Hemorrhage (ABC-ICH) project ran from June 1, 2015 to May 31, 2016 at Salford Royal National Health Service Foundation Trust, a large comprehensive stroke center and regional neurosurgical center in Greater Manchester, United Kingdom. A multidisciplinary team of stroke physicians, neurosurgeons, stroke nurses, and managers contributed to the project with support from a local innovation and improvement science center through a program of three 3-day workshops, monthly webinars, improvement coaching, and site visits. The ABC-ICH project aim was to reduce 30-day case fatality after acute ICH through consistent and effective delivery of the ABC acute care bundle. The ABC care bundle comprises evidence-based interventions recommended in the American Stroke Association ICH guidelines[10] and the Royal College of Physicians National Clinical Guideline for Stroke,[11] and we set the following process targets:

1. Rapid anticoagulant reversal, with delivery of 4-factor prothrombin complex concentrate (PCC) for vitamin-K antagonists and anti-Xa antagonists or idarucizumab for dabigatran within 90 minutes of arrival.
2. Delivery of intensive BP lowering to an SBP target of 130 to 140mmHg for patients arriving within 6 hours of onset with an SBP >150mmHg. We aimed for a needle-to-target time (NTT; time from the first dose of an intravenous antihypertensive to achieving target SBP) of <60 minutes.
3. Adherence to a care pathway prompting immediate neurosurgical referral of all patients with good premorbid function (modified Rankin Scale [mRS] score ≤2) and any of the following: GCS <9, posterior fossa ICH, an obstructed 3rd/4th ventricle, or hematoma volume >30ml (measured by the ABC/2 method[12]).

Improvements in ABC care bundle delivery were achieved through engagement of senior leaders, training and education including simulations, audit and feedback to clinical teams, and plan-do-study-act (PDSA) cycles to improve care processes. We made changes to improve speed of anticoagulation reversal prior to the period of data collection for the ABC-ICH project, including the use of point-of-care coagulation testing, a supply of PCC in the Emergency Department, and a protocol to proceed with treatment without hematology referral.[13] Key changes to optimize intensive BP lowering were the introduction of a standard protocol with a clear treatment escalation policy, the introduction of first-line, nurse-led treatment with intravenous glyceryl trinitrate, and the provision of a 1-page quick reference sheet. The care pathway was facilitated by engagement with senior clinicians in neurosurgery and critical care.

Measurement

A clinical registry was established on June 1, 2015, including all consecutive patients with spontaneous ICH admitted to Salford Royal Hospital between June 1, 2013 and May 31, 2017. Patients with traumatic ICH, hemorrhagic transformation of ischemic stroke, and primary subdural or subarachnoid hemorrhage were excluded. Baseline characteristics, clinical presentation, acute care processes, clinical observations, and diagnostic brain imaging characteristics were extracted from the electronic patient record (EPR) for entry into the registry. We collected whether patients were admitted directly to Salford Royal Hospital, transferred from elsewhere, or had their ICH as an in-patient. Brain scans were reviewed by experienced stroke clinicians to determine ICH location, intraventricular hemorrhage, and hematoma volume using the ABC/2 method.[12] We reviewed multiple overlapping databases to ensure complete case ascertainment including clinical coding, neurosurgical referral database, and national quality registry data, all of which were established and operational throughout the period of data collection. Time periods were defined as “before implementation” (June 1, 2013 to May 31, 2015), “implementation” (June 1, 2015 to May 31, 2016), and “after implementation” (June 1, 2016 to May 31, 2017).

Key process data were prospectively entered and regularly reviewed at team meetings from June 1, 2015.

Outcomes and Hypotheses

The primary outcome was 30-day all-cause case fatality. In-hospital and post-discharge deaths were ascertained by data linkage between the hospital EPR and the national statutory register of patient deaths. A survival check was performed for all cases on October 5, 2017, giving a minimum of 5 months of follow-up. Secondary outcomes were key process and care measures and included door-to-needle time (DNT) for anticoagulation reversal, NTT for intensive BP lowering, percentage of patients undergoing neurosurgery within 72 hours of arrival at the hospital, percentage of patients with a do-not-resuscitate (DNR) order within 24 hours of arrival, and percentage of patients admitted to critical care (high-dependence unit [HDU] or intensive care unit) within 72 hours of arrival. Our primary hypothesis was that implementation of the acute care bundle would be associated with a significant reduction in 30-day case fatality during the implementation period compared to the period before implementation at our center and contemporary data from the rest of England and Wales. Our secondary hypothesis was that in addition to improving relevant process targets, implementation of the care bundle would lead to enhanced supportive care, as measured by more admissions to higher-level care and fewer DNR orders within 24 hours of admission.

Statistical Analysis

Thirty-day case fatality for patients admitted to Salford with ICH was compared between time periods using Kaplan–Meier analysis with the log-rank test for statistical significance. Process and care measures were compared between time periods using the Kruskal–Wallis test. We fitted multivariate logistic regression models to compare 30-day case fatality between time periods, adjusting for key prognostic factors in ICH. A quasiexperimental analysis used difference-in-difference analysis to compare the change in 30-day case fatality rates before and after the bundle implementation with data from the national quality registry of stroke (the Sentinel Stroke National Audit Programme [SSNAP]). This was done to provide additional control against unmeasured confounders and to control for secular improvements in stroke outcomes unrelated to the intervention. Data from SSNAP included data on patients with ICH admitted to all stroke centers in England and Wales during the study period. Model-based causal mediation analysis[14,15] was performed to determine the average causal mediation effects for the care and process measures that changed as part of the implementation of the care. The proportion mediated is reported for the parts of the care bundle that were significant in improving the 30-day case fatality. The study was approved by the Health Research Authority (18/HRA/0384).

Results

A total of 973 patients were captured in the Salford ICH registry during the study period (Fig 1). Because they could not have benefited from the acute care bundle, we excluded all patients where a decision was made to restrict care to palliation only within 1 hour of arrival at the hospital (n = 66) or who were not under the care of stroke or neurosurgery specialists during their admission (n = 44). In addition, patients with missing data were removed (n = 3), leaving 353 in the before implementation group, 266 in the implementation group, and 241 in the after implementation group. There were no statistically significant differences in baseline clinical and imaging characteristics between the groups before (Table 1) and after (Table 2) excluding palliated patients or those under other specialties. Compared to the before implementation period, unadjusted 30-day case fatality fell significantly in the implementation period (21.4% vs 27.8%, $p = 0.07$), and this benefit was sustained in the after implementation period (15.4% vs 27.7%, $p < 0.001$; Fig 2). After adjusting for premorbid mRS, level of consciousness on arrival, infratentorial hemorrhage, age, intraventricular hemorrhage, ICH volume, and anticoagulant use, patients in the intervention period had lower odds of 30-day case fatality (odds ratio [OR] = 0.62, 95% confidence interval [CI] = 0.38–0.97, $p = 0.003$). This was sustained in the after implementation period (OR = 0.40, 95% CI = 0.24–0.61, $p < 0.0001$; Table 3). We repeated these analyses for all ICH patients, including patients for whom a decision was made to restrict care to palliation only within 1 hour of arrival at the hospital and those who were not under the care of stroke or neurosurgery specialists during their admission. For this sensitivity analysis and in contrast to the primary analysis, time from onset to arrival was significantly associated with death by 30 days (OR = 0.99, 95% CI = 0.97–1.00, $p = 0.03$) and therefore was included in the multifactorial model. With all patients now included, admission during the implementation period was no longer significantly associated with a reduced odds of death by 30 days (OR = 0.69, 95% CI = 0.42–1.06, $p = 0.09$), but admission after implementation remained strongly significantly associated with reduced odds of death by 30 days (OR = 0.41, 95% CI = 0.24–0.63, $p < 0.0001$). The quasiexperimental difference-in-difference analysis included 32,295 patients with ICH from 214 other hospitals in England and Wales. This demonstrated a 10.8 percentage point (95% CI = −17.9 to −3.7; $p = 0.003$) absolute reduction in 30-day case fatality associated with the implementation of the care bundle (Fig 3).

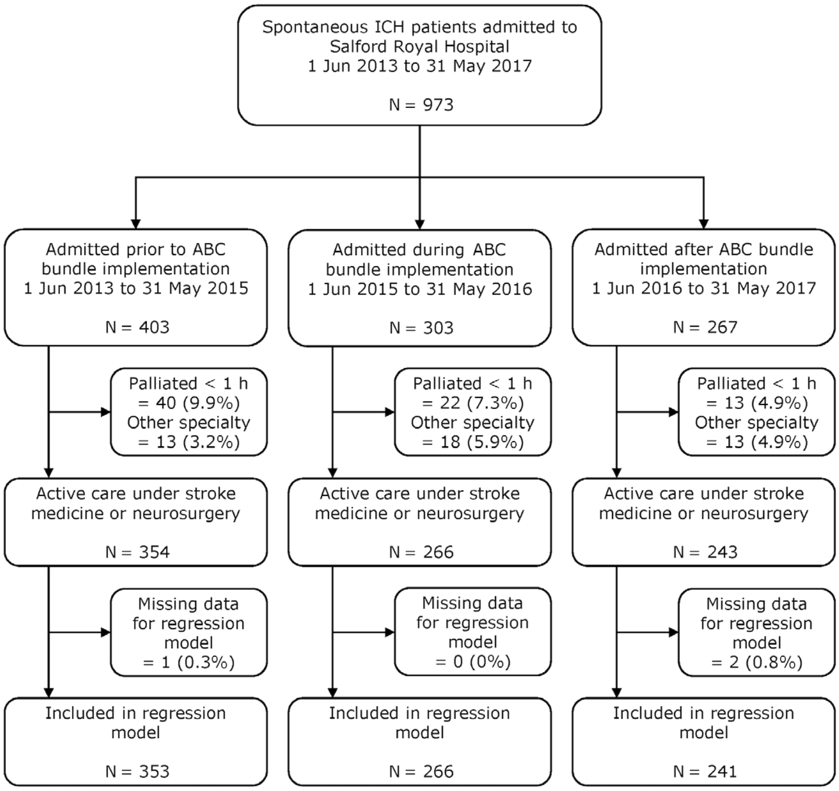

FIGURE 1: Summary of patients admitted before, during, and after bundle implementation. ICH = intracerebral hemorrhage.

Changes to improve DNT for anticoagulant reversal had been made prior to June 1, 2013.[13] No significant change in the median DNT was thus noted (Table 4) between the before implementation period (132.0 minutes, interquartile range [IQR] = 93.5–162.5 minutes) and implementation period (152.5 minutes, IQR = 87.0–210.2 minutes), but improvements were noted during the after implementation period (105.5 minutes, IQR = 75.5–200.5 minutes). During the implementation period (vs before implementation), more eligible patients received intravenous antihypertensive drugs to lower acute BP (86% vs 55%, $p < 0.0001$), and for eligible patients receiving intravenous antihypertensive drugs, the median NTT markedly improved (43 minutes vs 383 minutes, $p < 0.0001$). The median of each patient's mean SBP over 72 hours was lower in the implementation (152.8mmHg, IQR = 145.4–163.5mmHg) and after implementation groups (152.2mmHg, IQR = 145.6–162.3), compared to before implementation (166.7mmHg, IQR = 158.3–174.4). No significant difference was observed before and after implementation in the variability of SBP over 72 hours, as measured by the standard deviation of each patient's SBP recordings. Supportive care improved in both the implementation and after implementation periods, with more patients being admitted to HDU (18/347 [5.2%] before implementation, 32/266 [12.0%] during implementation, 25/243 [10.4%] after implementation) and less use of DNR orders within 24 hours (96/351 [27.4%] before implementation, 47/266 [17.7%] during implementation, 38/243 [15.8%] after implementation). During the after implementation period, but not the implementation period, more eligible patients underwent neurosurgery (16/40 [40.0%] before implementation, 20/54 [37.0%] during implementation, 19/28 [67.9%] after implementation).

Model-based mediation analysis gives an understanding of how the components of the care bundle individually contributed to the overall effect. The total effect is decomposed into 2 components: the natural direct effect and the natural indirect effect (NIE). A significant NIE suggests that the process mediated the overall effect. The mediation analysis (Table 5) demonstrated that the observed reduction in DNR orders within 24 hours mediated 52.8% of the association between care bundle implementation and lower 30-day case fatality and increased admission to HDU mediated 11.1%. As DNT for anticoagulation reversal was not significantly lower after implementation, it could not have been a mediating factor. Although all improved after bundle implementation, time from onset to surgery, intensive BP lowering, NTT, and change in SBP from arrival to 4 hours after arrival were not significant mediating factors. As a sensitivity analysis, we repeated the mediation analysis for all patients admitted during the study period, including patients for whom a decision was made to restrict care to palliation only within 1 hour of arrival at the hospital and

TABLE 1. Baseline Characteristics for All Consecutive Salford Royal Hospital Acute ICH Patients

Factor	Before Implementation, n = 403	During Implementation, n = 303	After Implementation, n = 267	p
Age, yr	71.5 (57.1–81.2)	69.5 (55.2–80.0)	72.8 (61.0–81.1)	0.09
Premorbid mRS [0–2], n (%)	321 (79.7%)	243 (80.2%)	231 (86.5%)	0.06
Anticoagulant, n (%)	56 (13.9%)	43 (14.2%)	34 (12.7%)	0.87
Sex, F, n (%)	213 (52.9%)	147 (48.5%)	149 (55.8%)	0.21
GCS	14 (10–15)	14 (10–15)	14 (10–15)	0.82
Route of arrival, n (%)	Direct 315 (78.2%), transfer 67 (16.6%), in-patient 8 (2.0%), other 13 (3.2%)	Direct 194 (64.0%), transfer 83 (27.4%), in-patient 8 (2.6%), other 18 (5.9%)	Direct 167 (62.5%), transfer 84 (31.5%), in-patient 3 (1.1%), other 13 (4.9%)	<0.0001
Palliated on admission, n (%)	40 (9.9%)	22 (7.3%)	13 (4.9%)	0.05
SBP on admission	169 (148-200)	166 (144-193)	163 (142-189)	0.06
Infratentorial, n (%)	51 (12.7%)	38 (12.5%)	33/265 (12.5%)	0.99
IVH, n (%)	157/402 (39.1%)	122 (40.3%)	95/265 (35.8%)	0.54
ICH volume, ml	17.6 (5.9–51.1), 1 missing	16.6 (5.0–46.1)	19.5 (6.3–48.9), 2 missing	0.53

Columns represent time periods in relation to ABC care bundle implementation: before implementation (June 1, 2013 to May 31, 2015), during implementation (June 1, 2015 to May 31, 2016), and after implementation (June 1, 2016 to May 31, 2017). Patients palliated on admission and/or not admitted under stroke or neurosurgery are included. All data are presented as median and interquartile range, unless otherwise stated. Where data are missing, the number of complete cases is shown as the denominator or the number missing is indicated.

F = female; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; SBP = systolic blood pressure.

those who were not under the care of stroke or neurosurgery specialists during their admission. Again, only access to HDU and DNR within 24 hours were significant mediators, mediating 12.5% and 56.0% of the overall association, respectively.

Discussion

Within the setting of an active quality improvement program to improve acute care for patients with ICH, implementation of the ABC bundle was associated with improved delivery of intensive BP lowering, better access to neurosurgery, improved supportive care, and a relative reduction in 30-day case fatality of over one-third, which was not accounted for by case mix or secular national trends. These improvements in care and survival were sustained for the year following the ABC-ICH project. This study supports the hypothesis that consistent and effective delivery of evidence-based, guideline-recommended care to acute ICH patients may lead to a marked improvement in survival, suggesting that existing therapeutic nihilism[3] may no longer be justified. We have shown that a comprehensive implementation strategy comprising executive and senior leader support, multidisciplinary working, continuous audit and feedback, PDSA cycles, education, and simulation training was effective in introducing, delivering, and sustaining the ABC bundle in the setting of a comprehensive stroke center.

Prior to the ABC-ICH project, we improved DNT for anticoagulant reversal,[13] and this did not improve further during the implementation period. Although this means it cannot have contributed significantly to the observed reduction in case fatality, there are both observational and clinical trial data to suggest that prompt reversal of anticoagulation improves survival,[4–6] making it an important component of the ABC care bundle. Marked improvements were made in the delivery of intensive BP lowering, and our finding that this did not mediate improved survival is consistent with the findings of the INTERACT2 trial, in which the intervention reduced disability and improved quality of life but did not improve survival. Our care pathway was based on existing evidence[8,16] and guidlelines[10,11] and was associated with a significant increase in the percentage of eligible patients undergoing acute neurosurgery. Although neurosurgery was not a significant mediator of the associated reduction in case

TABLE 2. Baseline Characteristics for Salford Royal Hospital Acute ICH Patients Admitted under Stroke Medicine or Neurosurgery and Not Palliated on Admission

Factor	Before Implementation, n = 353	During Implementation, n = 266	After Implementation, n = 241	*p*
Age, yr	69.8 (55.6–80.1)	68.5 (53.7–79.8)	71.2 (59.6–80.3)	0.11
Premorbid mRS [0–2], n (%)	286 (81.0%)	220 (82.7%)	212 (88.0%)	0.08
Anticoagulant, n (%)	47 (13.3%)	36 (13.5%)	29 (12.0%)	0.86
Sex, F, n (%)	186 (52.5%)	128 (48.1%)	127 (52.7%)	0.46
GCS	14 (11–15)	14 (11–15)	14 (11–15)	0.45
Route of arrival, n (%)	Direct 281 (79.6%), transfer 65 (18.4%), in-patient 7 (2.0%)	Direct 177 (66.5%), transfer 83 (31.2%), in-patient 6 (2.3%)	Direct 158 (65.6%), transfer 81 (33.6%), in-patient 2 (0.8%)	<0.0001
SBP on admission	168 (150–198)	165 (144–193)	162 (141–188)	0.09
Infratentorial hemorrhage, n (%)	37 (10.5%)	32 (12.0%)	28 (11.6%)	0.82
Intraventricular hemorrhage, n (%)	124 (35.1%)	98 (36.8%)	79 (32.8%)	0.63
ICH volume, ml	14.0 (5.4–38.5)	15.3 (5.0–42.3)	18.4 (5.9–42.3)	0.41

Columns represent time periods in relation to ABC care bundle implementation: before implementation (June 1, 2013 to May 31, 2015), during implementation (June 1, 2015 to May 31, 2016), and after implementation (June 1, 2016 to May 31, 2017). Patients palliated on admission and/or not admitted under stroke or neurosurgery were excluded. All data are presented as median and interquartile range, unless otherwise stated. All fields were complete for all patients.

F = female; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale; SBP = systolic blood pressure.

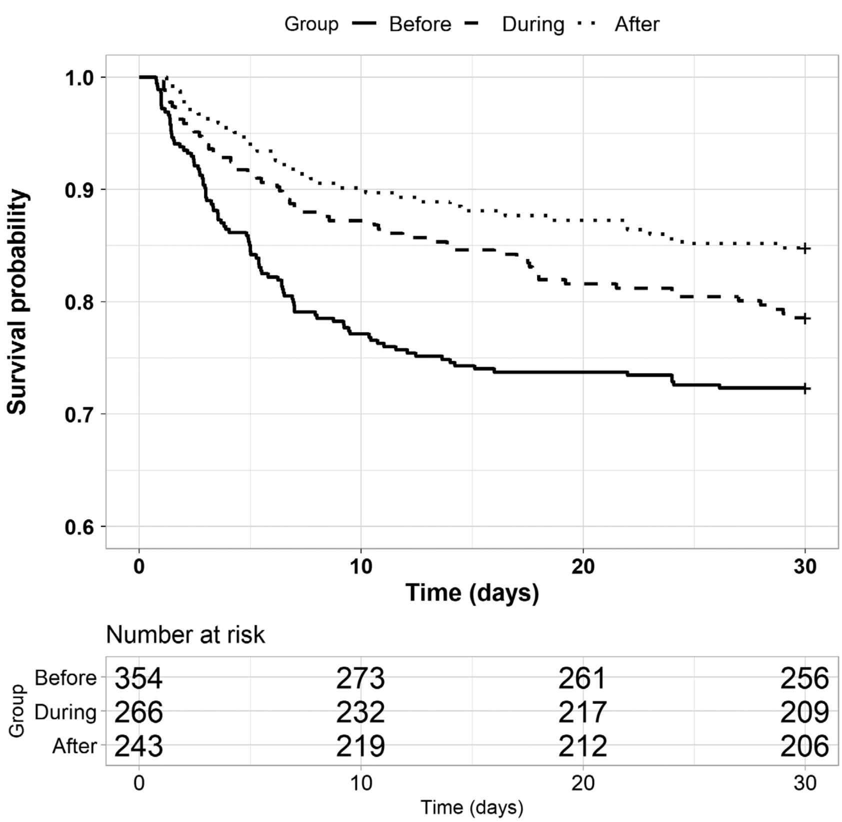

FIGURE 2: Survival after acute intracerebral hemorrhage at Salford Royal Hospital. Kaplan–Meier curve shows survival for the first 30 days after admission during the before implementation *(solid line)*, during implementation *(dashed line)*, and after implementation *(dotted line)* periods. Survival was more likely in the during implementation and after implementation periods ($p < 0.001$, log-rank test).

TABLE 3. Factors Associated with Death by 30 Days after Admission with Acute ICH at Salford Royal Hospital

Factor	Odds Ratio	Lower CI	Upper CI	*p*
Premorbid mRS, vs 0				
1	0.84	0.41	1.42	0.50
2	1.90	0.92	3.33	0.08
3	3.13	1.70	5.34	<0.0001
4	3.04	1.28	5.98	0.01
5	2.46	0.32	9.30	0.85
Age	1.06	1.04	1.08	<0.0001
GCS at arrival	0.82	0.77	0.87	<0.0001
Infratentorial, vs supratentorial	2.05	1.10	3.43	0.02
IVH	2.03	1.35	3.00	<0.0001
ICH volume	1.02	1.02	1.03	<0.0001
Taking anticoagulants	1.74	1.05	2.80	0.04
Implementation period, vs before implementation	0.62	0.38	0.97	0.03
After implementation period, vs before implementation	0.40	0.24	0.61	<0.0001

Results of a multivariate logistic regression model testing the association between admission period (before implementation, during implementation, after implementation) and death by 30 days, adjusting for key ICH prognostic indicators. Onset-to-arrival time and route of arrival (direct admission, transfer, inpatient stroke) were not significant and were therefore excluded from the model.
CI = confidence interval; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale.

fatality, this may be attributable to low statistical power, as only 6.4% of patients underwent surgery overall. Although this was not explicitly part of the ABC care bundle, we found that more patients were admitted to HDU and fewer had a DNR order within 24 hours of arrival once the care bundle was implemented. This suggests that a cultural shift toward a less nihilistic approach to ICH care occurred, perhaps as an indirect effect of ABC care bundle implementation. Our mediation analysis suggests that more than one-half of the association between improved survival and implementation of the care bundle is attributable to this reduction in early DNR orders, with a smaller percentage attributable to HDU admission. In support of this finding, a previous prospective, observational, cohort study demonstrated that up to one-third of ICH patients with a GCS ≤12 make a good recovery if DNR orders were limited, contrary to predictions based on severity grading scales, such as the ICH score.[17,18]

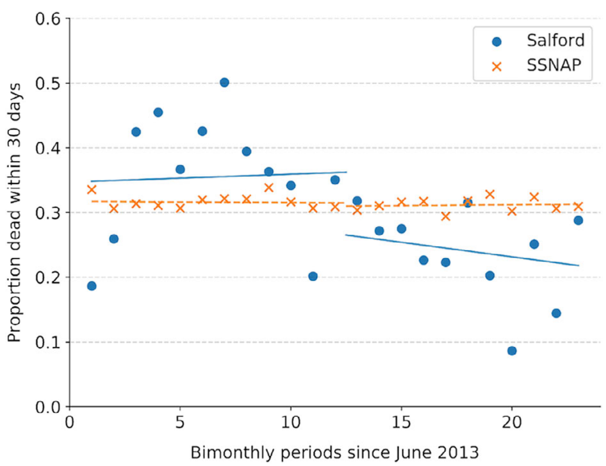

FIGURE 3: Difference-in-difference analysis: Salford Royal Hospital *(circles)* compared to the rest of England and Wales (*crosses*, n = 32,295). Points signify 30-day case fatality for patients admitted during each 2-month period from June 1, 2013 to May 31, 2017. A regression line for each group (Salford Royal Hospital, *solid line*; the rest of England and Wales, *dashed line*) before and after bundle implementation from June 1, 2015 was fitted. SSNAP = Sentinel Stroke National Audit Programme. [Color figure can be viewed at www.annalsofneurology.org]

Our study has some limitations. First, the study design prevents us from making firm conclusions regarding a causal relationship between the ABC care bundle and lower case fatality, although the use of the quasiexperimental difference-in-difference methodology provides support for a causal effect. Further testing in a cluster-randomized trial will be required to definitively test our study hypotheses. Second, we did not have sufficient resources to measure longer-term disability (for example, mRS score at 6 months). We do not therefore know what impact the bundle had on the disability profile in survivors. Our hypothesis is that the

TABLE 4. Process and Care Measures

Measure	Before implementation, n = 353	During Implementation, n = 266	After Implementation, n = 241	*p*
DNT, min	132.0 (93.5–162.5)	152.5 (87.0–210.2)	105.5 (75.5–200.5)	0.65
Intravenous antihypertensive, n/n eligible (% of eligible)	94/172 (54.7)	70/82 (85.4)	58/69 (84.1)	<0.0001
NTT, min	383.0 (219.5–924.5)	43.0 (27.5–75.0)	50.0 (35.0–65.0)	<0.0001
Mean SBP, 0–72 hours, mmHg	166.7 (158.3–174.4)	152.8 (145.4–163.5)	152.1 (145.6–162.3)	<0.01
SD of SBP, 0–72 hours, mmHg	25.7 (19.3–32.0)	25.0 (19.4–31.7)	25.0 (19.5–29.7)	0.88
Neurosurgery n/n eligible (% of eligible)	16/40 (40.0)	20/54 (37.0)	19/28 (67.9)	0.02
High-dependency unit, n (%)	19 (5.4)	32 (12.0)	25 (10.4)	<0.01
Intensive care unit, n (%)	50 (14.2)	47 (17.7)	49 (20.3)	0.14
DNR <24 hours, n (%)	96 (27.2)	47 (17.7)	38 (15.8)	<0.001

Key process and care measures during each study period at Salford Royal Hospital. All data are presented as median and interquartile range, unless otherwise stated. Where data are missing, the number of complete cases is shown as the denominator.
DNR = do not resuscitate; DNT = door to needle time; NTT = needle to target time; SBP = systolic blood pressure; SD = standard deviation.

care bundle will lead to a shift toward improved outcome across the entire range of mRS, a composite outcome of death and disability. For example, it may be that patients who would have died from their ICH will survive with severe disability, but also those who would have survived with severe disability without the bundle will survive with mild or moderate disability instead. The evidence underpinning the care processes changed by the care bundle supports this. The INTERACT2 trial demonstrated a reduction in disability across the entire range of the mRS.[7] Rapidly reversing anticoagulation will prevent small hematomas expanding,[5,6] thus preventing mild–moderate strokes from deteriorating to severe strokes or death. Individual patient data meta-analysis of trials of hematoma evacuation has shown a reduction in "unfavorable outcome" (defined as death plus the vegetative state or severe disability) with surgery in the patients we are targeting with our care pathway.[8] A multicenter prospective observational study has tested a policy of avoiding DNR orders in the first 5 days of care in a subgroup of patients with severe ICH (defined as GCS ≤12).[17] Thirty-day case fatality was predicted to be 50% but was observed to be 20.2%. At 90 days, 27.1% had died, 21.5% had severe disability, and 29.9% had moderately severe disability, but a better recovery (mRS = 0–3) was achieved by 29.9%. In other words, in this group of severe ICH patients whom most clinicians would consider to have a poor prognosis, nearly one-third made a good recovery. Third, changes were made to the centralized stroke pathway

TABLE 5. Mediation Analysis

Factor	Total Effect		NIE		NDE		% Mediated
	Estimate (*p*)	95% CI	Estimate (*p*)	95% CI	Estimate (*p*)	95% CI	
Access to HDU	−0.0594 (0.01)	−0.1104 to −0.01	−0.0070 (0.03)	−0.0164 to 0.00	−0.0524 (0.04)	−0.1032 to 0.00	11.1%
DNR within 24 hours	−0.0607 (0.02)	−0.1109 to −0.01	−0.0324 (<0.01)	−0.0581 to −0.01	−0.0284 (0.23)	−0.0770 to 0.02	52.8%

Results of analysis to determine factors mediating the association between bundle implementation and 30-day survival. Door-to-anticoagulant reversal time, intensive BP lowering, door-to-blood pressure target time, change in systolic blood pressure from 0 to 4 hours, admission to intensive care unit, and neurosurgery were not significant mediators.
CI = confidence interval; DNR = do-not-resuscitate order; HDU = high-dependency unit; NDE = natural direct effect; NIE = natural indirect effect.

in Greater Manchester in March 2015 that might be expected to impact on ICH care and outcomes. The time window from symptom onset for diverting patients to one of the 3 hyperacute stroke units (HASUs) changed from 4 hours to 48 hours, and once admitted, patients remained at the HASU for 72 hours, compared to 24 hours before the reorganization. We have shown that the ICH case mix did not change during the study period (Table 2), suggesting that the ABC-ICH project and not the pathway reorganization accounted for the changes observed at Salford.

In summary, ICH is a major cause of death and disability worldwide, and we present evidence suggesting that simple strategies to consistently and effectively deliver our ABC care bundle might lead to an improvement in survival. Further evaluation of the ABC care bundle in a cluster randomized trial is needed to establish clinical and cost effectiveness, including a measure of later disability as the primary outcome. If proven to be effective in prospective trials, implementation of the ABC care bundle could significantly reduce the substantial morbidity and mortality associated with this otherwise severe subtype of stroke.

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Author Contributions

A.R.P.-J., H.P., K.P., E.B., L.C., B.B., R.E., and M.M. contributed to the conception and design of the study; A.R.P.-J., E.B., M.M., K.P., L.C., J.R., S.L., C.S.-P., B.B., and R.E. contributed to the acquisition and analysis of data; A.R.P.-J., C.S.-P., K.P., B.B., and H.P. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

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