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Time for "code ICH"? – Workflow metrics of hyperacute treatments and outcome in patients with intracerebral haemorrhage

Running head: Time is brain for hyperacute ICH

Authors: Eva Bettschen[1*], Bernhard M. Siepen[1,2*], Martina B Goeldlin[1,2], Madlaine Mueller[1,2], Philipp Buecke[1], Ulrike Prange[1], Thomas R. Meinel[1,2], Boudewijn RH Drop[1], David Bervini[3], Tomas Dobrocky[4], Johannes Kaesmacher[2,4], Aristomenis K. Exadaktylos[5], Thomas C. Sauter[5], Bastian Vollbers[1,6], Marcel Arnold[1], Simon Jung[1], Urs Fischer[1,7], Werner Z'Graggen[1,3*]& David J Seiffge[1*]
[*]equally contributing authors

1 Department of Neurology, Inselspital Bern University Hospital and University of Bern, Bern, Switzerland
2 Graduate School of Health Sciences, University of Bern, Switzerland
3 Department of Neurosurgery, Inselspital Bern University Hospital and University of Bern, Bern, Switzerland
4 Institute of Neuroradiology, Inselspital Bern University Hospital and University of Bern, Bern, Switzerland
5 Emergency Department, Inselspital University Hospital Bern and University of Bern, Switzerland
6 Department of Neurology, University Hospital Erlangen, Germany
7 Department of Neurology, University Hospital Basel and University of Basel, Switzerland

Corresponding author
PD Dr. med. David Seiffge
Department of Neurology
Inselspital University Hospital Bern, University of Bern
Freiburgstrasse 18. CH-3010 Bern, Switzerland
Email: david.seiffge@insel.ch
Telephone: 0041-31-664 05 09

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Abstract:

Introduction:
Knowledge about uptake and workflow metrics of hyperacute treatments in patients with non-traumatic intracerebral haemorrhage (ICH) in the emergency department are scarce.

Methods:
Single centre retrospective study of consecutive patients with ICH between 01/2018-08/2020. We assessed uptake and workflow metrics of acute therapies overall and according to referral mode (stroke code, transfer from other hospital or other).

Results:
We enrolled 332 patients (age 73years, IQR 63-81 and GCS 14 points, IQR 11-15, onset-to-admission-time 284 minutes, IQR 111-708minutes) of whom 101 patients (35%) had lobar haematoma. Mode of referral was stroke code in 129 patients (38%), transfer from other hospital in 143 patients (43%) and arrival by other means in 60 patients (18%).
Overall, 143 of 216 (66%) patients with systolic blood pressure >150mmHG received IV antihypertensive and 67 of 76 (88%) on therapeutic oral anticoagulation received prothrombin complex concentrate treatment (PCC). Forty-six patients (14%) received any neurosurgical intervention within 3 hours of admission.
Median treatment times from admission to first IV-antihypertensive treatment was 38 minutes (IQR 18-72minutes) and 59 minutes (IQR 37-111 minutes) for PCC, with significant differences according to mode of referral (p<0.001) but not early arrival (≤6hours of onset, p=0.92). The median time in the emergency department was 139 minutes (IQR 85-220 minutes) and among patients with elevated blood pressure, only 44% achieved a successful control (<140mmHG) during ED stay. In multivariate analysis, code ICH concordant treatment was associated with significantly lower odds for in-hopsital mortality (aOR 0.30, 95%CI 0.12-0.73, p=0.008) and a non-significant trends towards better functional outcome measured using the modified Rankin scale score at 3 months (aOR for ordinal shift 0.54 95%CI 0.26-1.12, p=0.097).

Conclusion:
Uptake of hyperacute therapies for ICH treatment in the ED is heterogeneous. Treatment delays are short but not all patients achieve treatment targets during ED stay. Code ICH concordant treatment may improve clinical outcomes. Further improvements seem achievable advocating for a “code ICH” to streamline acute treatments.

Introduction

Spontaneous non-traumatic intracerebral haemorrhage is associated with significant morbidity and mortality and its incidence did not decline in the last decades[1, 2]. Mortality is as high as 40% at 1 month[1] and 56% at 1 year[3] while contemporary reports from Switzerland found a mortality of only 25% at 3 months[4].

The major pillars of acute treatment of intracerebral haemorrhage[5] are prevention of secondary haematoma expansion (by acute blood pressure control and reversal of anticoagulation) and neurosurgical interventions (haematoma evacuation and/or external ventricular drainage) for selected patients[6, 7]. Combining the aforementioned measures in a dedicated care bundle – anticoagulation reversal, blood pressure control and neurosurgical evaluation (ABC care bundle) – has been shown to reduce 30-day mortality[8] and a care bundle approach showed significant improvement in outcomes in the INTERACT-3 randomized controlled trial[9].

Current guidelines from the American Heart Association/American Stroke Association (AHA/ASA)[10, 7] and European Stroke Organisation (ESO)[6] however offer only weak treatment recommendations due to persistent uncertainties over the effects of individual treatment options (i.e. magnitude of blood pressure control, selected use of neurosurgery, optimal anticoagulation reversal). This relates to heterogeneous results from pivotal trials on acute blood pressure control[11, 12] and surgical treatment[13-15] and the absence of randomized controlled trials for anticoagulation reversal in patients with intracerebral haemorrhage except from a small phase-II trial comparing fresh-frozen-plasma with prothrombin complex concentrate for reversal of vitamin K antagonists[16].

We aimed to assess the uptake of three key treatment measures – blood pressure control, anticoagulation reversal and neurosurgical interventions – and accompanying metrics in hyperacute treatment of patients with intracerebral haemorrhage in the emergency department of a large tertiary academic hospital and determine factors associated with delivered treatments.

Methods

Patients and methods:

We performed a retrospective cohort study of all consecutive patients with non-traumatic intracerebral haemorrhage enrolled between 1 January 2018 to 31 August 2020 in the prospective Swiss Stroke Registry (SSR) at the Inselspital University Hospital in Bern, Switzerland. The SSR is a national prospective registry enrolling all patients with ischaemic and haemorrhagic stroke treated within 7 days of onset at certified Swiss Stroke Units. Among these patients, we enrolled all patients with acute non-traumatic intracerebral haemorrhage presenting within 24 hours of onset to our hospital in this study. We excluded patients with missing information on acute treatment metrics, in-hospital intracerebral haemorrhage and those who received comfort treatment/palliation in the emergency department. Institutional guidelines for treatment of ischaemic and haemorrhagic stroke at our centre are available online (http://www.neurologie.insel.ch/de/aerzte-und-zuweiser/richtlinien) and include specific recommendations for anticoagulation reversal, blood pressure control and neurosurgical referral since 2018.

Baseline variables:

We prospectively collected a pre-defined set of baseline variables using an electronic case report form on a secured web-server hosted by the Clinical Trial Unit Basel. We extracted the following variables: age, sex, pre-stroke modified Rankin Scale score (mRS), medical history (history of stroke, TIA or intracerebral haemorrhage, atrial fibrillation, arterial hypertension, hyperlipidaemia, diabetes mellitus, coronary heart disease, peripheral artery disease, current smoking), prior treatment (antiplatelet agents, oral anticoagulants, antihypertensive agents), clinical presentation (Glasgow Coma Scale/GCS, National Institute of Health Stroke Severity Scale/NIHSS, systolic/diastolic blood pressure on admission), haematoma location (CHARTS) and onset-to-hospital time (in minutes).

Acute treatments and metrics

We extracted information on hyperacute treatments delivered in the emergency department and its metrics from electronic records. For blood pressure treatment, we collected number and type of intravenous antihypertensive drugs and time to administration and time of first systolic blood pressure. For patients on prior therapeutic anticoagulation with vitamin K antagonists or direct factor Xa-inhibitors, we collected information on use of prothrombin complex concentrate (PCC, 4-factor) and time of administration. During the study period, andexanet alfa as specific reversal agent for direct factor Xa-inhibitors was not available in Switzerland. For patients on dabigatran, information on reversal with idarucizumab was collected. For all patients, we collected information on any neurosurgical intervention performed in the first 3 hours after admission along with type of intervention (external ventricular drainage/EVD or haematoma evacuation) and exact timing. We also collected the following information: do-not-resuscitate orders (DNR) issued in the emergency department, time in the emergency department (admission to transfer to ward/other unit), type of first hospitalisation (intensive care unit/ICU, neuro-intermediate care unit/neurosurgical lead, stroke unit/neurology lead or normal ward) and lengths of hospital stay (in days). Finally, we assessed mode of referral: a) stroke code (i.e. pre-notification with in-hospital pathway for thrombolysis and immediate access to imaging), transfer from other hospital (i.e. diagnosis of intracerebral haemorrhage at external hospital) or other referral (i.e. patient/next-of-kin, self-referral).

Primary outcomes:

The primary outcome was the uptake of specific therapies measured by the percentage of eligible patients receiving acute blood pressure control, anticoagulation reversal and/or immediate neurosurgical intervention, respectively. We defined the eligibility of these treatments in line with prior randomized controlled trials[11, 16] as follows: Patients were eligible for acute blood pressure control treatment if their admission systolic blood pressure was >150mmHg. For patients transferred from other hospitals, we did not include antihypertensive treatments received on other hospitals/during transport as we were only interested in workflow metrics in our centre. Patients were eligible for anticoagulation reversal if they were on prior therapeutic anticoagulation with a vitamin K antagonists (and INR>1.3 on admission) or a direct oral anticoagulant (apixaban, dabigatran, edoxaban or rivaroxaban; last intake <24 hours). Per default, all patients with intracerebral haemorrhage are referred for neurosurgical evaluation in the emergency department of our hospital. Acute blood pressure control was defined as any IV antihypertensive treatment with urapidil, labetalol or clonidine. Anticoagulation reversal was defined as

use of PCC for patients on prior vitamin K antagonist or direct factor Xa-inhibitor therapy and use of idarucizumab for patients on dabigatran therapy. Any neurosurgical intervention was defined as external ventricular drainage and/or haematoma evacuation performed either during the stay in the emergency department or within 3 hour of admission. We defined "Code ICH" concordant treatment as patients receiving all recommended treatments if applicable (i.e. blood pressure control if admission systolic blood pressure >150mmHg and anticoagulation reversal of on prior oral anticoagulation with a direct oral anticoagulant within <24hours of last intake or a vitamin K antagonist with INR >1.3).

Secondary outcomes

Secondary outcomes are time to first antihypertensive treatment, time to start of anticoagulation reversal and time in the emergency department. Secondary clinical outcomes are in-hospital mortality and functional outcome (measured using the modified Rankin scale score) at 3 months.

Statistical analysis:

Statistical analysis was performed using Stata version 16.0 (StataCorp., College Station, TX, USA). We presented absolute and relative count (%) for categorical variables, mean and standard deviation for normally distributed, continuous variables and median and interquartile range (IQR) for non-normally distributed variables. Patients were grouped according to referral mode: a) stroke code, b) transfer from other hospital or c) other mode of referral.

We compared groups using chi-square test or Fisher's exact test for categorical variables, as well as Kruskal-Wallis test for continuous variables.

We assessed association with treatment's received and baseline characteristics using binary logistic regression analysis for the following pre-defined variables. For acute blood pressure control, the following variables were included: Do-not-resuscitate order, age, female sex, history of ICH, hypertension, diabetes mellitus, lobar haematoma location, prior treatment with therapeutic anticoagulants, prior antiplatelet treatment, prior antihypertensive treatment, systolic blood pressure and blood glucose on admission, GCS, NIHSS, onset-to-admission time, mode of referral mode (stroke code, referral from other hospital or other). For anticoagulation reversal, we only included a different subset of variables based on biological plausibility and with fewer co-variables due to smaller sample size: age, female sex, systolic blood pressure and INR on admission, NIHSS and GCS on admission, lobar haematoma location and mode of referral and onset-to-admission time.

For secondary clinical outcomes, we performed multivariate binary (in-hospital mortality) and ordinal (modified Rankin scale score at 3 months) regression analysis adjusting for age, admission within 6 hours of onset, prior anticoagulation, NIHSS and GCS on admission and "code ICH" concordant treatment.

We calculated odds ratios (ORs) with corresponding, 95% confidence intervals (CIs) comparing the respective subgroups.

Results

After excluding patients with missing information on acute treatment (n=30) and those receiving comfort therapy/palliation in the emergency department (n=46), we enrolled 332 patients (81.4%, figure 1) over a study-period of 32 months (January 2018-August 2020). Baseline characteristics are displayed in table 1. In summary, 167 (50%) patients were female, the median age was 73 years (IQR 63-81), the median NIHSS was 8 points (IQR 3-16) and the median GCS on admission was 14 points (IQR 11-15) on admission and 101 patients (35%) had lobar haematoma location. The median onset-to-admission time was 284 minutes (IQR 111-708 minutes) and 190 patients (57.2%) arrived within 6 hours of onset.

Overall, 129 patients (38%) were stroke code admissions, 143 patients (43%) were transferred from other hospitals and 60 patients (18%) arrived by other means (i.e. next-to-kin, walk-in or patient self referral).

The median door-to-imaging time at our centre was 27 minutes (IQR 18-52 minutes), the median time in the emergency department was 139 minutes (IQR 85-220 minutes) and the median lengths of stay in our hospital was 7 days (IQR 4-11 days). After evaluation and hyperacute treatment in the emergency department, 91 patients (28%) were transferred to the ICU, 205 patients (62%) to the Neuro-IMC (neurosurgery lead), 12 patients (4%) to the Stroke Unit (neurology lead), 18 patients (5%) to the general ward and 4 patients (1%) to an external hospital.

Primary outcome: Uptake of specific therapies

Among the 332 patients enrolled, 216 patients (65%) had admission systolic blood pressure >150mmHg qualifying for acute blood pressure control and 76 patients (23%) were on prior therapeutic anticoagulation qualifying for anticoagulation reversal. Among 216 patients qualifying for blood pressure control, 143 patients (66%) received any blood pressure lowering treatment, 67 of 76 patients (88%) qualifying for anticoagulation reversal received PCC (all patients on VKA or Factor Xa inhibitors, no patient on dabigatran) and 46 of 332 patients (14%) received any immediate neurosurgical intervention. Eligibility and uptake of specific therapies is displayed in figure 2.

For acute blood pressure control, history of hypertension (aOR 6.8, 95%CI 1.4-33.8, p=0.019), diabetes mellitus (aOR 0.3, 95%CI 0.1-1.0, p=0.048) and admission blood pressure (per 5mmg HG increment aOR 1.2, 95%CI 1.0-1.3, p=0.008) were associated with receiving IV hypertensive treatment (Table S1). Only admission GCS was independently associated with use of PCC (aOR 0.2 95%CI 0.1-0.9, p=0.043).

Blood pressure control: acute treatment and metrics

Information on treatment metrics was available for 304 of 332 patients (92%). The median systolic blood pressure on admission was 164mmHg (IQR 144-184) and the median diastolic blood pressure 87mmHg (IQR 73-100). The proportion of patients with admission systolic blood pressure >150mmHg eligible for IV antihypertensive treatment and those receiving treatments differ significantly according to mode of referral (p<0.001) but not according to arrival ≤6 hours or > 6 hours from onset (p=308, figure 3).

The majority of 94% of patients received urapidil as first-line therapy. The median time from door to first IV antihypertensive treatment was 38 minutes (IQR 18-72 minutes) with significant differences according to mode of referral (p<0.001) but not according to time of arrival (p=0.671, figure 4). Taking into account the time-point of diagnosis (i.e. time-point of imaging for patients referred by stroke code or others, time-point of admission for patients transferred from other hospitals), the median time from diagnosis to treatment was 28 minutes (IQR 17-50 minutes) with significant differences according to mode of referral (stroke code: 41 minutes IQR 23-56 minutes; transfer: 18 minutes IQR 9-38 minutes; others: 30 minutes IQR 19-75minutes, p<0.001).

Among patients with admission systolic blood pressure >150mmHg, 62 of 141 patients (44%) with available follow-up blood pressure measurements in the ED achieved a successful control (<140mmHG) with no difference according to referral mode (p=0.953) nor time of arrival (p=0.820)

Oral anticoagulation: Use of PCC and metrics

Among 76 patients on therapeutic anticoagulation prior to symptom onset, 29 patients (38%) were on prior vitamin K antagonist treatment with INR>1.3 on admission and 47 patients on direct oral anticoagulants (31 patients on rivaroxaban, 10 patients on apixaban, 6 patients on edoxaban; no patient on dabigatran). There where additional 9 patients on prior vitamin K antagonist therapy with INR ≤1.3 on admission not qualifying for reversal therapy. Among patients transferred from other hospitals 9 of 14 patients (64%) on vitamin K antagonists and 6 of 15 patients (40%) on prior direct oral anticoagulant therapy received PCC prior to arrival in our hospital.

The proportion of patients on therapeutic anticoagulation on admission and treatment with PCC differed significantly according to mode of referral (p<0.001) but not according to time of arrival (p=0.933, figure 2). The

median time from door to PCC was 59 minutes (IQR 37-111 minutes) with significant differences according to mode of referral (p<0.001) but not arrival time (p=0.882, figure 4). No patient was taking dabigatran and therefore, no patient received idarucizumab.

Neurosurgical intervention

Among patients receiving any immediate neurosurgical intervention, 20 of 46 patients (44% of all neurosurgical interventions and 6% of all patients) received haematoma evacuation (+/- external ventricular drainage) and 26 patients (56% of all neurosurgical interventions and 8% of all patients) received isolated external ventricular drainage.

"Code ICH" concordant treatment, in-hospital mortality and functional outcome at 3 months

Overall, 56 of 332 patients died in hospital (16.9%) and the median modified Rankin scale score was 4 (IQR 2-6) at 3 months (3-months outcome available for 286 of 332 patients, 84.9%). Further, 248 of 332 patients (74.4%) received "Code ICH" concordant treatment (defined as patients receiving all recommended treatments if applicable, i.e. blood pressure control if admission systolic blood pressure >150mmHg and/or anticoagulation reversal of on prior oral anticoagulation with a direct oral anticoagulant within <24hours of last intake or a vitamin K antagonist with INR >1.3). In multivariate analysis adjusting for confounders, "Code ICH" concordant treatment was associated with significantly lower odds for in-hopsital mortality (aOR 0.30, 95%CI 0.12-0.73, p=0.008) and a non-significant trends towards better functional outcome measured using the modified Rankin scale score at 3 months (aOR for ordinal shift 0.54 95%CI 0.26-1.12, p=0.097).

Discussion

This study revealed the following findings: 1) The majority of patients qualifying for acute blood pressure control and anticoagulation reversal receive specific therapies although a significant percentage of patients remain potentially undertreated. 2) Immediate neurosurgical interventions are rare and affect only 1 out of 10 patients. 3) Time-to-first IV antihypertensive treatment and PCC use were short with still significant possibilities for improvement. 4) Delivered therapies and treatment metrics were heterogeneous according to mode of referral but did not differ between patients arriving ≤6 hours compared to patients arriving later after symptom onset. 5) A significant proportion of patients with elevated blood pressure does not achieve sufficient blood pressure control during ED stay. 6) "Code ICH" concordant treatment was associated with lower odds for in-hospital mortality and a non-significant trend towards better functional outcome at 3 months.

"Time is brain" is the mantra of acute ischaemic stroke treatment and multiple interventions aim to reduce pivotal metrics including the door-to-needle time[17] for intravenous thrombolysis or door-to-groin puncture time for endovascular therapy[18]. In contrast, knowledge about uptake of specific treatments and their metrics for intracerebral haemorrhage are scarce. Our study provides novel insights into uptake and treatment metrics of hyperacute treatment of intracerebral haemorrhage in a large tertiary academic hospital. Our results are of clinical importance as they demonstrate that although a high percentage of patients receives adequate treatment there are still a considerable number of potentially undertreated patients and possibility to improve treatment metrics.

Prior data on treatment delivery are scarce. Recently, a specific ABC-care bundle developed and implemented in the UK was associated with reduced mortality in patients with intracerebral haemorrhage[8]. The authors reported a rate of 54% of eligible patients receiving acute blood pressure control treatment before and 84% after implementation of the ABC-care bundle. In our cohort, the rate of 66% is comparable to that before implementation of the ABC-care bundle.

Time to start antihypertensive treatment in patients enrolled in the INTERACT-2 trial was short (time from randomization to start of treatment: 10 minutes in the intervention group and 30 minutes in the guideline group)[11] and and significantly longer in, ATACH-2[12] with a median randomization to start of nicardipin time of 71 minutes[19]. The door-to-needle time (38 minutes) or diagnosis-to-needle time (28 minute) for first antihypertensive treatment in our study seems in line with INTERACT-2 metrics. Only a minority of patients in our study achieved sufficient blood pressure control during ED stay although patients remained for approximately 2 hours in the ED before discharge to the floor.

Rate of anticoagulation reversal in our study was 88% for eligable patients. This rate is higher compared to prior publications reporting use of prothrombin concentrate complex in 70% of patients on prior direct oral anticoagulant therapy[20] and 76% of patients on prior vitamin K antagonist therapy[21]. The time-to-start of reversal therapy was considerable faster in our study (59 minutes) compared to the aforementioned ABC care bundle (132 minutes before implementation and 105 minutes after implementation)[8].

Immediate neurosurgical interventions within 3 hours of admission were rare in our study (mostly isolated external ventricular drainage). This number is in line with prior reports of 7%[8]. Rate of do-not-resuscitate orders issued in the emergency department (2%) were lower as reported in prior studies (33%[22] and 27%[8]) and after implementation of the ABC-care bundle (16%)[8] but a considerable proportion of patients (n=46, 12%) received comfort therapy right in the ED. Treatment on an ICU or Neurology/Neurosurgery-lead IMC/Stroke Unit was high (93%). This number is considerably higher than in the other studies (20% before implementation, 30% after implementation)[8].

Guideline recommendations[23, 7] and evidence from previous trials[11, 16, 9] suggest a benefit of blood pressure lowering and anticoagulation reversal within the first 6 hours. A surprising finding ouf our study was that treatment metrics did not differ for patients admitted within 6 hours of onset compared to those admitted later. We can only speculate about the reasons. One possible explanation is that primary care teams in our ED for intracerebral haemorrhage are the same as for ischemic stroke. In ischemic stroke, patients in late time windows frequently receive intravenous thrombolysis and mechanical thrombectomy based on the results of advanced imaging in our department and many treating physicins may believe that this applies also for the benefits of blood pressure control and anticoagulation reversal in the setting of intracerebral haemorrhage.
In our study, “Code ICH” concordant treatment defined as patients receiving blood pressure control and anticoagulation reversal if applicable, was associated with lower odds for in-hospital mortality and a non-significant trend towards better functional outcome at 3 months. Altough our study was not powerd to assess mortality and functional outcome, our findings are in line with reduced mortality[8] and improved functional outcome[9] found in other studies.

Our study has several strengths: 1) We report data from a tertiary academic hospital collected outside a randomized controlled trial or quality improvement program setting likely to reflect treatment uptake and metrics in many certified stroke centres in Europe. 2) We provide granular information on uptake and treatment metrics of key therapies for treatment of intracerebral haemorrhage providing a comprehensive picture of current management. 3) Data completeness for treatment uptake and metrics was high (92%).

Our study has several limitations: 1) We report data from a single centre study and not a multi-centre study probably limiting generalizability of our findings. 2) Although patient enrolment and basic data collection in the Swiss Stroke Registry is prospective, data on treatment uptake and metrics were collected retrospectively and therefore prone to bias. 3) We did not collect information on haematoma volume which may have influenced treatment decisions. 4) We did not perform a specific pre-/post-implementation analysis of our instutional guideline recommendations or any specific intervention to improve performance. 5) We assessed only treatments and metrics in the ED. The median stay in the ED was 132 minutes and all treatments are usually started in the ED, we therefore do not believe that assessing treatment metrics in the ED only has influenced our results. However, we might underestimate the number of patients who had successful blood pressure control as we did not account for blood pressure levels achieved at later time points in the ICU or stroke unit. 6) We only report the number of patients who finally received any neurosurgical intervention but were unable to assess the indication for neurosurgical interventionas for individual cases as patient-related factors for not performing surgery are usually not well documented. 7) Our study was not powered to assess any treatment effects of “Code ICH” concordant treatment and this was a retrospective not-randomized study, therefore, we urge caution in the interpretation of the results on clinical endpoints.

Overall, our data provide a comprehensive picture about current treatment of intracerebral haemorrhage in a tertiary academic hospital. While a large proportion of patients receives adequate treatment, further improvements in uptake and delivery seem feasible and necessary. Appropropriate treatment may improve

clinical outcomes. Our data advocate for a "Code ICH" to streamline hyperacute ICH treatment and underline the necessity for quality improvement and monitoring.

Statement of Ethics

As to Swiss legislation (law on highly specialized medicine; "Hochspezialisierte Medizin" HSM; Art. 39 Abs. 2bis KVG) and ethics approval, all patients treated in one of the certified Swiss Stroke Units or Stroke Centers are enrolled in the SSR database. Patients who refused data use for scientific purposes were excluded from this analysis. The current analysis was approved by the competent ethical board in Bern (Project-ID 2019-00689).

Conflict of interest:

The authors have no conflicts of interest to declare

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Author contributions:

Concept of the study: DJS
Data collection: EB, BMS, MM, MG, BD and DJS
Data analysis: DJS
Draft of the manuscript: DJS
Revisions of the manuscript for important intellectual content: TRM, JK, BV, SJ, UF, MA, AE, TS, SJ, PB, UP, TD, DB and WZG
Study supervision: DJS, WZG, UF and SJ

Data availability statement:

Data is not publicly available due to ethical reasons. Further enquiries can be directed to the corresponding author.

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Figures:

Figure 1: Study flow chart.

[figure 1 here]

Figure 2: Eligibility and uptake of specific treatments. Among patients with elevated blood pressure on admission (>150mmHg systolic), 66% of eligible patients received IV antihypertensive treatments in the emergency department (red bars, left). Among patients on therapeutic anticoagulation (Vitamin K antagonist and INR >1.3 or direct oral anticoagulant intake within 24 hours or unknown), 88% of eligible patients received Prothrombin complex concentrate (PCC). Among all patients, 14% received any neurosurgical intervention within the first 3 hours after admission.

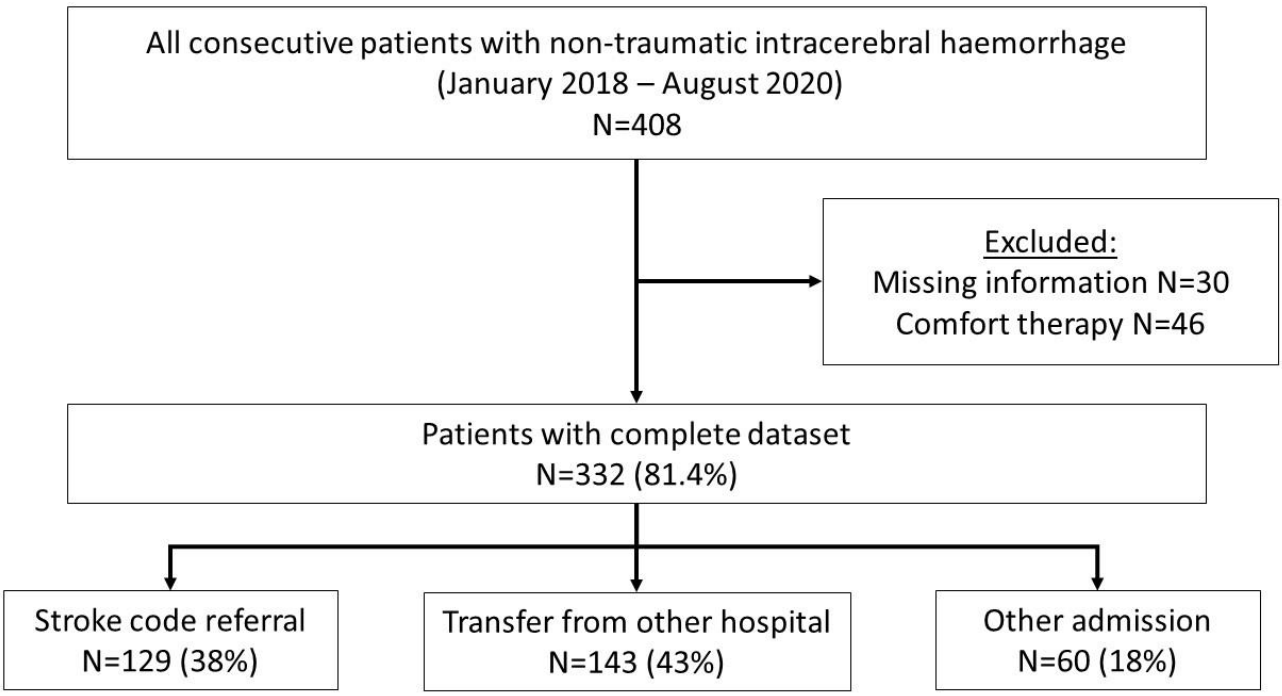
[figure 2 here]

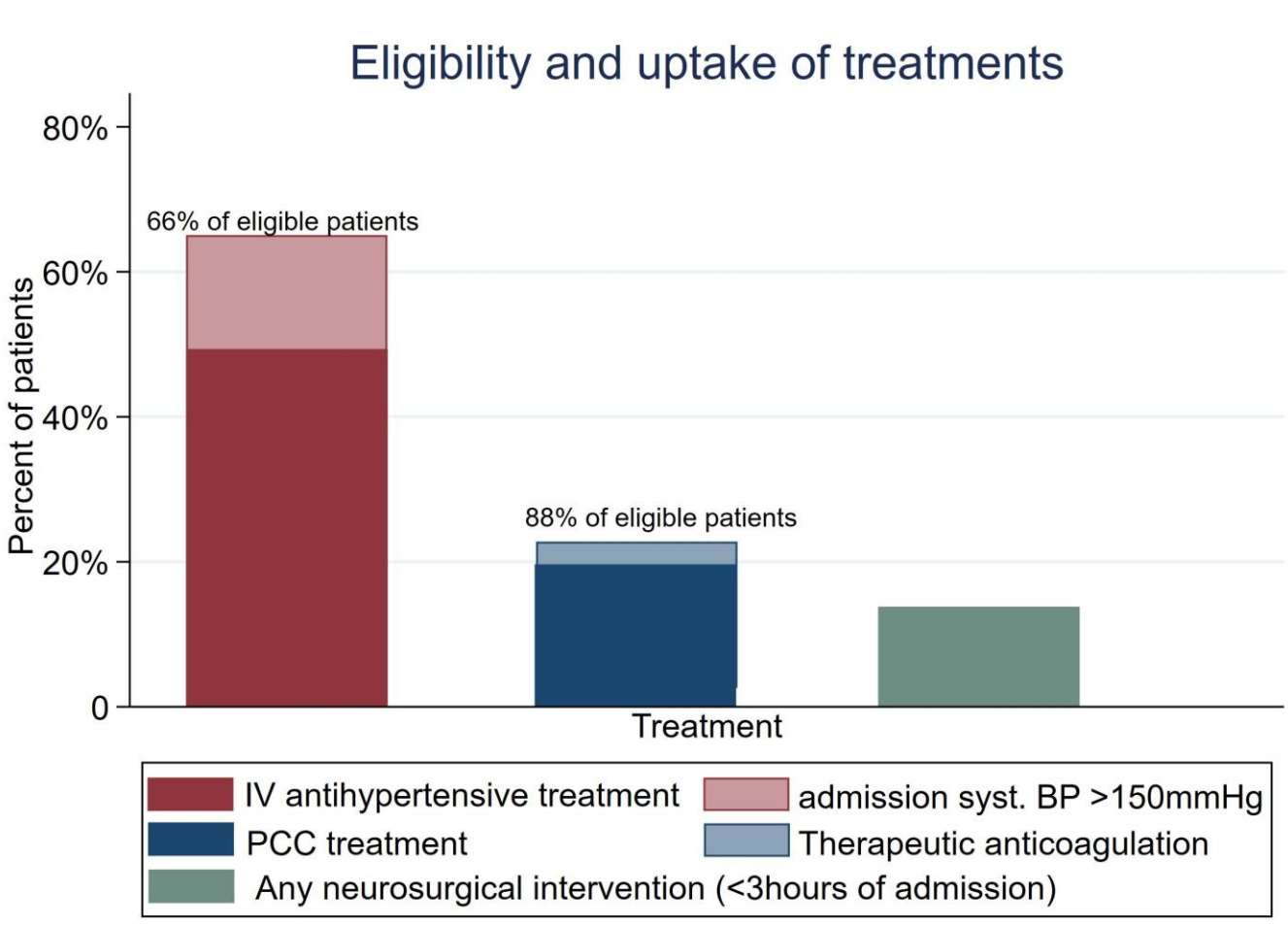
Figure 3: Eligibility and uptake of specific treatments according to mode of referral (stroke code, transfer from other hospital or other mode of referral) and time from onset to admission (≤6 hours vs >6 hours).

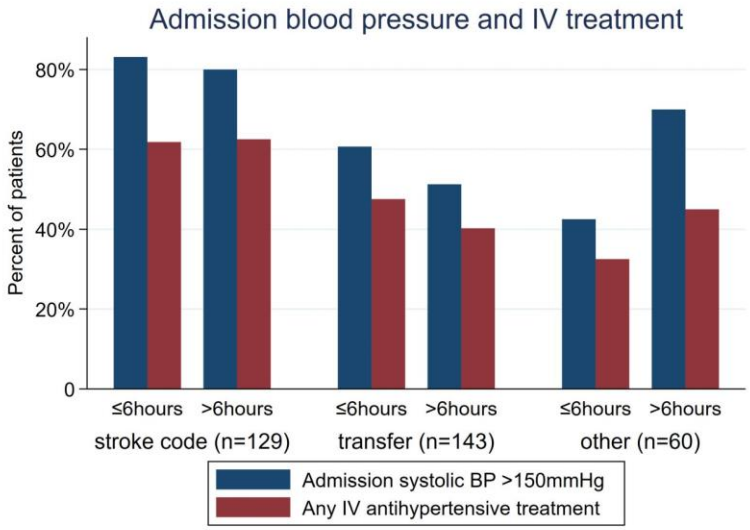
[figure 3 here]

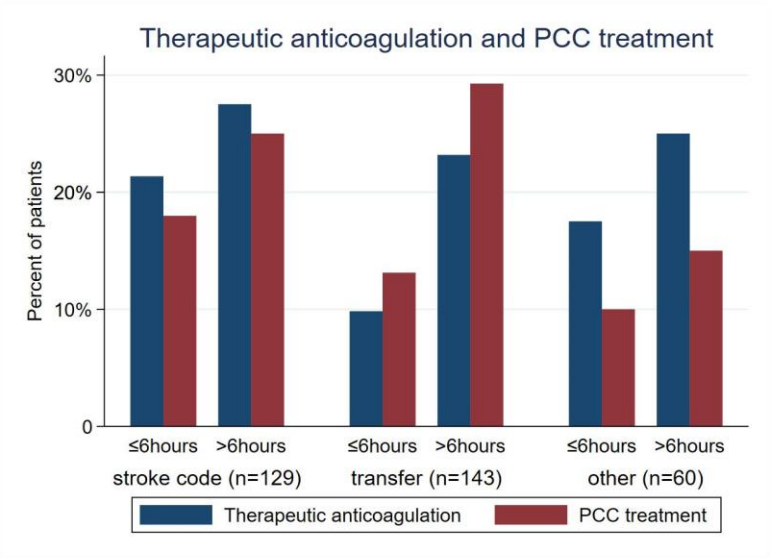
Figure 4: Treatment metrics with time from admission to imaging, first IV antihypertensive treatment, use of prothrombin complex concentrate (PCC) and discharge from emergency department (ED).

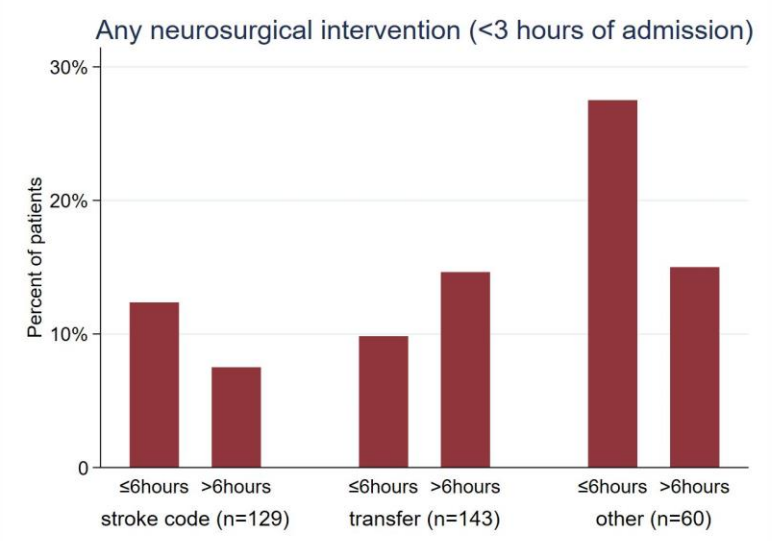
[figure 4 here]











Treatment metrics

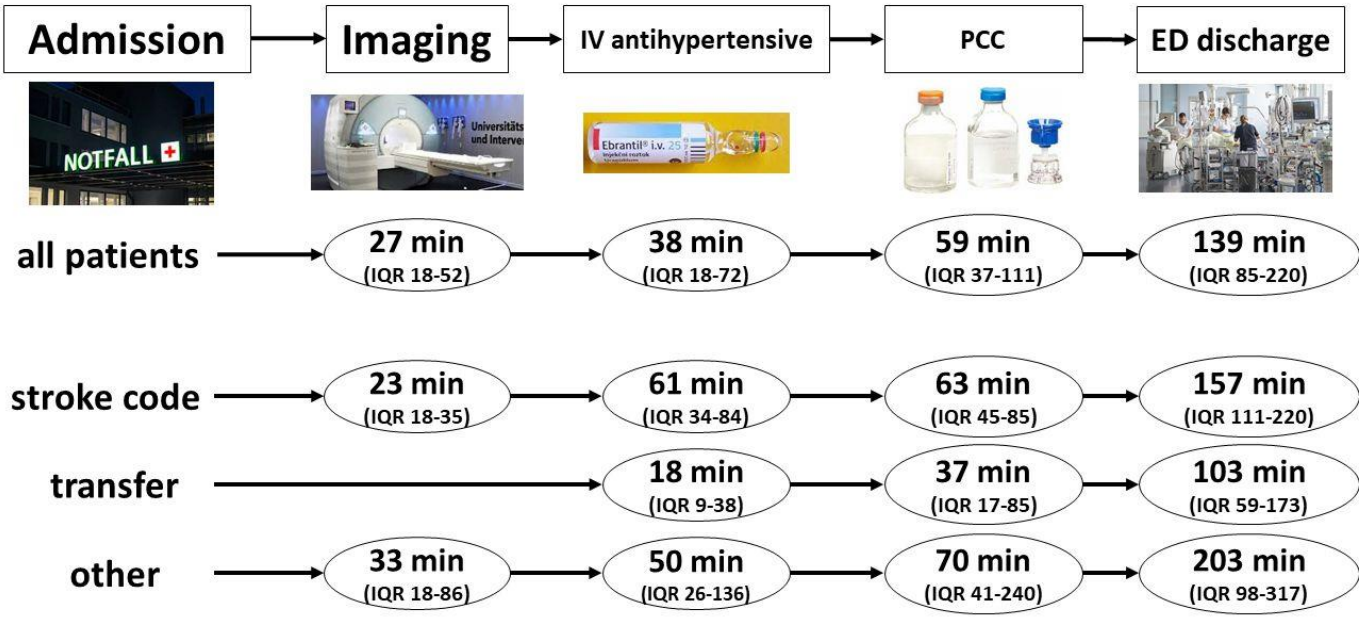


Table 1: Baseline characteristics on admission

	Total	Mode of referral			p-value
		Stroke code[a]	Transfer[b]	Other[c]	
	n=332	n=129	n=143	n=60	
Demographics					
Age [years], median (IQR)	73 (62-81)	79 (69-84)	72 (57-78)	65 (62-81)	<0.001
Female, No. (%)	165 (50)	66 (51)	64 (45)	35 (58)	0.192
Risk factors, No. (%)					
Hypertension	241 (73)	107 (84)	100 (70)	34 (57)	<0.001
Diabetes mellitus	49 (15)	26 (20)	16 (11)	7 (12)	0.084
Hyperlipidemia	122 (37)	70 (55)	28 (20)	24 (41)	<0.001
Current smoking	40 (12)	16 (13)	16 (11)	8 (13)	0.906
Atrial fibrillation	70 (21)	35 (27)	26 (18)	9 (15)	0.090
Coronary heart disease	43 (13)	21 (16)	18 (13)	4 (7)	0.178
Peripheral artery disease	10 (3)	6 (5)	3 (2)	1 (2)	0.371
Medical history, No. (%)					
Prior ischemic stroke	26 (8)	11 (9)	11 (8)	4 (7)	0.899
Prior TIA	12 (4)	6 (5)	3 (2)	3 (5)	0.429
Prior ICH	35 (11)	10 (8)	13 (9)	12 (20)	0.031
Concomitant medication, No. (%)					
Anticoagulants					
VKA	29 (9)	14 (11)	14 (10)	1 (2)	0.342
DOAC	47 (14)	19 (15)	17 (12)	11 (18)	0.333
Antiplatelets	83 (25)	47 (36)	25 (17)	11 (19)	<0.001
Lipid lowering drugs	71 (22)	38 (30)	20 (15)	13 (22)	0.013
Antihypertensives	170 (52)	83 (65)	62 (45)	26 (44)	0.002
Prestroke independence					
Pre-mRS 0-2, No. (%)	186 (82)	71 (78)	80 (87)	35 (80)	0.262
Clinical presentation on admission, median (IQR)					
NIHSS	8 (3-16)	10 (5-17)	4 (1-13)	5 (1-13)	<0.001
GCS	14 (11-15)	14 (11-15)	14 (12-15)	14 (10-15)	0.957
Systolic BP, mmHG	164 (144-184)	178 (157-201)	155 (141-170)	155 (135-180)	<0.001
Diastolic BP, mmHG	87 (73-100)	94 (79-105)	81 (68-96)	85 (75-96)	0.003
Bood glucose, mmol/l	7 (6-9)	7 (6-9)	7 (6-8)	7 (6-8)	0.326
Time metrics, min; median (IQR)					
Onset-to-admission time	284 (111-708)	147 (76-626)	455 (240-831)	197 (91-488)	<0.001
Door-to-imaging time	27 (18-52)	23 (18-35)	n/a	33 (18-86)	<0.001
ED lengths of stay	139 (85-220)	157 (111-220)	104 (59-173)	203 (98-317)	<0.001
Haematoma location, No. (%)					
Deep	146 (51)	69 (66)	55 (44)	22 (40)	0.014
Lobar	101 (35)	25 (24)	54 (43)	22 (40)	
Infratentorial	27 (9)	7 (7)	13 (10)	7 (13)	
Isolated intraventricular	9 (3)	2 (2)	3 (2)	4 (7)	
Undetermined	2 (1)	1 (1)	1 (1)	0	
Do-not-resuscitate order					
Issued in ED, No. (%)	7 (2)	4 (3)	2 (1)	1 (2)	0.600

[a] Pre-notification with in-hospital pathway for thrombolysis and immediate access to imaging

[b] Transfer from other hospital: i.e. diagnosis of intracerebral haemorrhage at external hospital

[c] Other referral: i.e. next-to-kin, walk-in or patient self referral