Justus-Liebig-Universität Gießen
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Konzepte und Implementierung therapeutischer Interventionen bei intrazerebralen Blutungen

Habilitationsschrift
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INHALTSVERZEICHNIS

1. EINFÜHRUNG

1.1 Epidemiologie und Prognose der intrazerebralen Blutung

Die nicht-traumatische intrazerebrale Blutung (ICB) macht etwa 10-20% aller Schlaganfälle aus und stellt die schwerwiegendste Form des Schlaganfalls dar[1].

Die weltweite Inzidenz von intrazerebralen Blutungen beträgt im Allgemeinen etwa 20 bis 30 Fälle pro 100.000 Personen pro Jahr, wobei es regionale Unterschiede gibt[2]. Trotz der Fortschritte, die in Europa bei der Reduzierung des Risikos für intrazerebrale Blutungen und der damit verbundenen Sterblichkeit erzielt wurden, deuten dennoch zunehmendes Alter der Bevölkerung sowie die zunehmende Prävalenz wichtiger Risikofaktoren wie Amyloidangiopathie und Bluthochdruck auf eine wahrscheinliche erneute Zunahme der Inzidenz durch intrazerebrale Blutungen in den kommenden Jahren hin[3]. Für das Jahr 2050 wird in Europa eine Zunahme der Belastung durch intrazerebrale Blutungen im Vergleich zu 2019 prognostiziert, mit einem Anstieg von 0,6% der Inzidenz und 8,9% der Mortalität, hauptsächlich aufgrund der alternden Bevölkerung[4].

Die ICB trägt weltweit signifikant zur Krankheitslast bei: DALY (Disability-Adjusted Life Years) ist eine Maßeinheit, die die Summe der verlorenen Lebensjahre durch vorzeitigen Tod und der durch Krankheit oder Behinderung beeinträchtigten Lebensjahre darstellt[5]. Die Krankheitslast gemessen in DALYs für die ICB beträgt 9-10 Jahre[5,6]. Dies spiegelt sich in einer hohen Mortalität, etwa 30-50% der Patienten versterben innerhalb der ersten 30 Tage nach der Blutung, als auch in der erheblichen Morbidität bei den Patienten, die oft langfristige neurologische Defizite erleiden, wider[7].

1.2 Risikofaktoren der intrazerebralen Blutung

1.2.1 Arterieller Hypertonus

Über 60 % der spontanen intrazerebralen Blutungen sind mit dem Vorliegen einer Hypertonie assoziiert und treten am häufigsten in der hinteren Schädelgrube, dem Pons, den Basalganglien und dem Thalamus auf. Diese Lokalisationen - oftmals als „typisch“ (loco typico) bezeichnet - sind besonders anfällig für die Ruptur von fragilen Gefäßen bei Druckbelastung[8]. Die Fragilität wird durch strukturelle Veränderungen der Gefäße bedingt, was als „vaskuläres Remodeling“ bezeichnet wird[9-11]. Hierunter versteht man die Entwicklung von Lipohyalinose, die durch Fett- und Hyalinablagerung in der Gefäßwand gekennzeichnet ist, sowie die Entstehung von echten Arteriolendissektionen, die als Charcot-Bouchard-Aneurysmen bekannt sind[9-11]. Diese kleinen Gefäßausbuchtungen der sog. „Rhexisgefäße“ sind besonders fragil und können unter hypertensiv-entgleisten Blutdruckwerten rupturieren, was zu Blutungen in tiefe Hirnregionen führt.

Präklinische Studien legen nahe, dass die Gefäßveränderungen durch eine Dysregulation von Matrix-Metalloproteinasen (MMPs), Elastin und Kollagen bedingt sind[12,13]. Weitere Mechanismen wie neurohormonale und entzündliche Störungen, das metabolische Syndrom sowie eine Dysregulation des Renin-Angiotensin-Systems können zu diesen Gefäßpathologien beitragen[14,15]. Ebenso wird postuliert, dass die Dysregulation von Zytokinen eine Schlüsselrolle bei der Umgestaltung des Immunsystems im Alter spielt, indem sie zu einem pro-inflammatorischen Zustand führt, der als „Inflamm-Aging“ bezeichnet wird und mit vielen altersbedingten, u.a. vaskulären Krankheiten assoziiert ist[16].

1.2.2 Amyloidangiopathie

Etwa 10-20 % der spontanen intrazerebralen Blutungen sind mit der zerebralen Amyloidangiopathie (CAA) assoziiert und treten am häufigsten in den lobären Regionen des Gehirns, insbesondere in den kortikalen Konvexitäten und im Subarachnoidalraum („atypische“ Lokalisation), auf[17,18]. Die Amyloidangiopathie ist die häufigste zerebrale Kleingefäßerkrankung bei älteren Menschen und ist zusätzlich auch mit einem erhöhten Risiko für ischämische Schlaganfälle und Demenz verbunden[17,19]. Pathophysiologisch stellt die Erkrankung eine Protein-Eliminationsstörungsangiopathie dar. Das β-Amyloid-Protein, das bei der CAA abgelagert wird, ist identisch mit dem, das auch bei der Alzheimer-Krankheit eine zentrale Rolle spielt[20]. Bei der zerebralen Amyloidangiopathie lagert sich das β-Amyloid in den Wänden kleiner und mittelgroßer Blutgefäße des Gehirns ab[17]. Diese vaskuläre Amyloidablagerung führt zu strukturellen Veränderungen der Gefäßwände, darunter fibrinoide Nekrosen, Mikroaneurysmen und Spaltbildungen in der Gefäßwand, was das Risiko für intrazerebrale Blutungen erhöht. Es wird angenommen, dass eine gestörte Clearance des β-Amyloids aus dem perivaskulären Raum eine zentrale Rolle bei der Entstehung der CAA spielt[21]. Diese Clearance-Störung kann durch altersbedingte vaskuläre Veränderungen und genetische Faktoren beeinflusst werden[22,23]. Genetische Varianten des Amyloid-Vorläuferproteins (APP) und das Apolipoprotein E sind mit einem erhöhten Risiko für CAA und damit verbundenen Blutungen assoziiert[22,24]. Zu weiteren „atypischen“ Lokalisationen zählen sekundär eingeblutete Raumforderungen, wie Kavernome oder Metastasen. Die vorliegende Habilitationsschrift konzentriert sich ausschließlich auf die Behandlung primärer bzw. spontaner intrazerebraler Blutungen.

1.2.3 Orale Antikoagulation und Thromboyztenfunktionshemmung

Die Einnahme einer oralen Antikoagulation (OAK) stellt einen weiteren Risikofaktor für intrazerebrale Blutungen dar und bedarf besonderer Aufmerksamkeit, da die Inzidenz von OAK-assoziierten Blutungen durch den zunehmenden Einsatz von OAKs bei Patienten mit Vorhofflimmern voraussichtlich steigen wird. Derzeit liegt die Inzidenz von intrazerebralen Blutungen unter oraler Antikoagulation bei etwa 10 pro 100.000 Patientenjahren[2,25]. Die Einnahme einer oralen Antikoagulation erhöht einerseits das Risiko für das Auftreten einer ICB um den Faktor 7–10[26], andererseits stellt die OAK-ICB auch einen Prädiktor für einen ungünstigeren Verlauf und eine ungünstigere Prognose der Erkrankung dar[27]. Gründe hierfür sind Faktoren wie größere Blutungsvolumina mit häufigerer Hämatomprogression sowie häufigerem Einbruch in das Ventrikelsystem, die unter Einnahme einer oralen Antikoagulation gehäuft auftreten und die Prognose einer ICB verschlechtern können[27,28].

Inwieweit eine thrombozytenfunktionshemmende Therapie letztlich die Charakteristik der Blutung sowie das klinische Outcome bei Patienten mit intrazerebraler Blutung beeinflusst, wird oftmals kontrovers diskutiert[29]. Im Vergleich zu einer ASS-Monotherapie jedoch ist eine doppelte thromboyztenaggregationshemmende Therapie, z.B. in Kombination mit einem P2Y12-Inhibitor wie Clopidogrel, mit einem erhöhten Blutungsrisiko assoziiert[30]. Entsprechend erfordert die Indikation eine sorgfältige Nutzen-Risiko-Abwägung, vor allem bei Patienten mit zusätzlichen prädisponierenden Faktoren für Blutungskomplikationen wie eine CAA.

1.3 Zielparameter für therapeutische Maßnahmen

Verlauf und Prognose der ICB hängen von verschiedenen Prädiktoren ab. Einige dieser Faktoren, wie das Alter der Patienten, das initiale Hämatomvolumen und die Lokalisation der ICB, können nicht verändert werden[31]. Neben diesen nicht modifizierbaren Faktoren gibt es jedoch auch potenziell veränderbare Variablen, deren gezielte therapeutische Beeinflussung die Prognose der Patienten erheblich verbessern kann. Zu diesen gehören vor allem sekundäre Schädigungsmechanismen, die nach der initialen Blutung auftreten und das Hirngewebe weiter schädigen. Dazu zählen insbesondere die Progression des Hämatoms, das perihämorrhagische Ödem und das Auftreten von Komplikationen infolge intraventrikulärer Blutungen[31,32]. Die gezielte Therapie zur Verhinderung dieser sekundären Schädigungsmechanismen stellt einen wichtigen Ansatzpunkt zur Verbesserung der klinischen Prognose nach einer intrazerebralen Blutung dar und unterstreicht die Bedeutung einer individualisierten Behandlungsstrategie.

1.3.1 Hämatomprogress

Wichtigstes Ziel der Akutbehandlung bei einer intrazerebralen Blutung ist die Verhinderung der Hämatomprogression, die bei etwa 30 % der Patienten auftritt[33]. Sie führt nicht nur durch das eigentliche Blutungsereignis, sondern durch die Vergrößerung des Hämatoms zu direkten Parenchymschädigungen. Um von einer Hämatomprogression zu sprechen, hat sich eine Definition etabliert, die eine relative Vergrößerung des Hämatoms um >33 % oder eine absolute Vergrößerung um 6 ml angibt[34].

Die Hämatomprogression ist ein entscheidender prognostischer Indikator für das funktionelle Outcome und die Mortalität und stellt zudem den wichtigsten therapeutischen Ansatzpunkt dar[31,35]. Das Risiko, eine Hämatomprogression zu entwickeln, ist innerhalb der ersten 3 Stunden nach dem Ereignis am höchsten[36]. Die schnelle und effektive Implementierung einer Therapie in den ersten Stunden nach dem Ereignis ist daher entscheidend, um die Hämatomprogression zu verhindern. Der Leitsatz „time is brain“ gilt demnach nicht nur für den ischämischen Schlaganfall, sondern auch für die intrazerebrale Blutung. Es wird angenommen, dass insbesondere Blutungsvolumina von >60 ml sowie Volumina im Bereich von 30-60 ml mit einem erhöhten Risiko für eine Hämatomprogression einhergehen[36,37]. Es sind einige bildgebende Parameter bekannt, die Patienten mit einem besonders hohen Risiko für eine Hämatomprogression identifizieren. Hierzu zählt unter anderem das „Spot Sign“, das als Kontrastmittelextravasation im Hämatom und somit als „aktive Blutung“ gewertet wird[33]. Im Nativ-CT wurden Parameter wie eine irreguläre Blutungskonfiguration oder Hypodensitäten innerhalb der Blutung als bildgebende Risikoprädiktoren identifiziert[38,39].

1.3.2 Perihämorrhagisches Ödem

Ein perihämorrhagisches Ödem (PHE) stellt einen weiteren sekundären Schädigungsmechanismus dar, der nach einer ICB auftritt und gleichzeitig einen potenziellen therapeutischen Ansatzpunkt bietet[40]. Das PHE entwickelt sich typischerweise innerhalb von 2-3 Wochen nach der initialen ICB und resultiert primär aus den Abbauprozessen des extravasalen Blutes im Parenchym. Die Pathogenese des PHE wird anfangs durch osmotische Gradienten induziert, die infolge der Freisetzung von Serumproteinen in das Interstitium sowie durch zelluläre Dysfunktionen entstehen[41]. Im weiteren Verlauf wird die Progression des Ödems durch eine gestörte Integrität der Blut-Hirn-Schranke verstärkt, was das Eindringen von Entzündungszellen erleichtert und neuroinflammatorische Prozesse aktiviert[41]. Diese Prozesse tragen zur Vergrößerung des Ödems bei, dessen Volumen in vielen Fällen die ursprüngliche hämorrhagische Läsion übertreffen kann und somit zu einer weiteren Druckschädigung des Gehirns führen kann. Sowohl das Ausmaß des PHE als auch die Dynamik der Ödementstehung sind entscheidende Determinanten für die sekundäre Schädigung nach einer ICB[40]. Der dadurch induzierte raumfordernde Effekt des PHE ist klinisch relevant, da er die Mortalität erhöhen und das funktionelle Outcome der betroffenen Patienten signifikant verschlechtern kann[40,42]. Das Ausmaß des PHE variiert jedoch individuell, was eine Herausforderung für die klinische Prognose darstellt. Aufgrund dieser pathophysiologischen Besonderheiten steht das perihämorrhagische Ödem im Fokus intensiver wissenschaftlicher Forschung und ist Gegenstand zahlreicher aktueller Studien, die darauf abzielen, neue therapeutische Strategien zur Minderung der durch das Ödem induzierten Schädigung zu entwickeln[43].

1.3.3 Intraventrikuläre Blutanteile

Im Rahmen einer intrazerebralen Blutung kann es sekundär zu einem Einbruch in das Ventrikelsystem kommen, was intraventrikuläre Blutanteile zur Folge hat. Auch primäre intraventrikuläre Blutungen sind möglich und werden als sekundäre Schädigungsmechanismen betrachtet. Etwa 45 % der Patienten mit einer ICB entwickeln eine intraventrikuläre Komponente, wobei die Lokalisation der Blutung eine entscheidende Rolle spielt[44]. Tief gelegene Hirnblutungen neigen aufgrund ihrer Nähe zu den Ventrikeln eher zu einem frühzeitigen Einbruch in das Ventrikelsystem, während lobäre Blutungen hierfür eine bestimmte Größe erreichen müssen. In der Akutphase sind intraventrikuläre Blutanteile besonders relevant, da sie durch eine Okklusion des dritten oder vierten Ventrikels einen akuten Hydrozephalus verursachen können und die Anlage einer externen Ventrikeldrainage (EVD) erforderlich machen[32,45]. Ohne therapeutische Maßnahmen kann der resultierende Anstieg des intrakraniellen Drucks zu sekundären Hirnschädigungen bis hin zur Herniation führen, was sich in der Bildgebung durch eine Erweiterung der Temporalhörner der Seitenventrikel zeigt. Auch nach einigen Tagen bis Wochen können intraventrikuläre Blutanteile weiterhin Komplikationen verursachen. Durch die Blockade der Resorptionswege des Liquors oder die Schädigung der Arachnoidalzotten kann sich ein Hydrozephalus malresorptivus entwickeln, so dass die Anlage eines (ventrikuloperitonealen) Shuntsystems notwendig ist[46]. Entsprechend ist die intraventrikuläre Blutung ein häufiger und bedeutender Begleitbefund bei intrazerebralen Blutungen, der sowohl in der Akutphase als auch im weiteren Verlauf zu erheblichen Komplikationen führen kann und eine frühzeitige therapeutische Intervention erfordert.

1.4 Offene Fragen und Zielsetzung

Ziel der vorliegenden Habilitationsschrift war eine systematische Untersuchung der therapeutischen Managementstrategien bei intrazerebralen Blutungen. Ziel dieser Managementstrategien sind die Vermeidung der Hämatomprogression, die Reduktion des perihämorrhagischen Ödems und die Behandlung intraventrikulärer Blutanteile. Therapeutische Akutmaßnahmen umfassen das Akutmanagement von Blutdruck, Hämostase, allgemein medizinischen Maßnahmen und die Behandlung intraventrikulärer Blutanteile. Im Nachfolgenden werden diese therapeutischen Interventionen im Hinblick auf ihre Wirksamkeit diskutiert und hierbei Fragestellungen und Ergebnisse der eigenen Forschungsarbeiten berücksichtigt.

Ein zentraler Bestandteil der vorliegenden Arbeit war die Prozess-Evaluation der Implementierung akutmedizinischer und intensivmedizinischer Maßnahmen. Es wurde untersucht, wie effektiv diese Maßnahmen im klinischen Alltag integriert sind, welche Herausforderungen bei der Implementierung auftreten und wie die Qualität der Umsetzung die Behandlungsergebnisse beeinflusst.

Im Einzelnen umfasste die Untersuchung folgende Fragestellungen:

1. Akutmanagement: Blutdrucksenkung
    a. Wie rasch und effektiv wird der Blutdruck nach Krankenhausaufnahme behandelt, und welchen Einfluss hat diese Behandlung auf das Outcome der Patienten?
2. Akutmanagement: Wiederherstellung der Hämostase
    a. Inwieweit beeinflusst die Applikation von Thrombozytenkonzentraten das Outcome bei Patienten mit Thrombozytopenie?

3. Akutmanagement: Allgemeine intensivmedizinische Maßnahmen
    a. Haben gebündelte intensivmedizinische Maßnahmen einen (synergistisch) signifikanten Einfluss auf das klinische Outcome?
    b. Inwieweit hat der Zeitpunkt der Krankenhausaufnahme (außerhalb vs. innerhalb regulärer Dienstzeiten) einen Einfluss auf interventionelle Maßnahmen wie EVD-Anlage und auf das funktionelle Outcome?
    c. Wie hoch ist die deutschlandweite Adhärenz, Leitlinienempfehlungen zur Einhaltung allgemeiner physiologischer Parameter umzusetzen?
4. Akutmanagement: Behandlung intraventrikulärer Blutanteile
    a. Welchen Effekt hat die intraventrikuläre Thrombolyse auf das klinische Outcome?

2. DISKUSSION IM KONTEXT EIGENER ARBEITEN

2.1 Akutmanagement: Blutdrucksenkung

2.1.1 Evidenz und offene Fragen

Hypertensive Blutdruckwerte in der Akutphase einer ICB sind mit einer erhöhten Wahrscheinlichkeit für Hämatomprogression und einem schlechteren funktionellen Outcome assoziiert. Daher empfiehlt die aktuelle Leitlinie, den Blutdruck bei Patienten mit ICB innerhalb der ersten zwei Stunden auf systolische Werte von unter 140 mmHg zu senken, jedoch nicht unter 110 mmHg[47].

Noch vor wenigen Jahren lautete die Empfehlung, den Blutdruck auf systolisch 160–180 mmHg zu halten, da man befürchtete, dass eine zu rasche Senkung ischämische Komplikationen verursachen könnte. Im Laufe der Zeit erschienen jedoch mehrere Studien, die zu einer Änderung der Leitlinien führten. Zu den bedeutendsten gehören die INTERACT-2- und die ATACH-2-Studie[48,49]. Die Phase-II-Studie der INTERACT-Studie aus dem Jahr 2008 zeigte, dass eine intensive Blutdrucksenkung auf 140 mmHg systolisch sicher ist und das Wachstum des Hämatoms verringern kann[50]. Auf dieser Grundlage wurde 2013 die Phase-III-Studie durchgeführt, in der 2.839 Patienten mit einem akuten Blutdruck von 150–220 mmHg untersucht wurden[51]. Diese Studie verglich die Standardtherapie (Blutdruckziel < 180 mmHg) mit einer intensiveren Therapie (Blutdruckziel < 140 mmHg) und fand einen Trend zu besseren Ergebnissen bei der intensiveren Therapie, jedoch ohne statistische Signifikanz[51]. Die US-amerikanische ATACH-2-Studie, veröffentlicht 2016, umfasste 1.000 Patienten und verglich eine intensive Blutdrucksenkung auf etwa 120 mmHg systolisch mit höheren Blutdruckwerten in der Kontrollgruppe, die etwa 140 mmHg betrugen. Obwohl beide

Studien ähnliche Zielblutdruckwerte festlegten, zeigte sich in ATACH-2 kein besseres klinisches Ergebnis bei der intensiveren Blutdrucksenkung[49]. Stattdessen war diese mit einer höheren Rate an unerwünschten Ereignissen verbunden. Beide Studien, INTERACT-2 und ATACH-2, verfehlten jeweils knapp ihren primären Endpunkt[51,52].

Nachfolgende Post-hoc-Analysen und Metaanalysen zeigten jedoch, dass eine Reduktion des systolischen Blutdrucks um jeweils 10 mmHg eine Verbesserung der Odds Ratio (OR) für ein günstiges funktionelles Outcome um 0,90 zur Folge hatte (0,87–0,94; $p < 0,0001$)[52]. Dies galt besonders für Patienten, die frühzeitig, innerhalb der ersten zwei Stunden, behandelt wurden[53]. Infolgedessen fand die Empfehlung einer raschen und intensiven Blutdrucksenkung (Zielbereich 110–140 mmHg) ihren Weg in die aktuellen Leitlinien[47].

Obwohl diese Empfehlung intuitiv klar erscheint und unabhängig von der Expertise des jeweiligen Zentrums unkompliziert umgesetzt werden kann, ist die Implementierung im klinischen Alltag dennoch von einigen Faktoren abhängig. Von besonderer Bedeutung ist hierbei der Zeitpunkt der Krankenhausaufnahme und der Beginn der Blutdrucksenkung.

(1) Unklar ist, ob Verzögerungen bei der Einleitung der Therapie durch längere Aufnahmezeiten, Verfügbarkeit strukturierter Protokolle und SOPs („standardized operating procedures“) oder logistische Hürden einen Einfluss auf das klinische Outcome haben.

2.1.2 Eigene Arbeiten: Konzepte und Implementierung

In dieses Kapitel eingeflossene eigene Arbeiten:

A1
Mrochen A, Sprügel MI, Gerner ST, Sembill JA, Lang S, Lücking H, Kuramatsu JB, Huttner HB. Blood Pressure and Anticoagulation Reversal Management during Off-Hours in Oral Anticoagulation-Associated Intracerebral Hemorrhage. Cerebrovasc Dis. 2020;49:177-184. doi: 10.1159/000507316

Das wichtigste Ziel der Akuttherapie bei intrazerebralen Blutungen ist die Verhinderung einer Hämatomvergrößerung durch sofortige, aggressive und kontrollierte systolische Blutdrucksenkung. Im Rahmen eigener Arbeiten wird untersucht, inwieweit diese Empfehlungen effizient umgesetzt werden und welchen Einfluss dies auf das klinische Outcome hat. Hierbei sollen insbesondere der Einfluss des Zeitpunktes der Krankenhausaufnahme und der Beginn der Blutdrucksenkung untersucht werden.

Basierend auf multizentrischen Kohortenstudien (RETRACE Teil 1 [NCT01829581] und Teil 2 [NCT03093233]) und dem UKER-ICH Register (NCT03183167) wurden Patienten mit intrazerebraler Blutung unter oraler Antikoagulation anhand des Aufnahmezeitpunktes gruppiert[54] (**A1**). Der primäre Endpunkt war das funktionelle Outcome nach drei Monaten, bewertet anhand der modifizierten Rankin-Skala (mRS), sowie die Mortalität. Sekundäre Endpunkte umfassten das Auftreten einer Hämatomprogression, den Anteil der Patienten mit systolischem Blutdruck <140 mmHg und die Erreichung von INR-Werten <1,3 innerhalb von vier Stunden. Zur Adjustierung von Basischarakteristika wurde eine Propensity-Score-Matching-Analyse durchgeführt.

Die Studienpopulation bestand nach dem Matching aus 76 von 126 NOAC-ICH-Patienten und 1.005 von 1.470 VKA-Patienten, die außerhalb der regulären

Arbeitszeiten aufgenommen wurden. Die funktionellen Ergebnisse und Sterblichkeitsraten zeigten keine signifikanten Unterschiede zwischen den während der regulären Arbeitszeiten und außerhalb dieser Zeiten aufgenommenen Patienten. Auch bei den sekundären Endpunkten wurden keine Unterschiede festgestellt. Die Ergebnisse deuten darauf hin, dass die Managementstrategien zur Blutdrucksenkung und Antikoagulationsumkehr unabhängig von der Aufnahmezeit ähnlich wirksam sind und mit vergleichbaren Raten von Hämatomvergrößerung und klinischen Ergebnissen verbunden sind.

2.2 Akutmanagement: Wiederherstellung der Hämostase

2.2.1 Evidenz und offene Fragen

Neben der Blutdruckkontrolle ist die Wiederherstellung der Hämostase eine zentrale Säule der Akutbehandlung bei intrazerebralen Blutungen. Ziel dieser Maßnahmen ist es, sekundäre Schädigungsmechanismen, insbesondere die Progression der Blutung, zu verhindern.

Bei Blutungen ohne vorherige Einnahme einer oralen Antikoagulation wurde der Einsatz von Tranexamsäure in randomisierten kontrollierten Studien untersucht, wobei kein signifikanter Einfluss auf das funktionelle Outcome festgestellt wurde[55]. Metaanalysen deuten jedoch darauf hin, dass eine Reduktion der Hämatomprogression möglich ist, insbesondere wenn Tranexamsäure innerhalb eines Zeitfensters von weniger als 4,5 Stunden nach Symptombeginn verabreicht wird[56]. Daher empfiehlt die Leitlinie, die Gabe von Tranexamsäure (1 g Bolus, gefolgt von 1 g intravenöser Infusion über 8 Stunden) innerhalb von 8 Stunden nach Beginn der Blutung zu erwägen (Konsens)[47].

Bei intrazerebralen Blutungen unter Therapie mit Vitamin-K-Antagonisten hat sich die frühzeitige, gewichtsadaptierte Gabe von Prothrombinkomplexkonzentrat (PPSB) als effektiv erwiesen, da diese Maßnahme mit einer Reduktion der Hämatomprogression assoziiert ist[57,58]. Die Leitlinie empfiehlt daher, dass bei Patienten mit ICB unter Vitamin-K-Antagonisten und einem erhöhten INR-Wert (> 1,2) Vitamin K (10 mg i.v.) infundiert und die INR mittels intravenöser Gabe von Prothrombinkomplexkonzentrat (PPSB mindestens 30 U/kg) normalisiert werden sollte (starker Konsens)[47].

Bei intrazerebralen Blutungen unter direkter oraler Antikoagulation hängt die Therapie von der Art des eingenommenen Antikoagulans und dem Zeitpunkt der letzten Einnahme ab. Für Patienten, die Dabigatran (einen direkten Thrombininhibitor) eingenommen haben, steht das spezifische Antidot Idarucizumab zur Verfügung[59]. Diese Therapieoption wurde in der REVERSE-AD-Studie durch ein günstiges Sicherheitsprofil und eine niedrige Rate thrombotischer Ereignisse (<5 % innerhalb von 30 Tagen) unterstützt[59]. Die Leitlinie empfiehlt, dass bei Patienten mit ICB unter Dabigatran die Gabe von Idarucizumab (2x2,5 g i.v.) erwogen werden kann (starker Konsens)[47].

Bei intrazerebralen Blutungen unter Einnahme von Faktor-Xa-Inhibitoren wie Apixaban und Rivaroxaban ist das rekombinante Faktor-Xa-Protein Andexanet alfa für die Akuttherapie verfügbar. In der 2019 veröffentlichten ANNEXA-4-Studie wurde die Anwendung dieses Mittels etabliert, und in der 2023 veröffentlichten ANNEXA-I-Phase-IV-Studie wurde Andexanet alfa im Vergleich zu einer Standardtherapie untersucht[60,61]. Die Studie wurde aufgrund des vorzeitigen Erreichens des primären Endpunktes (≤ 35 % Hämatomprogression, keine klinische Verschlechterung NIHSS ≥ 7, keine Rescue-Therapie) abgebrochen. Signifikante Unterschiede in klinischen Outcomeparametern nach 30 Tagen (funktionelles Outcome, Mortalität) wurden jedoch nicht festgestellt, während eine höhere Rate thrombotischer Ereignisse nach der Applikation beobachtet wurde (10,3 % vs. 5,6 % [p = 0,048])[61]. Die Leitlinie empfiehlt daher, dass bei Patienten mit ICB unter Rivaroxaban und Apixaban die Gabe von Andexanet alfa abhängig von der Dosis und dem letzten Einnahmezeitpunkt erwogen werden kann (starker Konsens)[47].

Für intrazerebrale Blutungen unter Thrombozytenfunktionshemmung hat sich die Gabe von Thrombozytenkonzentraten als nicht wirksam erwiesen[62]. Im Patch-Trial (n= 190) wurde der Einsatz von Thrombozytenkonzentraten im Vergleich zu offenen Kontrollen untersucht, wobei sich nach der Gabe eine signifikant erhöhte Rate für Tod oder schwere Behinderung zeigte[62]. Daher empfiehlt die aktuelle Leitlinie, dass bei Patienten mit akuter spontaner intrazerebraler Blutung unter Thrombozytenfunktionshemmung der Einsatz von Thrombozytenkonzentraten gegenwärtig nicht erfolgen sollte (starker Konsens)[47].

(1) Eine offene Frage, die sich aus den aktuellen Leitlinien ergibt, betrifft den potenziellen Nutzen von Thrombozytenkonzentraten bei Patienten mit intrazerebraler Blutung und gleichzeitiger Thrombozytopenie oder anderen Thrombozytenfunktionsstörungen. Während die aktuelle Evidenz und die Empfehlungen darauf hinweisen, dass Thrombozytenkonzentrate bei Patienten unter Thrombozytenfunktionshemmung keinen positiven Effekt auf das Outcome haben und möglicherweise sogar schädlich sein könnten, ist unklar, ob Patienten mit Thrombozytopenie von einer Substitution profitieren könnten. Insbesondere bleibt offen, ob in diesen speziellen Subgruppen eine Korrektur der Thrombozytenzahl das Risiko der Hämatomprogression senken und das funktionelle Outcome verbessern könnte.

2.2.2 Akutmanagement: Konzepte und Implementierung

In dieses Kapitel eingeflossene eigene Arbeiten:

A2
Mrochen A, Sprügel MI, Gerner ST, Sembill JA, Lang S, Lücking H, Kuramatsu JB, Huttner HB. Thrombocytopenia and Clinical Outcomes in Intracerebral Hemorrhage: A Retrospective Multicenter Cohort Study. Stroke. 2021;52:611-619. doi: 10.1161/strokeaha.120.031478

Um der oben genannten offenen Frage nachzugehen, wurde in einer multizentrischen, retrospektiven Studie der Einfluss der Thrombozytenzahl bei Krankenhausaufnahme auf die Hämatomprogression und das klinische Outcome bei Patienten mit intrazerebraler Blutung, sowohl mit als auch ohne vorangegangener thrombozytenaggregationshemmender Therapie, untersucht[63] (**A2**). Die Analyse basiert auf Daten aus den multizentrischen Kohortenstudien RETRACE und UKER-ICH, die insgesamt 2252 Patienten umfassen. Die Endpunkte der Untersuchung beinhalteten die Hämatomprogression, das funktionelle Outcome anhand der modifizierten Rankin-Skala und die Mortalität nach drei Monaten. Die Ergebnisse zeigen, dass bei 11,4% der Patienten mit thrombozytenaggregationshemmender Therapie und 14,0% der Patienten ohne thromboyztenaggregationshemmender Therapie eine Thrombozytopenie bei Krankenhausaufnahme bestand. Nach Adjustierung der Basischarakteristika, wie der Einnahme von Marcumar, dem Vorliegen einer intraventrikulären Blutung und dem Geschlecht, zeigte sich kein Unterschied in der Hämatomprogression zwischen den Gruppen mit normalen und reduzierten Thrombozytenwerten (<150 000/µl), sowohl bei Patienten mit als auch ohne thrombozytenaggregationshemmender Therapie. Das funktionelle Outcome unterschied sich ebenfalls nicht signifikant zwischen den Gruppen, was darauf

hindeutet, dass die Thrombozytenzahl keinen entscheidenden Einfluss auf die funktionellen Ergebnisse hat. Ein markanter Unterschied zeigte sich jedoch in der Sterblichkeitsrate: Bei Patienten mit thrombozytenaggregationshemmender Therapie und Thrombozytopenie war die Sterblichkeit nach drei Monaten signifikant höher (63,0%) im Vergleich zu Patienten mit normaler Thrombozytenzahl (41,4%).

Zusammenfassend deutet die Studie darauf hin, dass die Thrombozytenzahl keinen wesentlichen Einfluss auf die Hämatomvergrößerung oder die funktionellen Ergebnisse hat, unabhängig davon, ob die Patienten eine thrombozytenaggregationshemmende Therapie im Vorfeld hatten. Dennoch könnte die erhöhte Sterblichkeit bei Patienten mit thrombozytenaggregationshemmender Therapie und Thrombozytopenie auf die Notwendigkeit hinweisen, die Rolle von Thrombozytentransfusionen in dieser Patientengruppe weiter zu erforschen. Es bleibt zu klären, ob gezielte Behandlungen der Thrombozytopenie, wie Transfusionen, die klinischen Ergebnisse tatsächlich verbessern können.

2.3 Akutmanagement: Allgemein intensivmedizinische Maßnahmen

2.3.1 Evidenz und offene Fragen

Das intensivmedizinische Management bei intrazerebralen Blutungen spielt eine entscheidende Rolle. Neben der Blutdruckkontrolle sind insbesondere die Einhaltung physiologischer Basisparameter wie Temperatur, Blutzucker und Beatmungsparameter relevant.

Einer Einhaltung einer Normothermie bzw. moderaten Hypothermie werden günstige Effekte zur Vermeidung eines perihämorrhagischen Ödems nachgesagt, wenngleich keine Hinweise in randomisierten kontrollierten Studien existieren, dass dies mit einem klinisch-funktionellen Ergebnis assoziiert ist[64]. Es ist allerdings bekannt, dass Fieber generell mit erhöhter Sterblichkeit assoziiert ist. Entsprechend besteht die aktuelle Empfehlung der Leitlinien, dass bei Patienten mit ICB antipyretische Maßnahmen angewandt werden können (Konsensstärke: Konsens)[47,65].

Ein weiterer zentraler Aspekt des intensivmedizinischen Managements ist die Kontrolle des Blutzuckerspiegels. Die NICE-SUGAR-Studie untersuchte den Einfluss einer intensiven Blutzuckerkontrolle auf die Sterblichkeit bei kritisch kranken Patienten[66]. Dabei zeigte sich, dass eine strikte Blutzuckereinstellung (Zielbereich von 4,5 bis 6,0 mmol/l) im Vergleich zu einer moderaten Einstellung (Zielbereich von ≤10 mmol/l) mit einer höheren Mortalität assoziiert war[66]. Diese Ergebnisse legen nahe, dass eine zu aggressive Blutzuckersenkung bei kritisch kranken Patienten, und somit auch bei Patienten mit ICB, vermieden werden sollte und stattdessen ein moderater Zielbereich vorteilhafter ist.

Wenngleich für viele Einzelmaßnahmen bei der ICB derzeit noch keine starke Evidenz aus randomisierten kontrollierten Studien vorliegt, hat sich zunehmend der Ansatz etabliert, mehrere Maßnahmen zu bündeln und so ihre Wirksamkeit zu maximieren[67,68]. Dies wurde unter anderem in der prospektiven INTERACT-III-Studie untersucht, bei der bestimmte Zielwerte wie ein systolischer Blutdruck von unter 140 mmHg, eine Körpertemperatur von maximal 37,5 °C und ein Blutzuckerspiegel im Bereich von 6,1 bis 7,8 mmol/l bei Patienten ohne Diabetes eingehalten wurden[68]. Die Ergebnisse dieser Studie zeigten, dass die Umsetzung gebündelter therapeutischer Maßnahmen mit einem besseren funktionellen Outcome nach sechs Monaten assoziiert war. In der Ordinalanalyse zeigte sich eine OR von 0,86 (95 %-Konfidenzintervall 0,76–0,97; p = 0,015)[68].

Jedoch wirft die Anwendung gebündelter Therapieansätze in der klinischen Praxis weiterhin offene Fragen auf.

(1) Die INTERACT-III-Studie wurde vorwiegend in Ländern mit niedrigen bis mittleren Einkommen durchgeführt, in denen standardisierte SOPs zuvor häufig nicht etabliert waren. Es bleibt daher unklar, wie die Implementierung dieser Behandlungsparameter in Ländern mit Gesundheitssystemen, wie z.B. in Europa, aktuell stattfindet und wie die Adhärenz neurologischer Intensivstationen ist.

(2) Ist aktuell noch unklar, wie die strikte Einhaltung dieser SOPs in Ländern mit Gesundheitssystemen, wie beispielsweise in Europa, auf das funktionelle Outcome der Patienten auswirkt.

(3) Zum anderen stellt sich die Frage, wie das klinische Outcome optimal quantifiziert werden sollte[69]. Während die modifizierte Rankin-Skala derzeit weit verbreitet ist,

bieten alternative Maße wie DALYs eine umfassendere Perspektive, indem sie sowohl verlorene Lebensjahre (YLL) als auch Jahre mit Behinderung (YLD) berücksichtigen[4,70]. Es ist daher zu klären, ob und wie die Verwendung von DALYs zusätzliche Einblicke in die Krankheitslast und das funktionelle Outcome liefern kann. Darüber hinaus bleibt unklar, wie sekundäre Schädigungsmechanismen wie Hämatomprogression, intraventrikuläre Blutung und perihämorrhagisches Ödem die Krankheitslast in Bezug auf DALYs beeinflussen.

Eine detaillierte Untersuchung dieser Zusammenhänge könnte dazu beitragen, gezielte therapeutische Maßnahmen zur Reduktion der Krankheitslast und Verbesserung des langfristigen Outcomes zu entwickeln.

2.3.2 Eigene Arbeiten: Konzepte und Implementierung

In dieses Kapitel eingeflossene eigene Arbeiten:

A3
Mrochen A, Alhaj Omar O, Pelz J, Lehrieder D, Neugebauer H, Knier B, Ringmaier C, Stetefeld H, Schönenberger S, Chen M, Schneider H, Alonso A, Lesch H, Totzeck A, Erdlenbruch F, Hiller B, Diel N, WOrm A, Claudi C, Gerner ST, Huttner HB, Schramm P Guideline-recommended basic parameter adherence in neurocritical care stroke patients: observational multicenter individual participant data analysis. European Stroke Journal. 2024; accepted 09/24.

A4
Mrochen A, Song Y, Harders V, Sembill JA, Sprügel MI, Hock S, Lang S, Engelhorn T, Kallmünzer B, Volbers B, et al. Influence of bundled care treatment on functional outcome in patients with intracerebral hemorrhage. *Front Neurol*. 2024;15:1357815. doi: 10.3389/fneur.2024.1357815

A5
Haupenthal D, Kuramatsu JB, Volbers B, Sembill JA, **Mrochen A**, Balk S, Hoelter P, Lücking H, Engelhorn T, Dörfler A, et al. Disability-Adjusted Life-Years Associated With Intracerebral Hemorrhage and Secondary Injury. *JAMA Netw Open*. 2021;4:e2115859. doi: 10.1001/jamanetworkopen.2021.15859

Leitlinien betonen die Notwendigkeit, grundlegende physiologische Parameter wie Temperatur, Blutzucker, Blutdruck und Sauerstoffwerte engmaschig zu überwachen und gezielt zu behandeln. Es ist jedoch aktuell unklar, inwieweit diese Empfehlungen auf den Intensivstationen umgesetzt werden. Wir untersuchten, inwieweit leitlinienbasierte Behandlungsziele für diese physiologischen Parameter in der neurointensivmedizinischen Versorgung umgesetzt werden und zielten darauf ab, Faktoren, die mit der Adhärenz dieser Parameter bei Patienten mit ischämischem Schlaganfall und hämorrhagischem Schlaganfall assoziiert sind, zu identifizieren[71] **(A3)**.

Diese multizentrische Beobachtungsstudie wurde an acht Universitätskliniken in Deutschland durchgeführt und analysierte 474 beatmete Patienten zwischen dem 1. Januar und dem 31. Dezember 2021. Die Adhärenz wurde als Anteil der Messungen

innerhalb der therapeutischen Zielbereiche für den systolischen Blutdruck (SBP, situations-angepasst), den mittleren arteriellen Blutdruck (MAP, 60-90 mmHg), Blutzuckerwerte (80-180 mg/dl), Körpertemperatur (<37,5 °C), den arteriellen Sauerstoffpartialdruck (PaO2, 80-120 mmHg) und den arteriellen Kohlendioxidpartialdruck (PaCO2, 35-45 mmHg) während der initialen 96 Stunden des Krankenhausaufenthalts in 4-Stunden-Intervallen definiert.

Insgesamt lagen 70,7% aller Messungen innerhalb der festgelegten therapeutischen Bereiche, einschließlich SBP (71,3%), Temperatur (68,3%), MAP (71,4%), PaO2 (65,2%), PaCO2 (75,0%) und Blutzucker (80,7%). Es wurden keine Faktoren (Alter, initialer NIHSS) gefunden, die mit einer höheren Adhärenz assoziiert waren.

Diese multizentrische Studie zeigt eine insgesamt hohe Einhaltung der leitlinienbasierten Behandlungsziele und unterstreicht die hohen Standards, die auf deutschen neurologischen Intensivstationen aufrechterhalten werden. Die Ergebnisse dieser Studie bilden eine wichtige Grundlage für zukünftige randomisierte kontrollierte Studien, um den Einfluss dieser Parameter auf langfristige Ergebnisse zu untersuchen mit dem Ziel, die Patientenversorgung zu verbessern und therapeutische Strategien bei neurovaskulären Erkrankungen zu optimieren.

Im Rahmen einer weiteren Studie wurden die Assoziationen einer gebündelten Therapie (Blutdruck-, Temperatur- und Blutzuckermanagement) mit klinischem Outcome untersucht[72] **(A4)**. Zudem wurden Zusammenhänge mit sekundären Schädigungsmechanismen wie der Hämatomprogression und dem maximalen perihämorrhagischen Ödem identifiziert. Hierfür wurden 1.322 Patienten aus der prospektiven UKER-ICH-Kohortenstudie einem Screening unterzogen. Die jeweiligen

Zielbereiche für ein erfolgreiches Therapiebündel waren wie folgt definiert: systolischer Blutdruck 110–160 mmHg, Glukose 80–180 mg/dL und Körpertemperatur 35,5–37,5°C über die ersten 72 Stunden. Der primäre Endpunkt war ein günstiges klinisches Ergebnis nach 12 Monaten (modifizierte Rankin-Skala 0–3). Sekundäre Endpunkte umfassten die Mortalität nach 12 Monaten, das Auftreten einer Hämatomprogression und die Entwicklung des maximalen perihämorrhagischen Ödems. Zur Analyse des Behandlungseffektes eines Therapiebündels wurde die Methode des „augmented inverse probability weighting“ verwendet. Hierbei wurden mögliche Confounder berücksichtigt, die mit dem Therapiebündel als auch dem primären und sekundären Outcome assoziiert sind. Insgesamt verblieben 681 Patienten für die Analyse, 182 Patienten erfüllten alle drei Therapiebündel-Kriterien und wurden mit 499 Kontrollen verglichen. Der absolute Behandlungseffekt derjenigen Patienten, die die Kriterien für das Therapiebündel erfüllten, betrug 9,3%, 95% Konfidenzintervall (CI, 1,7 bis 16,9), p<0,001). Die Mortalität nach 12 Monaten war bei diesen Patienten ebenso signifikant reduziert (absoluter Behandlungseffekt: −12,8%, 95% CI (−19,8 bis −5,7), p<0,001). Es ergab sich keine Assoziation mit Hämatomprogression oder perihämorrhagischen Ödem. Signifikante Treiber des Therapiebündel-Effekts auf das primäre Ergebnis waren die Kontrolle des systolischen Blutdrucks (Behandlungseffekt 15,9%) und die Aufrechterhaltung der Normothermie (absoluter Behandlungseffekt 10,9%).

Die strikte Einhaltung dieses „Therapiebündels“ über die ersten 72 Stunden während der akuten Krankenhausversorgung bei Patienten mit intrazerebraler Blutung war unabhängig mit einer verbesserten funktionellen Langzeitprognose assoziiert, primär bedingt durch die Kontrolle des systolischen Blutdrucks und die Aufrechterhaltung der

Normothermie. Diese Ergebnisse erfordern eine prospektive Validierung, um diesen Effekt, insbesondere in westlichen Ländern, nachzuvollziehen.

Eine weitere Studie behandelt einen zum mRS alternativen Outcomeparameter, die gesundheitsbezogenen Lebensjahre (DALYs). Ziel dieser Studie war es, den Zusammenhang zwischen intrazerebralen Blutungen und DALYs auf individueller Ebene zu untersuchen[5] **(A5)**. Die Kohortenstudie analysierte konsekutive Patienten mit oraler Antikoagulation-assoziierter oder primärer spontaner intrazerebraler Blutung, die zwischen dem 1. Januar 2006 und dem 31. Dezember 2020 im Universitätsklinikum Erlangen aufgenommen wurden.

Im Fokus standen die Auswirkungen der intrazerebralen Blutung und der damit verbundenen sekundären Schädigungsmechanismen auf die DALYs, einschließlich Jahre verlorener Lebenszeit (YLL) und Jahre mit Behinderung (YLD). Dabei wurden Faktoren wie Hämatomlokalisation, Blutungsvolumen und sekundäre Schädigungsmechanismen, die Hämatomprogression, intraventrikuläre Blutung und perihämorrhagischem Ödem umfassen, untersucht. Unter den 1322 Patienten mit intrazerbraler Blutung waren 615 (46,5%) Frauen, das durchschnittliche Alter bei Krankenhausaufnahme betrug 71 Jahre. Die durchschnittlichen DALYs aufgrund der intrazerebralen Blutung lagen bei 9,46 Jahren, davon 5,72 Jahre als YLL und 3,74 Jahre als YLD. Es zeigten sich signifikante Unterschiede in den durchschnittlichen DALYs je nach Hämatomvolumen (<10 ml ICH: 7,05 DALYs; 10-30 ml ICH: 9,91 DALYs; >30 ml ICH: 12,42 DALYs; $P < 0,001$) und Blutungslokalisation (tiefe Lage: 10,60 DALYs; lobär: 8,18 DALYs; Kleinhirn: 8,14 DALYs; Hirnstamm: 12,63 DALYs; $P < 0,001$).

Die Krankheitslast aufgrund der sekundären Komplikationen ergab signifikante Unterschiede in den Kohorten-basierten DALYs (Mittelwerte [Standardabweichung]: 0,94 DALYs für Hämatomprogression, 2,45 DALYs für intraventrikuläre Blutanteile und 1,96 DALYs für perihämorrhagisches Ödem ($P < 0,001$). Auf individueller Patienten-Basis ergaben sich durchschnittlich 7,14 DALYs für Hämatomprogression, 4,58 DALYs für intraventrikuläre Blutanteile und 3,35 DALYs für perihämorrhagisches Ödem bei Patienten mit intrazerebraler Blutung, die von sekundären Komplikationen betroffen waren.

Diese Ergebnisse zeigen, dass intrazerebrale Blutungen und deren Komplikationen eine erhebliche Krankheitslast darstellen. Die Studie liefert wichtige Erkenntnisse für die öffentliche Gesundheitsstrategie und legt nahe, dass intraventrikuläre Blutungen und perihämorrhagisches Ödem wesentliche Faktoren für die globale Krankheitslast darstellen. Die DALYs erweisen sich als nützliches Maß zur Bewertung von Behandlungsergebnissen in klinischer Forschung.

2.4 Akutmanagement: Behandlung intraventrikulärer Blutanteile

2.4.1 Evidenz und offene Fragen

In der Akutphase einer intraventrikulären Blutung spielen intraventrikuläre Blutanteile eine entscheidende Rolle, da sie durch eine Verlegung des dritten oder vierten Ventrikels einen akuten Hydrozephalus hervorrufen können[32,45]. Diese Okklusion führt zu einem Anstieg des intrakraniellen Drucks, der sekundäre Hirnschädigungen verursachen und im schlimmsten Fall eine Herniation nach sich ziehen kann[73]. Bildgebend äußert sich der okklusive Hydrozephalus oft durch eine Erweiterung der Temporalhörner der Seitenventrikel. Die resultierende Liquorzirkulationsstörung macht häufig die Anlage einer externen Ventrikeldrainage (EVD) notwendig, um den Hirndruck zu senken und das Risiko weiterer Komplikationen zu minimieren. Die aktuelle Leitlinie empfiehlt bei Patienten mit akuter spontaner, supratentorieller Blutung und intraventrikulärer Ausdehnung sowie einer Verlegung des dritten und/oder vierten Ventrikels die Erwägung einer EVD, insbesondere wenn klinische oder radiologische Zeichen eines Hydrozephalus vorliegen[47]. Eine zusätzliche Option bei einem kommunizierenden Hydrozephalus und einem offenem 3. und 4. Ventrikel die lumbale Drainage. Sie unterstützt die Drainage von intrathekalen Blutansammlungen und kann langfristig die Notwendigkeit eines dauerhaften Liquorshunts sowie die damit einhergehende Morbidität verringern[74]. Die Applikation des Fibrinolytikums Alteplase über die EVD zur intrathekalen Thrombolyse ist eine weitere therapeutische Option bei ausgeprägten intraventrikulären Blutungen[75]. Hierzu lieferte die CLEAR-III-Studie wichtige Ergebnisse, die die Sicherheit des Verfahrens und eine Reduktion der Mortalität bestätigten[75]. Die Leitlinien empfehlen entsprechend, eine intraventrikuläre Fibrinolyse mit einer Dosierung von 1 mg Alteplase alle 8 Stunden, maximal bis zu 12

Gaben oder bis zur Wiederherstellung der Durchgängigkeit des dritten und vierten Ventrikels, als Therapieoption in Erwägung zu ziehen (starker Konsens)[47].

(1) Allerdings bleibt die Frage offen, inwiefern diese Behandlung auch zu einem verbesserten funktionellen Outcome führt.

(2) Zudem ist unklar, wie gut das vorgeschlagene Akutmanagement bei intraventrikulären Blutungen, insbesondere die EVD-Anlage und intraventrikuläre Fibrinolyse, im klinischen Alltag umgesetzt wird und welchen Einfluss der Zeitpunkt der Aufnahme auf die Qualität der Versorgung hat.

2.4.2 Eigene Arbeiten: Konzepte und Implementierung

In dieses Kapitel eingeflossene eigene Arbeiten:

A6
Kuramatsu JB, Gerner ST, Ziai W, Bardutzky J, Sembill JA, Sprügel MI, **Mrochen A**, Kölbl K, Ram M, Avadhani R, et al. Association of Intraventricular Fibrinolysis With Clinical Outcomes in Intracerebral Hemorrhage: An Individual Participant Data Meta-Analysis. *Stroke*. 2022;53:2876-2886. doi: 10.1161/strokeaha.121.038455

A7
Mrochen A, Sprügel MI, Gerner ST, Madžar D, Kuramatsu JB, Hoelter P, Lücking H, Schwab S, Huttner HB. Invasiveness and Clinical Outcomes of Off-Hour Admissions in Patients with Intracerebral Hemorrhage. *J Stroke Cerebrovasc Dis*. 2020;29:104505. doi: 10.1016/j.jstrokecerebrovasdis.2019.104505

Die intraventrikuläre Fibrinolyse konnte in einer Phase-III Studie belegen, dass sie die Sterblichkeit bei supratentoriellen Blutungen mit Ventrikeleinbruch reduzieren kann[75]. Der Einfluss auf die funktionelle Behinderung ist bislang noch unklar. Daher war das Ziel dieser Studie, den Effekt der intraventrikulären Lyse auf die funktionelle Behinderung zu untersuchen[76] (**A6**).

Diese Metaanalyse von Einzelfall-Daten umfasste insgesamt 1501 Patienten aus zwei randomisierten Studien und sieben Beobachtungsstudien, die zwischen 2004 und 2015 eingeschlossen wurden. Untersucht wurden Patienten mit einer intrazerebralen Blutung, die aufgrund eines akuten Hydrozephalus durch intraventrikuläre Blutanteile mit einer externen Ventrikeldrainage versorgt wurden. Es erfolgte ein Vergleich von denjenigen Patienten, die eine intraventrikuläre Lyse erhielten, und solchen Patienten, die einer Standardbehandlung (einschließlich Placebo) unterzogen wurden. Der primäre Endpunkt war ein günstiges funktionelles Ergebnis (mRS 0-3) nach 6 Monaten. Sekundäre Ergebnisse umfassten die ordinale Verschiebungsanalyse der

mRS-Werte, die Gesamtmortalität und intrakranielle Nebenwirkungen. Zur Berechnung der absoluten Behandlungseffekte wurde eine umfassende Confounder-Analyse vorgenommen.

Der Vergleich der Behandlung von 596 Patienten mit intraventrikulärer Lyse mit 905 Patienten mit Standardbehandlung ergab einen absoluten Behandlungseffekt von 9,3% (95% CI, 4,4-14,1) zur Erreichung des primären Endpunktes. Die Behandlung mit intraventrikulärer Lyse war mit einer signifikanten Verschiebung hin zu besseren funktionellen Ergebnissen über den gesamten Bereich der modifizierten Rankin-Skala hinweg assoziiert (OR 1,75). Zudem fand sich eine reduzierte Mortalität nach 6 Monaten. Ergänzende explorative Analysen ergaben, dass eine frühzeitige Behandlung (≤48 Stunden) nach Symptombeginn mit einem absoluten Behandlungseffekt von 15,2% (95% CI, 8,6-21,8) zur Erreichung des primären Ergebnisses assoziiert war.

Im Vergleich zur Standardbehandlung war die Verabreichung von IVF bei Patienten mit akutem Hydrozephalus durch intrazerebrale und intraventrikuläre Blutung signifikant mit einer Verbesserung der funktionellen Ergebnisse nach 6 Monaten verbunden. Grund hierfür war im Gegensatz zur CLEAR-Studie möglicherweise die Auswahl der Zielpopulation: Der Behandlungseffekt war mit einem frühen Zeitfenster von <48 Stunden verknüpft, was eine Zielpopulation für zukünftige Studien definiert.

In einer weiteren Studie wurde untersucht, ob der Zeitpunkt der Krankenhausaufnahme das Outcome von Patienten mit einer intrazerebralen Blutung, die mittels invasiver Maßnahmen wie einer EVD oder konservativ behandelt wurden, maßgeblich beeinflusst[77] (**A7**).

Basierend auf dem UKER-Register (NCT03183167) wurden ICH-Patienten nach Aufnahmezeitpunkt (innerhalb vs. außerhalb der regulären Arbeitszeiten) gruppiert. Der primäre Endpunkt war das funktionelle Outcome nach drei Monaten, bewertet anhand der modifizierten Rankin-Skala. Von insgesamt 1.269 ICH-Patienten wurden 438 (34,5%) während der regulären Arbeitszeiten aufgenommen. Die Sterblichkeitsraten unterschieden sich nicht signifikant zwischen den Gruppen. Patienten, die während der regulären Arbeitszeiten aufgenommen wurden, zeigten jedoch einen signifikant höheren Anteil an günstigem funktionellen Outcome (mRS 0-3) nach drei Monaten (42,3% vs. 33,8%; p=0,004). Zudem wurde im Rahmen der Studie gezeigt, dass die Wahrscheinlichkeit eines günstigen Outcomes bei Patienten, die während der regulären Arbeitszeiten aufgenommen wurden und keine neurochirurgischen Eingriffe benötigten, signifikant erhöht war (keine externe Ventrikeldrainage: OR: 1,67 [1,13-2,48], p<0,05; keine Hämatomevakuation: OR: 1,51 [1,07-2,14], p<0,05).

Diese Ergebnisse legen nahe, dass die Verfügbarkeit von spezialisierten Behandlungen und Interventionen während der regulären Arbeitszeiten möglicherweise zu einem besseren Outcome bei den Patienten führen. Zudem unterstreicht dies die Notwendigkeit, SOPs konsequent zu implementieren.

3. ZUSAMMENFASSENDE DISKUSSION EIGENER ARBEITEN UND AUSBLICK

Ein zentraler Bestandteil der Habilitationsschrift ist die Analyse der Prozesse zur Implementierung akutmedizinischer Maßnahmen zur Behandlung intrazerebraler Blutungen sowie die Optimierung der damit verbundenen therapeutischen Strategien. In der vorangegangenen Diskussion wurden die vorhandene Evidenz und aktuelle Leitlinien zu den vier Kernaspekten der Therapie – Blutdruckmanagement, hämostatisches Management, allgemein intensivmedizinische Maßnahmen sowie die Behandlung intraventrikulärer Blutanteile – systematisch dargestellt. Zudem wurden offene Fragen erörtert, die in der vorliegenden Habilitationsschrift adressiert wurden.

Im Folgenden soll eine zusammenfassende Diskussion einen Überblick über die Ergebnisse der eigenen Arbeiten in Bezug auf diese vier Kernaspekte der Therapie geben. Darüber hinaus wird ein Ausblick auf zukünftige Forschungsschwerpunkte und potenzielle Entwicklungen zur Verbesserung der Versorgung von Patienten mit intrazerebralen Blutungen gegeben.

3.1 Blutdruckmanagement: Implementierung in den klinischen Alltag

In den aktuellen Leitlinien wird eine frühzeitige Blutdrucksenkung zur Verhinderung einer Hämatomprogression empfohlen[47]. Der Leitsatz „time is brain“ gilt hierbei ebenfalls, da eine rasche und zielgerichtete Behandlung, vor allem in der Notaufnahme oder auf der Intensivstation, maßgeblich zur Prognose beiträgt[48,49]. Dies wirft die Frage auf, inwieweit diese Therapie im klinischen Alltag effektiv umgesetzt werden kann, insbesondere in Abhängigkeit vom Zeitpunkt der Krankenhausaufnahme, beispielsweise während der sogenannten „off-hours“ (außerhalb der regulären Arbeitszeiten)[54,77].

Eine multizentrische Beobachtungsstudie im Rahmen dieser Arbeit untersuchte die Effektivität der Blutdrucksenkung bei Patienten mit intrazerebralen Blutungen und analysierte Unterschiede zwischen Behandlungszeiten innerhalb und außerhalb der regulären Arbeitszeiten[54]. Die Ergebnisse zeigten, dass die Blutdrucksenkung unabhängig von der Aufnahmezeit effektiv durchgeführt wurde[54,77]. Es ergaben sich weder Unterschiede im funktionellen Outcome noch in der Hämatomprogression, unabhängig davon, ob die Patienten während oder außerhalb der regulären Arbeitszeiten behandelt wurden[54,77].

Die Ergebnisse könnten sich darauf zurückführen lassen, dass die teilnehmenden Zentren spezialisierte Universitätskliniken mit den erforderlichen strukturellen Voraussetzungen und standardisierten SOPs für die Behandlung von ICB-Patienten waren. Diese Kliniken konnten die Leitlinienempfehlungen zur Blutdrucksenkung sowohl während der regulären Dienstzeiten als auch in den „off-hours“ konsequent umsetzen.

Ob diese Ergebnisse jedoch flächendeckend in Deutschland, insbesondere in Krankenhäusern ohne neurologische Fachabteilungen oder spezialisierte Stroke Units, reproduzierbar sind, bleibt unklar. Zukünftige Studien sollten daher untersuchen, inwieweit die in spezialisierten Zentren beobachteten Ergebnisse auf andere Versorgungssettings, z.B. Krankenhäuser ohne neurologische Fachabteilungen, übertragbar sind.

3.2 Hämostatisches Management: Umgang mit Thrombozytopenie und Thrombozytenfunktionsstörung

Ein weiterer Kernaspekt der Therapie der ICB, der im Rahmen der Habilitationsschrift untersucht wurde, betrifft das hämostatische Management bei intrazerebralen Blutungen. Thrombozytentransfusionen wurden lange als potenziell effektive Maßnahme für Patienten mit Thrombozytenfunktionsstörungen angesehen, beispielsweise durch die Einnahme von Thrombozytenaggregationshemmern[78]. Die PATCH-Studie zeigte jedoch, dass Thrombozytentransfusionen bei ICB-Patienten unter Thrombozytenfunktionshemmern keinen klinischen Nutzen in Bezug auf das funktionelle Outcome brachten[62]. Im Gegenteil, sie waren sogar mit schlechteren Ergebnissen assoziiert.

Der genaue Grund für dieses Ergebnis bleibt unklar. Es wird jedoch vermutet, dass proinflammatorische und prothrombotische Effekte der Transfusionen sekundäre Schädigungsmechanismen des Gehirns verstärken könnten. Die PATCH-Studie ließ allerdings offen, ob spezifische Patientengruppen, wie beispielsweise Patienten mit schwerer Thrombozytopenie, von Transfusionen profitieren könnten, da Patienten mit Thrombozytopenie in dieser Studie ausgeschlossen wurden.

In einer Studie im Rahmen dieser Habilitationsschrift wurde daher untersucht, ob Patienten mit ICB und gleichzeitig vorliegender Thrombozytopenie ein erhöhtes Risiko für Hämatomprogression oder ein schlechteres funktionelles Outcome aufweisen[63]. Verschiedene Schwellenwerte zur Definition einer Thrombozytopenie (150 000/µl, 100 000/µl und 50 000/µl) wurden berücksichtigt. Es zeigte sich, dass Patienten mit Thrombozytopenie weder mit noch ohne vorherige Einnahme von

Thrombozytenfunktionshemmern ein signifikant erhöhtes Risiko für Hämatomprogression im Vergleich zu Patienten mit normwertiger Thrombozytenzahl hatten. Dies legt nahe, dass eine erhöhte Neigung zur Hämatomprogression möglicherweise erst bei sehr niedrigen Thrombozytenzahlen (<10 000/µl) besteht.

Als Schlussfolgerung der Studie kann postuliert werden, dass die Gabe von Thrombozytenkonzentraten bei Patienten mit Thrombozytenzahlen im Bereich von 50 000/µl - 150 000/µl weiterhin restriktiv und nur nach sorgfältiger Nutzen-Risiko-Abwägung erfolgen sollte.

Daraus ergibt sich die Frage, ob es alternative hämostatische Strategien gibt, die bei dieser Patientengruppe von Nutzen sein könnten. Im Vergleich zu Thrombozytentransfusionen hat die TICH-2-Studie gezeigt, dass Tranexamsäure insbesondere bei Patienten unter Thrombozytenfunktionshemmung sicher eingesetzt werden kann und die Hämatomexpansion signifikant reduziert[55]. Allerdings wurde kein eindeutiger Nutzen für das funktionelle Langzeit-Outcome nachgewiesen. Die systemische Wirkung von Tranexamsäure, die auf der Hemmung der Fibrinolyse basiert, stellt eine kostengünstige und schnell verfügbare Option dar. Studien deuten zudem darauf hin, dass das Risiko thromboembolischer Komplikationen bei der Anwendung von Tranexamsäure gering ist[55,79,80]. Besonders bei Patienten mit gemischten Gerinnungsstörungen – wie einer Kombination aus schwerer Thrombozytopenie und erhöhter fibrinolytischer Aktivität – könnte Tranexamsäure eine ergänzende Rolle spielen.

Unklar bleibt, ob die kombinierte Anwendung von Tranexamsäure und Thrombozytentransfusionen bei spezifischen Subgruppen von ICB-Patienten

synergistische Effekte erzielen oder die Komplikationsrate erhöhen könnte. Die derzeitige Evidenz spricht weiterhin dafür, Thrombozytentransfusionen bei ICB-Patienten unter Thrombozytenaggregationshemmern kritisch zu hinterfragen. Gleichzeitig sollte Tranexamsäure als potenziell wirksame Option zur Reduktion der Hämatomexpansion weiter evaluiert werden.

3.3 Allgemein intensivmedizinische Maßnahmen: Therapiebündel als Perspektive

Wie bereits im Zusammenhang des Blutdruckmanagements diskutiert, stellt sich die Frage, inwieweit die Empfehlungen der Leitlinien in verschiedenen Versorgungssettings umgesetzt werden können. Die INTERACT-3-Studie untersuchte ein Versorgungssetting in Ländern mit niedrigem und mittlerem Einkommen und analysierte, ob die Implementierung standardisierter SOPs für das Blutdruckmanagement sowie für zusätzliche Maßnahmen wie Temperatur- und Blutzuckerkontrolle im Rahmen einer gebündelten Therapie („bundle care“) das funktionelle Outcome und die Mortalität verbessern kann[68]. Die Ergebnisse zeigten, dass in der Care-Bundle-Gruppe die Wahrscheinlichkeit für ein ungünstiges Outcome (mRS 3–6) reduziert war (common odds ratio 0,86; 95 % CI 0,76–0,97; p = 0,015)[68]. Vor diesem Hintergrund stellt sich die Frage, ob ähnliche Interventionen auch in Deutschland eine signifikante Verbesserung der Behandlungsergebnisse bewirken könnten oder ob die bestehenden Behandlungsstandards hierzulande bereits ausreichend hoch sind, um einen Behandlungseffekt nach einer solchen Intervention erzielen zu können.

Im Rahmen dieser Habilitationsarbeit wurden die bestehenden Behandlungsstandards anhand der Adhärenz an leitlinienbasierte Empfehlungen für das Blutdruckmanagement sowie die Kontrolle von Temperatur und Blutzucker bei vaskulären intensivmedizinischen Erkrankungen in den ersten 96 Stunden der Behandlung untersucht[71]. Die Gesamtadhärenz betrug 70,3 %, ein vergleichsweise hoher Wert. Dennoch zeigten sich signifikante Unterschiede zwischen den Zentren ($F = 15.49$, $p < 0.05$), was verdeutlicht, dass selbst in spezialisierten, tertiären

Einrichtungen variierende Standards zu unterschiedlichen Adhärenzgraden und potenziell zu variierenden Outcomes führen können[71].

Zusätzlich wurde untersucht, ob ein „care bundle“ im Vergleich zur „standard care“ auch in einer spezialisierten neurointensivmedizinischen Klinik einen Therapieeffekt bietet[72]. So wurde die Anwendung eines multimodalen Therapiebündels innerhalb der ersten 72 Stunden nach Symptombeginn analysiert. Dieses Bündel umfasste Maßnahmen wie die Kontrolle des systolischen Blutdrucks, der Körpertemperatur und des Blutzuckerspiegels. Der absolute Behandlungseffekt bei Patienten, die die Kriterien für das Therapiebündel erfüllten, betrug 9,3 % (95 % Konfidenzintervall [CI]: 1,7–16,9; $p < 0,001$)[72]. Die Mortalität nach 12 Monaten war bei diesen Patienten ebenfalls signifikant reduziert (absoluter Behandlungseffekt: −12,8 %; 95 % CI: −19,8 bis −5,7; $p < 0,001$)[72].

Im Vergleich zu internationalen Studien wie der INTERACT-3-Studie, die überwiegend Patienten mit hypertensiven, tiefen intrazerebralen Blutungen einschloss, umfasste die untersuchte Kohorte nur zu 50 % solche Patienten[68,72]. Dennoch konnte gezeigt werden, dass die positiven Effekte des Therapiebündels auch bei Patienten mit Blutungen an anderen Lokalisationen bestehen. Die Ergebnisse basieren auf einer nicht selektierten Real-World-Kohorte, die unter strukturierten Bedingungen mit etablierten SOPs behandelt wurde. Dies unterstreicht die Bedeutung eines systematischen und strukturierten Vorgehens in der Patientenversorgung, auch in spezialisierten Einrichtungen.

3.4 Behandlung intraventrikulärer Blutanteile: Auswahlkriterien für eine gezielte Therapie

Eine weitere therapeutische Strategie, die im Rahmen der Habilitationsarbeit untersucht wurde, ist die intraventrikuläre Fibrinolyse. Die randomisierte CLEAR-III-Studie bestätigte deren Sicherheit im Vergleich zu Placebo bei Patienten mit intrazerebralen Blutungen mit verhältnismäßig kleineren parenchymalen Blutungen, aber größeren intraventrikulären Blutanteilen[76]. Während die Mortalitätsrate durch die intraventrikuläre Fibrinolyse gesenkt werden konnte, blieb der primäre Endpunkt des funktionellen Outcomes neutral. Es wird jedoch vermutet, dass spezifische Patientengruppen von dieser Therapie profitieren könnten, wobei Kriterien wie der Zeitpunkt der Applikation und das Volumen der intrazerebralen Blutung eine Rolle spielen könnten.

Um diese Hypothese zu prüfen, wurde eine individualisierte Meta-Analyse durchgeführt, die Daten aus veröffentlichten Studien und großen Beobachtungskohorten integrierte[76]. Ziel war es, patientenspezifische Merkmale zu identifizieren, die mit einer günstigen funktionellen Erholung assoziiert sind. Der Vergleich der intraventrikulären Fibrinolyse mit der Standardbehandlung ergab einen absoluten Behandlungseffekt von 9,3 % (95 % CI, 4,4–14,1) für die Erreichung des primären Endpunkts eines günstigen funktionellen Outcomes[76]. Ergänzende explorative Analysen zeigten, dass eine frühzeitige Behandlung (≤48 Stunden nach Symptombeginn) mit einem noch größeren absoluten Behandlungseffekt von 15,2 % (95 % CI, 8,6–21,8) assoziiert war[76].

Die Unterschiede zwischen der CLEAR-III-Studie, deren Ergebnisse hinsichtlich des funktionellen Endpunkts neutral blieben, und der Meta-Analyse könnten auf das Studiendesign zurückzuführen sein. In Beobachtungsstudien wurden Patienten meist anhand klinischer Expertise ausgewählt, was zu einer breiteren Patientengruppe führte. Die CLEAR-III-Studie hingegen schloss mehr Patienten mit schlechterer Prognose ein, beispielsweise solche mit thalamischen Blutungen und weniger mit großen ICB-Volumina (≥19,2 ml)[75]. Darüber hinaus unterstreicht die Analyse, dass eine frühe Behandlung (<48 Stunden) entscheidend für den Therapieerfolg ist, was den „time is brain"-Ansatz auch bei intrazerebralen Blutungen bestätigt und gleichzeitig eine Zielpopulation für diese therapeutische Strategie definiert.

3.5 Ausblick: standardisiertes und individuelles Therapiekonzept

Eine kürzlich in der Fachzeitschrift *AHA Stroke* erschienene Konsenserklärung (Code ICH: A Call to Action“) betont die Notwendigkeit eines Protokolls, das sich an den etablierten Strategien zur Behandlung des akuten ischämischen Schlaganfalls orientiert[81]. Ziel ist es, durch frühzeitige Intervention, gebündelte Versorgung und zeitbasierte Standards das Outcome von Patienten mit intrazerebralen Blutungen (ICB) zu verbessern. Das vorgeschlagene Versorgungspaket umfasst Maßnahmen wie die rasche Blutdrucksenkung, die Normalisierung der Hämostase bei antikoagulierten Patienten, die Behandlung von Hirnödemen sowie neurochirurgische Interventionen[81]. Die Erklärung unterstreicht, dass zeitkritische Ansätze nicht nur für den ischämischen, sondern auch für den hämorrhagischen Schlaganfall von entscheidender Bedeutung sind[81].

Diese Habilitationsschrift unterstützt diese Forderung nach einem strukturierten Vorgehen und betont die Bedeutung der schnellen Umsetzung therapeutischer Strategien, insbesondere bei der Blutdrucksenkung und der intraventrikulären Fibrinolyse. Es konnte gezeigt werden, dass in spezialisierten Zentren die Adhärenz an bestehende Leitlinien insgesamt hoch ist und Maßnahmen auch außerhalb der regulären Arbeitszeiten erfolgreich umgesetzt werden[54,71,72,77]. Gleichzeitig führte die strukturierte Anwendung eines multimodalen Therapiebündels zu einer signifikanten Verbesserung der funktionellen Prognose und einer Reduktion der Mortalität[72]. Die Analyse offenbarte jedoch auch signifikante Unterschiede in der Adhärenz zwischen den teilnehmenden Zentren[71]. Dies weist trotz hoher Versorgungsstandards auf die Notwendigkeit einer zentrenübergreifenden Standardisierung hin, um die Behandlungsergebnisse konstant zu verbessern.

Diese Notwendigkeit wird zusätzlich dadurch untermauert, dass intrazerebrale Blutungen, aber insbesondere auch die sekundären Schädigungsmechanismen, zu einer erheblichen Krankheitslast führen, die über die unmittelbare Behandlung hinausgeht und langfristige Auswirkungen auf die Lebensqualität der Patienten hat[5]. Patienten mit größeren Hämatomen (>30 ml) wiesen eine deutlich höhere Krankheitslast auf (12,42 DALYs) im Vergleich zu denen mit kleineren Hämatomen (<10 ml: 7,05 DALYs)[5].

Daher sollte neben der Standardisierung auch ein individuelles Therapiekonzept entwickelt werden, das Kriterien wie das zeitliche Fenster, die Thrombozytenzahl, eine vorangegangene orale Antikoagulation, den Ventrikeleinbruch sowie das Volumen der intraventrikulären Blutanteile berücksichtigt, um den Therapieerfolg weiter zu optimieren.

Während internationale Studien wie INTERACT-3 die Wirksamkeit von Therapiebündeln in ressourcenschwächeren Ländern nachgewiesen haben, besteht in gut ausgestatteten Gesundheitssystemen wie in Deutschland weiterhin Bedarf an prospektiven Studien, die die gebündelte Intervention von Therapiemaßnahmen evaluieren. Diese Habilitationsschrift fokussiert sich vor allem auf konservative Therapieansätze. Perspektivisch sollten jedoch auch neurochirurgische Interventionen wie EVD-Anlage und Operationen in das Therapiebündel integriert werden. Die erste randomisierte Studie zur neurochirurgischen Behandlung von lobären intrazerebralen Blutungen („ENRICH“) konnte erstmals positive Ergebnisse liefern. Diese Ergebnisse unterstreichen das Potenzial neurochirurgischer Ansätze in der Behandlung intrazerebraler Blutungen. Laufende Studien wie DIST und EMINENT-ICH werden weitere Erkenntnisse zur Effektivität und Sicherheit dieser Interventionen liefern.

In Kombination mit jüngsten Fortschritten in der konservativen Behandlung – wie der optimierten Blutdruckeinstellung und der effektiven Antagonisierung von Antikoagulanzien – ergeben sich zunehmend konkrete Perspektiven, intrazerebrale Blutungen künftig ähnlich systematisch und protokollbasiert zu behandeln wie ischämische Schlaganfälle. Dieser integrative Ansatz bietet die Chance, die Behandlungsergebnisse weiter zu verbessern und den Weg für standardisierte multimodale Therapiekonzepte zu ebnen.

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Blood Pressure and Anticoagulation Reversal Management during Off-Hours in Oral Anticoagulation-Associated Intracerebral Hemorrhage

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Keywords
Intracerebral hemorrhage · Oral anticoagulation · Vitamin K antagonist · Non-vitamin K oral anticoagulant · Clinical outcome · Off-hour

Abstract
Background: Prevention of hematoma enlargement in oral anticoagulation-associated intracerebral hemorrhage (OAC-ICH) focuses on blood pressure (BP) reduction and OAC reversal. We investigated whether treatment efficiency and clinical outcomes differ between OAC-ICH patients admitted outside versus during regular working hours. ***Methods:*** Based on pooled data of multicenter cohort studies, we grouped OAC-ICH patients (vitamin K antagonist [VKA], non-vitamin K oral anticoagulant [NOAC]) according to on- vs. off-hour admission. Primary outcome was the functional outcome using the modified Rankin scale (mRS) dichotomized into favorable (mRS 0–3) and unfavorable (mRS 4–6) and mortality at 3 months. Secondary outcome measures included the occurrence of hematoma enlargement, the proportions of patients with systolic BP <140 mm Hg and with anticoagulation treatment achieving international normalized ratio (INR) levels <1.3 at 4 h. Propensity score matching (PSM) was performed to account for imbalances in baseline characteristics. ***Results:*** The study population consisted of 76/126 NOAC-ICH patients and 1,005/1,470 VKA patients presenting during off-hours. Functional outcome and mortality rates were not significantly different among PSM patients with VKA-ICH and NOAC-ICH during on- vs. off-hours (mRS 4–6 VKA-ICH: on-hour: 239/357 [66.9%] vs. 253/363 [69.7%] off-hour; $p = 0.43$; NOAC-ICH: on-hour 26/42 [61.9%] vs. off-hour: 37/57 [64.9%]; $p = 0.76$; mRS 6 VKA-ICH: on-hour: 127/357 [35.6%] vs. off-hour: 148/363 [40.8%]; $p = 0.15$; NOAC-ICH: on-hour 17/42 [40.5%] vs. off-hour: 16/57 [28.1%]; $p = 0.20$). There were no differences detectable regarding the secondary outcome measures (i.e., hematoma enlargement, the proportion of patients who achieved systolic BP levels <140 mm Hg at 4 h as well as anticoagulation treatment achieving INR levels <1.3 at 4 h) in OAC patients. ***Conclusion:*** Our study implies that BP reduction and anticoagulation reversal management are well established and associated with similar rates of hematoma enlargement and clinical outcomes in on- vs. off-hour admitted OAC-ICH patients.

Introduction

Minimization of hematoma enlargement represents the main focus of acute treatment of patients with vitamin K antagonists (VKA-) and non-vitamin K oral antagonists

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(NOAC-) related intracerebral hemorrhage (ICH). Treatment regimens comprise blood pressure (BP) reduction to systolic BP levels of 140 mm Hg alongside with rapid anticoagulation reversal using specific antidotes or replacing coagulation factors [1–7]. Previous studies in ischemic stroke reported an "off-hour effect" with increased rates of mortality and poor functional outcome of patients admitted outside regular working hours [8, 9]. Specifically, in patients undergoing endovascular treatment, this aspect may be more pronounced [10, 11]. It is essentially unestablished whether the efficiency of BP reduction and anticoagulation reversal management differs between on- vs. off-hour admissions in oral anticoagulation (OAC-) associated ICH.

Methods

Study Participants

Detailed information and methods of the multicenter RETRACE program (part 1 recruited patients from January 1, 2006, until December 31, 2010 [NCT01829581] and part 2 from January 1, 2011, until December 31, 2015 [NCT03093233]) have been published previously [3, 12–15].

Data Acquisition and Definitions

Patients with secondary etiologies such as aneurysms, arteriovenous malformations, tumorous lesions, trauma, or coagulopathies other than anticoagulation were excluded. VKA-ICH was defined as ICH on effective treatment with VKA and when an international normalized ratio (INR) value >1.5 was documented on hospital admission [3]. NOAC-ICH was defined when patients were known to be on treatment with NOAC at ICH onset [13]. On-hour admission was defined as hospital admission within regular working hours (8:30 a.m. to 4:30 p.m.) on weekdays. Off-hour hospital admission was defined as admission outside regular working hours on weekdays, weekends (Saturday and Sunday), and public holidays [16].

Demographic, clinical, and laboratory data were collected as previously described [12]. Medical history of arterial hypertension, diabetes mellitus, prior stroke, congestive heart failure, abnormal kidney, and premorbid modified Rankin Scale (mRS) were assessed [17]. Laboratory and clinical parameters on admission and during hospital stay were obtained by institutional databases and medical charts, and hematoma characteristics (including ICH location, intraventricular hemorrhage, and ICH volume) were assessed as previously described [3]. Hematoma enlargement was scored in patients with an ICH volume increase of >33% from initial to follow-up imaging [3, 18]. Data on mortality and functional outcome mRS were assessed by standardized mailed questionnaires or semi-structured telephone-interviews at 3 months.

Primary and Secondary Outcomes

Primary outcome measures were (i) functional outcome at 3 months among patients with NOAC-ICH and VKA-ICH assessed by the mRS and categorized into favorable (mRS 0–3) and unfavorable (mRS 4–6) and (ii) mortality after 3 months [3, 17].

Secondary outcomes consisted of (i) occurrence of hematoma enlargement, (ii) proportion of patients with systolic BP levels <140 mm Hg at 4 h, and (iii) proportion of patients who received anticoagulation reversal treatment (including dosage, timing, and rate of patients who achieved INR levels <1.3 at 4 h).

Statistical Analysis

We performed statistical analyses using the statistical package SPSS 21.0 (www.spss.com) and R 2.12.0 (www.r-project.org). The significance level was set at $\alpha = 0.05$, and 2-sided statistical tests were performed. Categorical data are presented as counts (percentage in brackets) and analyzed using the Pearsons χ^2 and the Fisher's exact test. Nonnormally distributed data are presented as median (interquartile range) and analyzed using the Mann-Whitney U test. To compare repeated measurements of BP, we used the Wilcoxon signed-rank test as nonparametric test. Propensity score matching was performed using a balanced, parallel, fixed ratio (1:many) nearest-neighbor approach at a caliper of 0.1, based on significant and relevant differences in baseline characteristics between on-hour and off-hour VKA patients (age, National Institutes of Health Stroke Scale, intraventricular hemorrhage, and ICH volume [19]).

Results

Off-hour Admission and Baseline Characteristics for VKA- and NOAC-ICH Patients

For the present analysis, we investigated a total of 1,470 patients with VKA-ICH and 126 patients with NOAC-ICH (Fig. 1, Tables 1, 2). The majority of VKA- and NOAC-ICH patients presented outside regular working hours (VKA: off-hour: $n = 1{,}005$ [68.4%] vs. on-hour: $n = 465$ [31.6%], NOAC: off-hour: $n = 76$ [60.3%] vs. on-hour: $n = 50$ [39.7%]). Off-hours VKA-ICH patients showed a significant higher National Institutes of Health Stroke Scale (NIHSS), (13 [6–21] vs. 10 [4–18]; $p < 0.01$), a reduced Glasgow Coma Scale-Score (13 [10–15] vs. 14 [11–15]; $p = 0.01$), and a higher rate of intraventricular hemorrhage (447 [44.5%] vs. 108 [38.7%], $p < 0.05$) compared to on-hour VKA patients (Table 1). There was no difference regarding the time from symptom onset to hospital admission between on- and off-hour VKA patients (98 min [60–266 min] vs. 101 min [60–260 min]; $p = 0.97$).

Off-hour NOAC patients did not differ significantly from on-hours NOAC-ICH patients with regard to any clinical baseline parameter (Table 2). To adjust for differences in baseline characteristics of VKA patients and to minimize confounding, we performed a propensity score matching after which all parameters among off-hours versus on-hours VKA-ICH patients were evenly balanced (online suppl. Table 1, see www.karger.com/doi/10.1159/000507316).

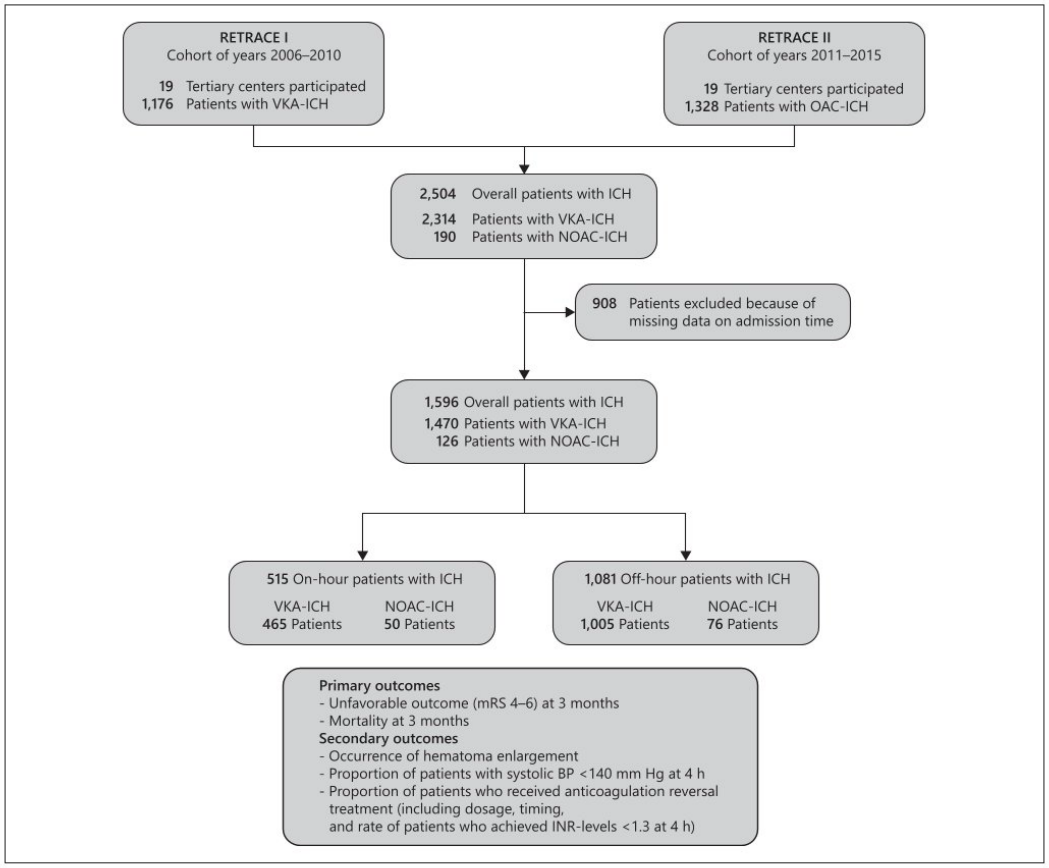

Fig. 1. Flow chart of study participants. Overall, data of 2,504 patients with ICH (2016–2010 years: 1,176; 2011–2015 years: 1,328 patients) consisting of 2,314 patients with VKA- and 190 patients with NOAC-related ICH were eligible for analysis. After exclusion of 908 patients because of missing data on admission time 1,470 patients with VKA-ICH and 126 patients for NOAC-ICH remained for analysis of primary and secondary outcomes. ICH, intracerebral hemorrhage; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulation; RETRACE, German-Wide Multicenter Analysis of Oral Anticoagulation-Associated Intracerebral Hemorrhage; VKA, vitamin K antagonist; mRS, modified Rankin scale; BP, blood pressure; INR, international normalized ratio.

Primary Outcomes

The proportion of patients with unfavorable outcome or mortality after 3 months was not significantly different among on- vs. off-hour OAC- (NOAC- and PS-matched VKA-) patients (mRS 4–6 in OAC-ICH: on-hour: 265/399 [66.4%] vs. off-hour 290/420 [69.0%]; $p = 0.42$; mRS 6 in OAC-ICH: on-hour: 144/399 [36.1] vs. off-hour 164/420 [39.0]; $p = 0.38$). Accordingly, there was no difference in the proportion of patients with unfavorable functional outcome or mortality after 3 months, respectively, among both patients with VKA-ICH and NOAC-ICH admitted in on- versus off-hours (mRS 4–6 in VKA-ICH: on-hours: 239/357 [66.9%] vs. 253/363 [69.7%] off-hour patients; $p = 0.43$; NOAC-ICH: on-hour 26/42 [61.9%] vs. off-hour: 37/57 [64.9%]; $p = 0.76$; mRS 6 in VKA-ICH: on-hours: 127/357 [35.6%] vs. off-hour patients: 148/363 [40.8%]; $p = 0.15$; NOAC-ICH: on-hour 17/42 [40.5%] vs. off-hour: 16/57 [28.1%]; $p = 0.20$, Fig. 2).

Table 1. Characteristics of the entire cohort of VKA-ICH patients separated for admission during on- or off-hour

	On-hour (n = 465)	Off-hour (n = 1,005)	p value
Age, years	76 (71–81)	76 (70–81)	0.35
Gender, female	186 (40.0)	418 (41.6)	0.56
Prior comorbidities			
Hypertension	407 (87.5)	888 (88.4)	0.61
Diabetes mellitus	154 (33.1)	303 (30.1)	0.25
Prior stroke/TIA	145 (31.2)	328 (32.6)	0.58
Congestive heart failure	82 (17.6)	188 (18.7)	0.62
Abnormal kidney function	113 (24.4)	250 (24.9)	0.81
Abnormal liver function	10 (2.2)	30 (3.0)	0.36
Premorbid mRS	0 (0–1)	0 (0–1)	0.93
APT	47 (10.1)	110 (10.9)	0.63
Admission status			
Temperature, °C	36 (36–37)	36 (36–37)	0.92
GCS	14 (11–15)	13 (10–15)	0.01
NIHSS	10 (4–18)	13 (6–21)	0.00
Symptom onset to admission, min	98 (60–266)	101 (60–260)	0.97
Mechanical ventilation	165 (35.5)	398 (39.6)	0.19
Initial INR	3.0 (2.0–3.0)	3.0 (2.0–3.0)	0.55
Initial imaging			
ICH volume, cm^3	12.0 (5.0–31.2)	15.0 (6.0–36.0)	0.05
Intraventricular hemorrhage	180 (38.7)	447 (44.5)	0.04
Location			
Deep	210 (45.2)	499 (49.7)	0.11
Cerebellar	39 (8.4)	105 (10.4)	0.22
Brainstem	19 (4.1)	37 (3.7)	0.71

Number given for patients with available data n (%), IQR; 25th–75th percentile.
APT, antiplatelet therapy; GCS, Glasgow Coma Scale (range 3–15, deep coma to alert); ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale (ranging from 0, no deficit, –40, severe neurological deficit; 40 is the maximum because in comatose ataxia is not scored); mRS, modified Rankin Scale prior to admission (range 0–5, no functional deficit to severe disability); TIA, transient ischemic attack; VKA, vitamin K antagonist.

Table 2. Characteristics of the entire cohort of NOAC-ICH patients separated for admission during on- or off-hour

	On-hour (n = 50)	Off-hour (n = 76)	p value
Age, years	79 (74–83)	78 (73–82)	0.59
Gender, female	20 (40.0)	38 (50.0)	0.27
Prior comorbidities			
Hypertension	47 (94.0)	70 (92.1)	0.69
Diabetes mellitus	13 (26.0)	28 (36.8)	0.20
Prior stroke/TIA	16 (32.0)	34 (44.7)	0.15
Congestive heart failure	10 (20.0)	17 (22.4)	0.75
Abnormal kidney function	11 (22.0)	16 (21.1)	0.90
Abnormal liver function	0 (0)	4 (5.3)	0.10
Premorbid mRS	0 (0–2)	1 (0–2)	0.73
APT	10 (20.0)	11 (14.5)	0.42
Admission status			
Temperature, °C	36 (36–37)	36 (36–37)	0.89
GCS	14 (8–15)	14 (11–15)	0.42
NIHSS	9 (3–18)	10 (5–17)	0.55
Symptom onset to admission, min	134 (59–586)	88 (53–333)	0.21
Mechanical ventilation	13 (26.0)	27 (35.5)	0.26
Initial INR	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.11
Initial imaging			
ICH volume, cm^3	14.0 (3.5–36.5)	9.0 (4.0–21.5)	0.36
Intraventricular hemorrhage	19 (38.0)	31 (40.1)	0.75
Location			
Deep	27 (54.0)	38 (50.0)	0.66
Cerebellar	4 (8.0)	10 (13.2)	0.37
Brainstem	19 (28.0)	31 (41.3)	0.71

Number given for patients with available data n (%), IQR; 25th–75th percentile.
APT, antiplatelet therapy; GCS, Glasgow Coma Scale (range 3–15, deep coma to alert); ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale (ranging from 0, no deficit, –40, severe neurological deficit; 40 is the maximum because in comatose ataxia is not scored); NOAC, non-vitamin K antagonist oral anticoagulant; mRS, modified Rankin Scale prior to admission (range 0–5, no functional deficit to severe disability); TIA, transient ischemic attack; VKA, vitamin K antagonist.

Secondary Outcomes

The proportion of patients who experienced hematoma enlargement was not significantly different among on- vs. off-hour patients (OAC-ICH: on-hour: 154/427 [46.1%] vs. off-hour 180/455 [53.9%]; p = 0.29). There was no difference in both VKA- and NOAC-ICH patients (hematoma enlargement: VKA-ICH: on-hours: 135/377 [35.8%] vs. 156/379 [41.2%] in off-hours patients; p = 0.13; NOAC-ICH: on-hours: 19/50 [38.0%] vs. 24/76 [31.6%] in off-hours patients; p = 0.46, Table 3).

The BP and anticoagulation reversal managements are provided in Figure 3 and Table 3. All patients showed a significant reduction in systolic BP levels from admission to 4 h which remained stable over the first 12 h after admission (VKA on-hour at admission: 162 mm Hg (145–186 mm Hg) versus VKA on-hour at 4 h: 142 mm Hg (128–160 mm Hg); z = –10.90, p = 0.00; VKA off-hour at admission: 170 mm Hg (150–190 mm Hg) versus VKA off-hours at 4 h: 140 mm Hg (123–160 mm Hg); z = –12.46, p = 0.00; NOAC on-hour at admission: 159 mm Hg (139–180 mm Hg) versus on-hour at 4 h: 142 mm Hg (130–163 mm Hg); z = –3.50, p = 0.00; NOAC off-hour at admission: 173 mm Hg (150–200 mm Hg) versus NOAC off-hours at 4 h: 140 mm Hg (118–150 mm Hg); z = – 6.47, p = 0.00; Fig. 3, Table 3). The proportion of patients who achieved systolic BP levels of <140 mm Hg was not significantly different among patients with on- vs. off-hours in both VKA- and NOAC-ICH patients (<140 mm Hg: VKA-ICH: on-hours: 202 [47.8%] vs. 212/418 [50.7%] in off-hours patients; p = 0.39. NOAC-ICH: on-hours: 25/50 [50.0%] vs. 42/73 [55.3%] in off-hours patients; p = 0.56).

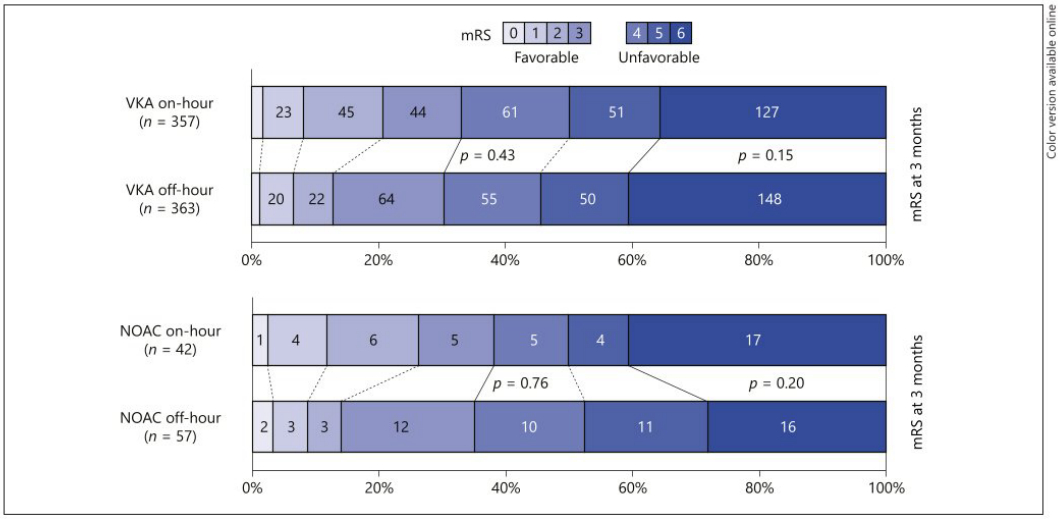

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Fig. 2. Functional outcome according to on- and off-hour admission for VKA and NOAC-ICH patients after 3 months. Distribution of functional outcome was assessed after 3 months using the mRS. A total of 720 (357 on- and 363 off-hour patients) VKA-related ICH patients were available for outcome analysis after PS matching. An unadjusted cohort of 99 NOAC patients (42 on-hour and 57 off-hour patients) was investigated for outcome analysis. Dashed lines separate each score on the mRS. The thick lines illustrate the proportion of patients with unfavorable outcome and mortality, respectively. mRS 0 indicates no symptoms; mRS 1, no significant disability; mRS 2, slight disability and inability to carry out all prestroke activities; mRS 3, moderate disability, but able to walk without personal assistance or wheelchair; mRS 4, moderate to severe disability, needs assistance to attend to own bodily needs, unable to walk without assistance; mRS 5, severe disability, requires constant attention and care, bedridden; mRS 6, death. mRS, modified Rankin scale; VKA, vitamin K antagonist; NOAC, non-vitamin K oral anticoagulant.

The proportion of patients who received anticoagulation reversal treatment using PCC – as well as the dosage of PCC administered and the time from admission to reversal treatment – was not significantly different among patients with on- versus off-hours in both VKA- and NOAC-ICH patients (received PCC: VKA-ICH: on-hours: 338/423 [79.9%] vs. 343/423 [81.1%] in off-hours patients; $p = 0.66$; NOAC-ICH: on-hours: 37/50 [74.0%] vs. 52/76 [68.4%] in off-hours patients; $p = 0.50$; Table 3). The proportion of patients who achieved INR-levels <1.3 at 4 h was not significantly different among on- vs. off-hours VKA patients (INR <1.3: 208/368 [56.5%] vs. 210/368 [57.1%]; $p = 0.88$; Table 3).

Discussion

In essence our analysis suggests that both BP reduction and anticoagulation reversal management are well established and do not differ among OAC patients admitted during on- vs. off-hours in Germany. We did not anticipate this finding, given various clinical conditions including ischemic stroke in which the "off-hour-effect" exerts clinical relevance [20–24]. This specifically holds true in the setting of increasing complexity of interventions required during off-hours, for example, endovascular stroke treatment [8, 9]. Thus, the indicated combination therapy of targeted BP titration alongside with advanced hemostatic management may have harbored the potential to swamp backup-lacking treating physicians in non-tertiary centers during off-hours, notably in settings of reduced staffing structures. Yet, as demonstrated here, BP and OAC reversal treatment appear sufficiently established resulting in similar rates of hematoma enlargement, and related clinical outcomes, in on vs. off-hour-admitted OAC-ICH patients. These data are in line with findings from primary spontaneous ICH patients of the INTERACT2 trial (OAC-ICH <4%) verifying that off-hour admission was not associated with an increased risk for major disability or mortality [16, 25].

Table 3. Hemostatic treatment and clinical outcome for NOAC and PS-matched VKA-related ICH patients according to admission time

	VKA			NOAC		
	on-hour (n = 423)	off-hour (n = 423)	p value	on-hour (n = 50)	off-hour (n = 76)	p value
BP values, mm Hg						
Initial systolic BP	162 (145–186)	170 (150–190)	0.02	159 (139–180)	173 (150–200)	0.05
4-h systolic	142 (128–160)	140 (123–160)	0.51	142 (130–163)	140 (118–150)	0.05
8-h systolic	139 (120–152)	135 (120–151)	0.51	137 (121–146)	132 (120–145)	0.58
12-h systolic	135 (120–150)	136 (120–150)	0.78	132 (125–141)	135 (120–150)	0.74
16-h systolic	138 (125–150)	138 (125–150)	0.72	127 (120–140)	134 (120–150)	0.64
4 h systolic BP <140 mm Hg	202 (47.8)	212/418 (50.7)	0.39	25 (50.0)	42 (55.3)	0.56
Hemostatic treatment						
Reversal therapy	338 (79.9)	343 (81.1)	0.66	37 (74.0)	52 (68.4)	0.50
Amount, IU	2,000 (1,500–2,500)	2,000 (1,500–3,000)	0.53	2,000 (1,500–3,000)	2,000 (1,850–3,000)	0.79
Admission, reversal treatment, min	95 (60–180)	103 (64–171)	0.54	130 (76–194)	78 (56–136)	0.06
Follow-up laboratory values						
INR control	1.2 (1.0–1.5)	1.2 (1.0–1.5)	0.12	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.23
INR <1.3 after 4 h	208/368 (56.5)	210/368 (57.1)	0.88	25/38 (65.8)	51/65 (78.5)	0.16
Follow-up imaging						
Hematoma enlargement (>33%)	135/377 (35.8)	156/379 (41.2)	0.13	19/50 (38.0)	24/76 (31.6)	0.46
Clinical outcome						
Early care limitation <24 h	30 (7.1)	32 (7.6)	0.79	3 (6.0)	4 (5.3)	0.86
Mortality at 3 months	127/357 (35.6)	148/363 (40.8)	0.15	17/42 (40.5)	16/57 (28.1)	0.20
mRS 4–6 at 3 months	239/357 (66.9)	253/363 (69.7)	0.43	26/42 (61.9)	37/57 (64.9)	0.76

Number given for patients with available data n (%), IQR; 25th–75th percentile.
Hematoma enlargement was defined as volume increase of >33% compared to initial imaging.
BP, blood pressure; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; mRS, modified Rankin Scale; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

With regard to the specific BP and anticoagulation reversal management, all patients showed a significant reduction in systolic BP levels from admission to 4 h which remained stable thereafter, indicating established treatment standards at participating institutions that sufficiently work in off-hours. In line, reversal treatment was initiated without obvious differences in dosing or timing compared to on-hours. Of note in this regard, NOAC patients analyzed here were treated with prothrombin complex concentrates (specific antidotes not available during study period [4, 5]) which may have resulted in increased uncertainty of hemostatic treatment specifically in off-hours [13]. Yet, the rates of hematoma enlargement were comparable during on- vs. off-hours arguing in favor of the assumption that standardized stroke care and implementations of standard operating procedures may overcome the "off-hour effect," at least in noninvasive treatments for ICH patients [9]. To which extent a possible off-hour effect exists in ICH patients requiring invasive surgical interventions needs to be investigated separately.

Some limitations may weaken presented study findings and decrease generalizability, notably the retrospective design of this study. Certain extent of imprecision in measurement of hematoma enlargement and BP assessments appears possible as well as the limited numbers of patients with NOAC-related ICH. Further, outcome was assessed using individual study protocols which may lead to potential imprecision in time-point estimation or assessment methodology. Finally, the OAC-ICH patients were recruited in a multicenter retrospective study design. Consequently, the definition of off-hour and also structural characteristics of each participating center (i.e., staffing characteristics, availability of imaging) may vary and was not registered in its details.

In conclusion, among patients admitted during on- vs. off-hours, there were no significant efficacy differences in acute BP management and anticoagulation reversal treatment in VKA- or NOAC-ICH. Similar rates of hematoma enlargement and clinical outcomes indicate no relevant off-hour effect in OAC-ICH, highlighting the significance of standardized stroke care and implementations of standard operating procedures.

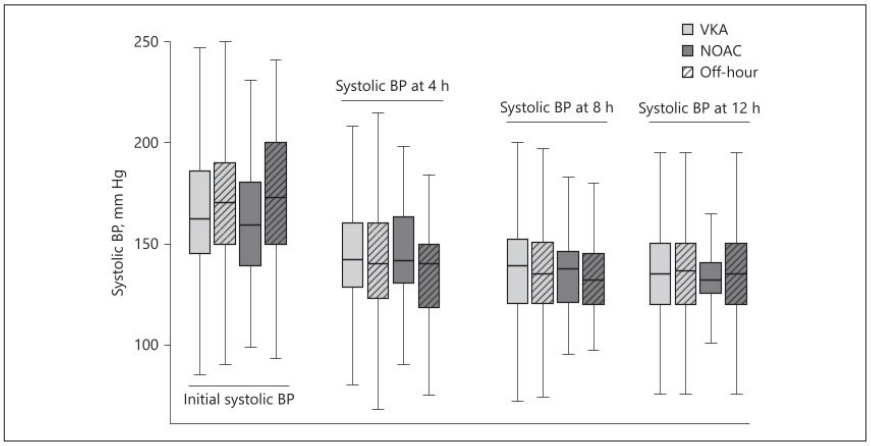

Fig. 3. Analysis of BP management for (matched) VKA- and NOAC patients with ICH during on- and off-hours at 4 h intervals. Boxplot distribution of systolic BP values (mm Hg) at admission, 4, 8, and 12 h separated for VKA patients (gray) and NOAC patients (dark) during on- and off-hours (patterned plots). It shows the highest and lowest quartile of systolic BP as lines (whiskers) and the 2 interquartiles as a box and the median as a black line in the box. Off-hour patients (matched VKA- and NOAC-related ICH) presented with significantly increased systolic BP compared to on-hour patients (matched VKA on-hour: 162 mm Hg [145–186 mm Hg] vs. off-hour: 170 mm Hg [150–190 mm Hg]; $p = 0.02$, NOAC on-hour: 159 mm Hg [139–180 mm Hg] vs. off-hour: 173 mm Hg [150–200 mm Hg]; $p = 0.05$). The median systolic BP did not differ ($p > 0.05$) between on- and off-hour patients at 4, 8, and 12 h intervals neither for VKA- nor for NOAC patients. VKA, vitamin K antagonist; NOAC, non-vitamin K oral anticoagulant; BP, blood pressure.

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Statement of Ethics

The study was approved by the local Ethics Committees and Institutional Review Boards based on the central vote from Friedrich-Alexander-University Erlangen-Nuremberg, Germany (Re.No-4409 and 30_16B, 115_17B). Consent was obtained by patients or legal representatives.

Disclosure Statement

The authors have no conflicts of interest to disclose regarding this manuscript.

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Author Contributions

A.M., M.I.S., and H.B.H. conception and design of the study. A.M., M.I.S., S.T.G., J.A.S., S.L., H.L., J.B.K., and H.B.H. acquisition and analysis of data. A.M., M.I.S., S.T.G., J.A.S., S.L., H.L., J.B.K., and H.B.H. drafting the text and figures.

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Stroke

CLINICAL AND POPULATION SCIENCES

Thrombocytopenia and Clinical Outcomes in Intracerebral Hemorrhage

A Retrospective Multicenter Cohort Study

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BACKGROUND AND PURPOSE: The impact of platelets on hematoma enlargement (HE) of intracerebral hemorrhage (ICH) is not yet sufficiently elucidated. Especially the role of reduced platelet counts on HE and clinical outcomes is still poorly understood. This study investigated the influence of thrombocytopenia on HE, functional outcome, and mortality in patients with ICH with or without prior antiplatelet therapy (APT).

METHODS: Individual participant data of multicenter cohort studies (multicenter RETRACE program [German-Wide Multicenter Analysis of Oral Anticoagulation-Associated Intracerebral Hemorrhage] and single-center UKER-ICH registry [Universitätsklinikum Erlangen Cohort of Patients With Spontaneous ICH]) were grouped into APT and non-APT ICH patients according to the platelet count, that is, with or without thrombocytopenia (cells <150×10^9/L). Of all patients, 51.5% (1124 of 2183) were on vitamin K antagonist. Imbalances in baseline characteristics including proportions of vitamin K antagonist patients were addressed using propensity score matching. Outcome analyses included HE (>33%), as well as mortality and functional outcome, after 3 months using the modified Rankin Scale, dichotomized into favorable (modified Rankin Scale score, 0–3) and unfavorable (modified Rankin Scale score, 4–6).

RESULTS: Of overall 2252 ICH patients, 11.4% (52 of 458) under APT and 14.0% (242 of 1725) without APT presented with thrombocytopenia on admission. The proportion of patients with HE was not significantly different between patients with or without thrombocytopenia among APT and non-APT ICH patients after propensity score matching (HE: APT patients: 9 of 40 [22.5%] thrombocytopenia versus 27 of 115 [23.5%] nonthrombocytopenia, P=0.89; non-APT patients: 54 of 174 [31.0%] thrombocytopenia versus 106 of 356 [29.8%] nonthrombocytopenia, P=0.77). In both (APT and non-APT) propensity score matching cohorts, there were no significant differences regarding functional outcome. Mortality after 3 months did not differ among non-APT patients, whereas the mortality rate was significantly higher for APT patients with thrombocytopenia versus APT patients with normal platelet count (APT: 29 of 46 [63.0%] thrombocytopenia versus 58 of 140 [41.4%] nonthrombocytopenia, P=0.01; non-APT: 95 of 227 [41.9%] thrombocytopenia versus 178 of 455 [39.1%] nonthrombocytopenia, P=0.49).

CONCLUSIONS: Our study implies that thrombocytopenia does not affect rates of HE and functional outcome among ICH patients, neither in patients with nor without APT. In light of increased mortality, the significance of platelet transfusions for ICH patients with thrombocytopenia and previous APT should be explored in future studies.

Key Words: cohort studies ■ hematoma enlargement ■ intracerebral hemorrhage ■ platelet count ■ thrombocytopenia

One essential function of platelets is to contribute to the maintenance of hemostasis by initiating coagulation. Platelet hypofunction and low platelet count may result in impaired hemostasis.[1,2] In patients with intracerebral hemorrhage (ICH), the role of platelets on the occurrence of hematoma enlargement (HE)

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Nonstandard Abbreviations and Acronyms

APT	antiplatelet therapy
HE	hematoma enlargement
ICH	intracerebral hemorrhage
mRS	modified Rankin Scale
PSM	propensity score matching
VKA	vitamin K antagonist

is insufficiently established. Previous studies focused on platelet dysfunction, rather than total count of thrombocytes, and hypothesized that it may contribute to ICH expansion.[3–5]

However, substituting thrombocytes in ICH patients with platelet dysfunction, that is, concomitant antiplatelet therapy (APT), as done in the PATCH trial, did not reveal beneficial effects.[6] Reasons include that the influence of platelet transfusion is not large enough to modify HE under APT.[7] Up to now, the significance of thrombocytopenia and the role of a low platelet count on HE are unestablished. The present study explored the influence of thrombocytopenia on HE and functional outcome in patients with ICH under or without APT.

METHODS

Study Participants and Study Design

The authors declare that all supporting data are available within the article and its Data Supplement. We pooled patient data from the multicenter RETRACE program (German-Wide Multicenter Analysis of Oral Anticoagulation-Associated Intracerebral Hemorrhage; part 1: from January 1, 2006, until December 31, 2010 [https://www.clinicaltrials.gov; unique identifier: NCT01829581]) and from the prospective single-center UKER-ICH registry (Universitätsklinikum Erlangen Cohort, patients with spontaneous ICH; from January 1, 2006, until December 31, 2015 [https://www.clinicaltrials.gov; unique identifier: NCT03183167]). Detailed information and methods have been published previously.[8–13] The study was approved by the local ethics committees and institutional review boards based on the central vote from Friedrich-Alexander-University Erlangen-Nuremberg, Germany (Re. No-4409 and 30_16B, 115_17B).[8] Consent was obtained by patients or legal representatives. We excluded patients with ICH related to secondary etiologies (aneurysms, arteriovenous malformations, tumorous lesions, trauma, or coagulopathies other than oral anticoagulation).[8–11]

Definitions

We defined vitamin K antagonist (VKA) ICH as ICH on effective anticoagulation with VKAs and when an international normalized ratio value >1.5 was documented on hospital admission.[8] APT-ICH was defined as APT at onset of ICH including all administrations of acetylsalicylic acid, dipyridamole, P2Y12 P2Y12 (purinergic receptor p2y, g protein-coupled, 12) platelet receptor inhibitor, or glycoprotein IIb/IIIa inhibitor ICH.[9–11] Thrombocytopenia was defined as platelet count <150 cells×10^9/L.[3,14]

Data Acquisition

As described previously, data collected included medical history of arterial hypertension, diabetes, prior ischemic/hemorrhagic stroke, congestive heart failure, and abnormal kidney or liver function.[13] Additionally, premorbid modified Rankin Scale (mRS) was assessed.[15] Laboratory parameters including the initial platelet count, clinical parameters on admission (Glasgow Coma Scale and National Institutes of Health Stroke Scale), and parameters during hospital stay were retrieved through institutional databases and medical charts. In patients with spontaneous ICH (UKER-ICH registry, single-center), the administration of platelet transfusion within the first 24 hours after admission was recorded. We evaluated hematoma characteristics (ICH location, intraventricular hemorrhage, and ICH volume) as described previously.[8] Analyses of mortality and functional outcome (mRS) at 3 months were based on standardized mailed questionnaires or semistructured telephone interviews.[15]

Outcome Analyses

Outcome measure was the occurrence of HE defined as an ICH volume increase of >33% (relative) and >6 mL (absolute) from initial to follow-up imaging.[8,16] Additionally, outcome parameters were (1) mortality at 3 months and (2) functional outcome at 3 months. Functional outcome was grouped into favorable (mRS score, 0–3) and unfavorable (mRS score, 4–6) outcome, as described previously.[17]

Statistical Analysis

Statistical analyses were performed using the SPSS 21.0 package (www.spss.com) and R 2.12.0 (www.r-project.org). Non-normally distributed data are shown as median (±interquartile range) and calculated using the Mann-Whitney *U* test. Further baseline characteristics are presented as categorical variables (total number and frequency in brackets, compared using Person χ^2 and Fisher exact tests). The significance level was set at α=0.05, and 2-sided statistical tests were performed. To adjust for possible confounding factors, we performed propensity score matching (PSM) with a balanced, parallel, fixed ratio (1:many) nearest-neighbor approach at a caliper of 0.2. Based on significant and relevant differences in baseline characteristics between patients with platelet count <150 cells×10^9/L, we defined sex, intraventricular hemorrhage, and prior VKA medication as confounding factors.[18] To account for clustering, generalized estimating equation models with an exchangeable working correlation structure of PSM cohorts were used.[19] We adjusted for age, hematoma volume, intraventricular hemorrhage, reversal treatment, and centers. For evaluation of significant subgroup differences between APT and non-APT patients, interaction terms were included. Outcome analyses of (PSM) cohorts were performed using 3 definitions of thrombocytopenia (<150, 100, and 50 cells×10^9/L).[14]

RESULTS

Platelet Count and Baseline Characteristics for APT and Non-APT Patients

The present analysis consisted in total of 2252 patients with ICH (1176 VKA-ICH patients from RETRACE program and 1076 spontaneous ICH patients from the UKER registry). Sixty-nine patients were excluded because of missing data on platelet count, and 458 APT and 1725 non-APT patients remained for analysis (Figure 1). There were 52 APT patients and 242 non-APT patients with thrombocytopenia while the majority of APT and non-APT patients revealed a platelet count ≥150 cells×10^9/L on admission (non-APT, 1483 of 1725 [86.0%]; APT, 406 of 458 [88.6%]). Tables 1 and 2 provide the baseline clinical characteristics of non-APT and APT patients with normal versus reduced platelet counts.

In unadjusted analysis, among non-APT patients with thrombocytopenia, there was a significant lower proportion of female patients and significantly more patients with abnormal liver function compared with non-APT patients with normal platelet count (female sex: 85 of 242 [35.1%] thrombocytopenia versus 667 of 1483 [45.0%] nonthrombocytopenia, $P<0.01$; abnormal liver function: 25 of 242 [10.3%] thrombocytopenia versus 57 of 1483 [3.8%] nonthrombocytopenia, $P<0.01$). Further, more non-APT and APT patients with thrombocytopenia were on VKA and consequently presented with higher international normalized ratio values on admission compared with patients with normal platelet count (VKA: non-APT: 160 of 242 [66.1%] thrombocytopenia versus 847 of 1483 [57.1%] nonthrombocytopenia, $P=0.01$; APT: 20 of 52 [38.5%] thrombocytopenia versus 97 of 406 [23.9%] nonthrombocytopenia, $P=0.02$). Patients with ICH on APT and thrombocytopenia showed significantly higher median National Institutes of Health Stroke Scale score on admission (19 [7–32] versus 13 [5–25]; $P=0.04$) and a higher rate of intraventricular hemorrhage (191 of 406 [47.0%] versus 32 of 52 [61.5%]; $P=0.05$) compared with patients on APT with normal platelet count. Before analysis of outcomes, we adjusted for differences in baseline characteristics (sex, intraventricular hemorrhage, and prior VKA medication) using PSM for both APT and non-APT ICH patients. Thereafter, baseline characteristics among patients with versus without thrombocytopenia were evenly balanced (Tables I and II in the Data Supplement).

Outcome Analysis: HE

The proportion of patients with HE (relative, >33%) was not significantly different among patients with versus without thrombocytopenia both in APT and non-APT ICH patients both in crude data analysis (non-APT ICH: 54 of 174 [31.0%] thrombocytopenia versus 275 of 1123 [24.5%] nonthrombocytopenia, $P=0.07$; APT ICH: 9 of 40 [22.5%] thrombocytopenia versus 50 of 310 [16.1%] nonthrombocytopenia, $P=0.31$), as well as after PSM (both APT and non-APT) (HE: APT patients: 9 of 40 [22.5%] thrombocytopenia versus 27 of 115 [23.5%] nonthrombocytopenia, $P=0.89$; non-APT patients: 54 of 174 [31.0%] thrombocytopenia versus 106 of 356 [29.8%] nonthrombocytopenia, $P=0.77$; Table 3). Accordingly, with HE defined as absolute >6 mL, there was no significant difference between both in APT and non-APT ICH patients (Table III in the Data Supplement).

Additionally, subgroup analyses showed no significant association between thrombocytopenia and HE, neither among (PSM) ICH patients under APT nor non-APT (Table 3).

Outcome Analysis: Mortality and Functional Outcome

In both (ie, APT and non-APT) PSM cohorts, there were no significant differences regarding functional outcome (APT: mRS score, 4–6: 38 of 46 [82.6%] thrombocytopenia versus 104 of 140 [74.3%] nonthrombocytopenia; $P=0.25$; non-APT: mRS score, 4–6: 158 of 227 [69.6%] thrombocytopenia versus 309 of 455 [67.9%] nonthrombocytopenia; $P=0.65$; Table 3; Figure 2). Mortality after 3 months did not differ among non-APT patients, whereas the mortality rate was significantly higher for APT patients with thrombocytopenia versus APT patients with normal platelet count (APT: mRS score, 6: 29 of 46 [63.0%] thrombocytopenia versus 58 of 140 [41.4%] nonthrombocytopenia; $P=0.01$; non-APT: mRS score, 6: 95 of 227 [41.9%] thrombocytopenia versus 178 of 455 [39.1%] nonthrombocytopenia; $P=0.49$; Table 3; Figure 2). Additionally, subgroup analyses showed no significant association between thrombocytopenia and functional outcome or mortality, neither among (PSM) ICH patients under APT nor non-APT (Table 3). To analyze a significant difference between the APT and non-APT groups, interaction terms revealed no significant difference with exception of mortality after 3 months between APT and non-APT patients ($P=0.048$; Table 3).

Similarly, in ordinal shift analysis, there was no significant shift in the mRS distribution (odds ratio, 1.17 [0.88–1.55]; $P=0.29$), whereas ordinal shift analysis revealed a significant shift toward higher mRS (odds ratio, 2.10 [1.06–3.98]; $P=0.03$).

To analyze whether there were associations of HE with the extent of thrombocytopenia, we performed outcome analyses of PSM cohorts for both APT and non-APT patients with additional thresholds of 100 and 50 cells×10^9/L. Similarly to the threshold of 150 cells×10^9/L, primary and secondary outcomes were not

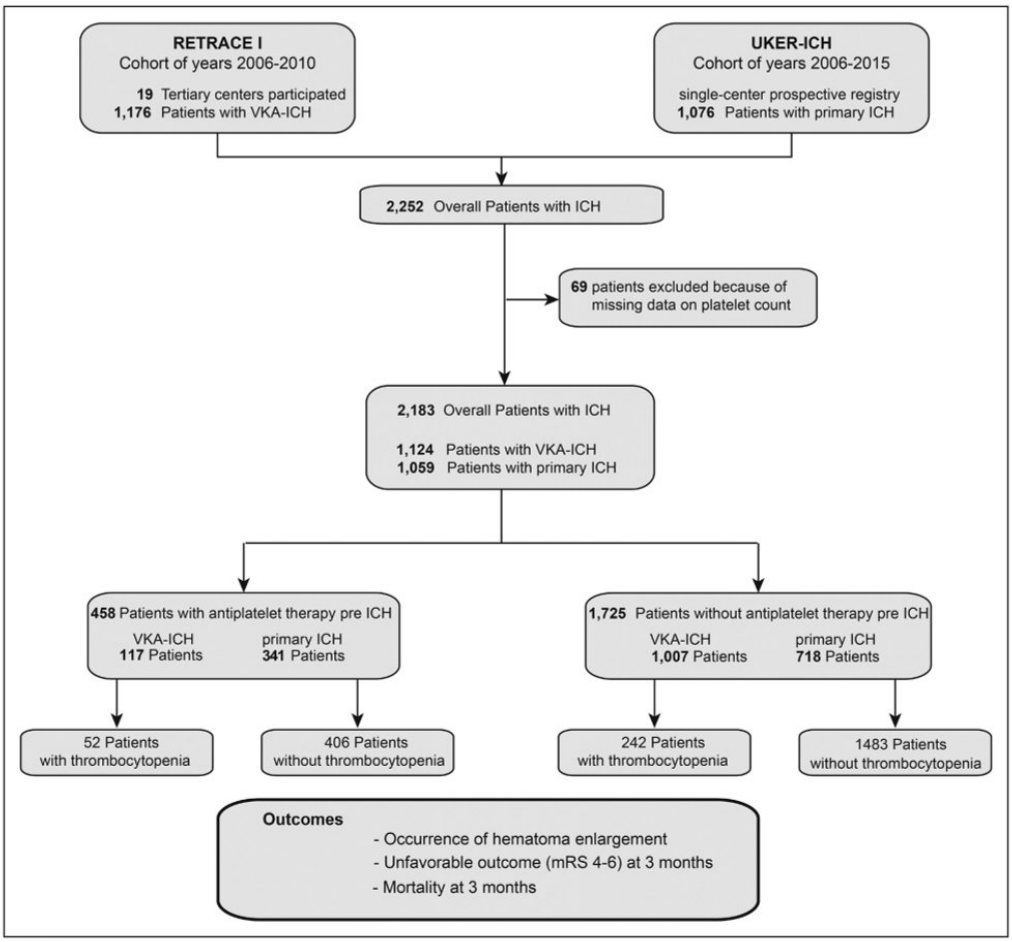

Figure 1. Flowchart of study participants.
Overall, 2252 patients with intracerebral hemorrhage (ICH; years 2006–2010: 1176 patients with vitamin K antagonist [VKA] ICH; years 2006–2015: 1076 patients with spontaneous ICH) were recruited for analysis. Sixty-nine patients were excluded because of missing data on platelet count. Four hundred fifty-eight patients with platelet therapy and 1725 patients without platelet therapy pre-ICH remained for analysis of primary and secondary outcomes. mRS indicates modified Rankin Scale; RETRACE, German-Wide Multicenter Analysis of Oral Anticoagulation-Associated Intracerebral Hemorrhage; and UKER-ICH, Universitätsklinikum Erlangen Cohort of Patients With Spontaneous Intracerebral Hemorrhage.

significantly altered in patients with thrombocytopenia <100 cells and 50 cells×10^9/L, respectively (Table 3).

DISCUSSION

As key findings, the present study demonstrates that ICH patients with thrombocytopenia, as compared with those with normal platelet counts, do not experience increased HE rates and show comparable functional outcomes, irrespective of previous antiplatelet treatment. Generally, platelet function may be altered by either dysfunction or absolute count and could lead to deranged coagulation and hemorrhage.[20] In the setting of ICH, platelet dysfunction, for example, induced by APT, has been addressed previously.[3,4,6,11] While some analyses suggested that APT may contribute to ICH expansion,[2–4] a recent larger multicenter study revealed that APT does not increase risk for HE in spontaneous ICH.[11] Nonetheless, for the present analysis, to account for the potential bias of platelet dysfunction, we grouped our patients into prior APT and non-APT intake.

Contrary, regarding platelet count, to our knowledge, we here investigated for the first time the role of

Table 1. Characteristics of ICH Patients With Platelet Therapy Separated for Platelet Count Before PSM

	Patients with thrombocytes ≥150×10³/L (n=406)	Patients with thrombocytes <150×10³/L (n=52)	*P* value
Age, y (IQR)	75 (68–81)	74 (69–80)	0.47
Female sex, n (%)	186 (45.8)	17 (32.7)	0.07*
Prior comorbidities			
Hypertension, n (%)	369 (90.9)	48 (92.3)	0.81
Diabetes, n (%)	157 (38.7)	19 (36.5)	0.74
Prior ischemic stroke/TIA, n (%)	134 (33.0)	15 (28.8)	0.55
Prior hemorrhagic stroke/major bleeding, n (%)	46 (11.3)	5 (9.6)	0.71
Congestive heart failure, n (%)	68 (16.7)	13 (25.0)	0.14
Abnormal kidney function, n (%)	73 (18.0)	13 (25.0)	0.22
Abnormal liver function, n (%)	21 (5.2)	3 (5.8)	1.00
Premorbid mRS (IQR)	1 (0–2)	1 (0–2)	0.80
VKA, n (%)	97 (23.9)	20 (38.5)	0.02*
Admission status			
GCS (IQR)	13 (6–15)	13 (4–14)	0.30
NIHSS (IQR)	13 (5–25)	19 (7–32)	0.04
Symptom onset to admission, min (IQR)	240 (92–624)	160 (92–381)	0.08
Time from first to second CT, h (IQR)	21 (12–32)	20 (9–28)	0.59
Initial INR (IQR)	1.06 (1.00–1.34)	1.19 (1.05–2.57)	0.00
Mean arterial blood pressure, mm Hg (IQR)	117 (102–130)	117 (104–137)	0.63
Clinical parameters during hospital stay			
Mechanical ventilation, n (%)	153 (37.7)	31 (59.6)	0.00
Surgical evacuation, n (%)	32 (7.9)	9 (17.3)	0.04
External ventricular drain, n (%)	83 (20.4)	17 (32.7)	0.04
Initial imaging			
ICH volume, cm³ (IQR)	14.50 (4.87–43.20)	21.49 (4.42–62.01)	0.47
Intraventricular hemorrhage, n (%)	191 (47.0)	32 (61.5)	0.05*
Location, n (%)			
Lobar	194 (47.8)	17 (32.7)	0.40
Deep	159 (39.2)	27 (51.9)	0.08
Cerebellar	32 (7.9)	5 (9.6)	0.79
Brain stem	17 (4.2)	2 (3.8)	1.00
Hemostatic treatment			
Reversal treatment, n (%)	79/97 (81.4)	20/20 (100)	0.04
Time from onset to reversal treatment, min (IQR)	180 (144–270)	190 (149–420)	0.39
Time from admission to reversal treatment, min (IQR)	110 (72–175)	101 (58–153)	0.54
Vitamin K, n (%)	70/79 (88.6)	14/19 (73.3)	0.10
Fresh frozen plasma, n (%)	19/79 (24.1)	6/20 (30.0)	0.58
PCC, n (%)	66/79 (83.5)	17/20 (85.0)	0.87
PCC amount, median IU (IQR)	1800 (1200–2400)	2000 (1725–2625)	0.14
PCC, IU/kg (IQR)	19.05 (14.27–26.25)	16.26 (9.52–16.26)	0.55
Platelet transfusion, n (%)	9/309 (2.9)	1/32 (3.1)	0.95

Number (n) given for patients with available data, n (%); IQR, 25th to 75th percentile. GCS: range, 3–15 (deep coma to alert); NIHSS ranging from 0 (no deficit) to 40 (severe neurological deficit), 40 is the maximum because in comatose, ataxia is not scored; mRS before admission: range, 0–5 (no functional deficit to severe disability). CT indicates computed tomography; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PCC, prothrombin complex concentrate; PSM, propensity score matching; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

*Differences in baseline characteristics used as factors for PSM.

Table 2. Characteristics of ICH Patients Without Platelet Therapy Separated for Platelet Count Before PSM

	Patients with thrombocytes ≥150×10³/L (n=1483)	Patients with thrombocytes <150×10³/L (n=242)	*P* value
Age, y (IQR)	74 (66–80)	74 (67–81)	0.16
Female sex, n (%)	667 (45.0)	85 (35.1)	0.00*
Prior comorbidities			
Hypertension, n (%)	1224 (82.5)	201 (83.1)	0.84
Diabetes, n (%)	354 (23.9)	60 (24.8)	0.75
Prior ischemic stroke/TIA, n (%)	291 (19.6)	53 (21.9)	0.41
Prior hemorrhagic stroke/major bleeding, n (%)	128 (8.6)	18 (7.4)	0.54
Congestive heart failure, n (%)	142 (9.6)	30 (12.4)	0.17
Abnormal kidney function, n (%)	267 (18.0)	52 (21.5)	0.20
Abnormal liver function, n (%)	57 (3.8)	25 (10.3)	0.00
Premorbid mRS (IQR)	0 (0–2)	0 (0–2)	0.64
VKA, n (%)	847 (57.1)	160 (66.1)	0.01*
Admission status			
GCS (IQR)	13 (8–15)	13 (8–15)	0.72
NIHSS (IQR)	13 (5–24)	14 (6–25)	0.15
Symptom onset to admission, min (IQR)	160 (70–378)	135 (65–333)	0.21
Time from first to second CT, h (IQR)	20 (10–30)	15 (8–27)	0.04
Initial INR (IQR)	1.97 (1.03–2.92)	2.27 (1.18–3.10)	0.00
Mean arterial blood pressure, mm Hg (IQR)	118 (103–133)	120 (103–133)	0.76
Clinical parameters during hospital stay			
Mechanical ventilation, n (%)	565 (38.1)	97 (40.1)	0.55
Surgical evacuation, n (%)	141 (9.5)	33 (13.6)	0.05
External ventricular drain, n (%)	303 (20.4)	56 (23.1)	0.33
Initial imaging			
ICH volume, cm³ (IQR)	15.00 (5.19–42.22)	16.92 (6.61–54.55)	0.12
Intraventricular hemorrhage, n (%)	665 (44.8)	118 (48.8)	0.26*
Location, n (%)			
Lobar	594 (40.1)	84 (34.7)	0.11
Deep	655 (44.2)	130 (53.7)	0.01
Cerebellar	130 (8.8)	21 (8.7)	1.00
Brain stem	79 (5.3)	5 (2.1)	0.03
Hemostatic treatment			
Reversal treatment, n (%)	730/847 (86.2)	133/160 (83.1)	0.31
Time from onset to reversal treatment, min (IQR)	210 (130–360)	195 (125–362)	0.74
Time from admission to reversal treatment, min (IQR)	112 (65–210)	107 (62–227)	0.81
Vitamin K, n (%)	629/727 (86.5)	110/129 (85.3)	0.70
Fresh frozen plasma, n (%)	67/728 (9.2)	18/130 (13.8)	0.10
PCC, n (%)	633/730 (86.7)	114/132 (86.4)	0.91
PCC amount, IU; median (IQR)	1800 (1200–2400)	2000 (1500–2500)	0.08
PCC, IU/kg (IQR)	21.43 (15.89–30.74)	20.53 (14.56–30.58)	0.84
Platelet transfusion, n (%)	0/636 (0)	7/82 (8.5)	0.00

Number (n) given for patients with available data, n (%); IQR, 25th to 75th percentile. GCS: range, 3–15 (deep coma to alert); NIHSS ranging from 0 (no deficit) to 40 (severe neurological deficit), 40 is the maximum because in comatose, ataxia is not scored; mRS before admission: range, 0–5 (no functional deficit to severe disability). CT indicates computed tomography; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PCC, prothrombin complex concentrate; PSM, propensity score matching; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

*Differences in baseline characterstics used as factors for PSM.

Table 3. Outcomes According to Different Thresholds of Thrombocytes of PSM Cohorts With and Without APT

	Without APT pre-ICH					APT pre-ICH					*P* for interaction
	Thrombocytes ≥150×10⁹/L	Thrombocytes <150×10⁹/L	*P* value	Odds ratio (95% CI)	*P* value	Thrombocytes ≥150×10⁹/L	Thrombocytes <150×10⁹/L	*P* value	Odds ratio (95% CI)	*P* value	
Hematoma enlargement (>33%), n (%)	106/356 (29.8)	54/174 (31.0)	0.77	0.94 (0.57–1.5)	0.79	27/115 (23.5)	9/40 (22.5)	0.89	1.25 (0.36–4.39)	0.73	0.81
mRS 3 mo 4–6, n (%)	309/455 (67.9)	158/227 (69.6)	0.65	1.10 (0.65–1.73)	0.83	104/140 (74.3)	38/46 (82.6)	0.25	0.28 (0.04–2.11)	0.22	0.37
3-mo mortality, n (%)	178/455 (39.1)	95/227 (41.9)	0.49	1.30 (0.78–2.12)	0.32	58/140 (41.4)	29/46 (63.0)	0.01	0.32 (0.07–1.51)	0.15	0.048
	Thrombocytes ≥100×10⁹/L	Thrombocytes <100×10⁹/L	*P* value	Odds ratio (95% CI)	*P* value	Thrombocytes ≥100×10⁹/L	Thrombocytes <100×10⁹/L	*P* value			
Hematoma enlargement (>33%), n (%)	146/493 (29.6)	14/37 (37.8)	0.29	0.52 (0.17–1.55)	0.24	36/150 (24.0)	0/5 (0)	0.34			0.99
mRS 3 mo 4–6, n (%)	429/631 (68.0)	38/51 (74.5)	0.34	1.94 (0.63–6.0)	0.25	135/178 (75.8)	7/8 (87.5)	0.68			0.67
3-mo mortality, n (%)	248/631 (38.3)	25/51 (49.0)	0.17	0.78 (0.23–2.64)	0.68	82/178 (46.1)	5/8 (62.5)	0.48			0.73
	Thrombocytes ≥50×10⁹/L	Thrombocytes <50×10⁹/L	*P* value			Thrombocytes ≥50×10⁹/L	Thrombocytes <50×10⁹/L	*P* value			
Hematoma enlargement (>33%), n (%)	159/521 (30.5)	1/9 (11.1)	0.29								
mRS 3 mo 4–6, n (%)	457/668 (68.4)	10/14 (71.4)	1.00								
3-mo mortality, n (%)	268/668 (40.1)	5/14 (35.7)	0.79								

Hematoma enlargement was defined as volume increase of >33% compared with initial imaging. Generalized estimating equations models of PSM cohorts were adjusted for age, hematoma volume, intraventricular hemorrhage, reversal treatment, and centers. For evaluation of significant subgroup differences between APT and non-APT patients, interaction terms were included. Number (n) given for patients with available data, n (%); IQR, 25th to75th percentile. APT indicates antiplatelet therapy; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; and PSM, propensity score matching.

thrombocytopenia in ICH patients and its associations with HE and clinical outcomes. One small prospective study investigated platelet function and count within the first 7 days after ICH and found a significant decrease in platelet count within the first 4 days after ICH (Nadir: 149±9 IU/mm^3).[3] They concluded that platelet dysfunction and also reduced platelet count may be a consequence of ICH and related to the brain injury. Yet, on admission, thrombocytopenia and its possible effect on HE or clinical outcome was not specifically analyzed. We here demonstrate that thrombocytopenia does not affect the rates of HE and functional outcome among ICH patients. This aspect may be supported from previous studies that investigated the (general) bleeding risk depending on platelet counts.[21,22] These studies revealed that bleeding risk becomes clinically relevant not before platelet counts of <10 IU/mm^3. Therefore, our thresholds of thrombocytes (150, 100, and 50 IU/mm^3) may still have been too high to detect significant associations with HE.[21]

Nevertheless, our data verify an increased mortality of ICH patients with APT and thrombocytopenia compared with those APT patients with normal platelet count. As this finding cannot be attributed to different rates of HE, other possible explanations may include unmeasured confounding not addressed in our adjusted baseline characteristics. Inherited or acquired conditions like cancer, cancer treatments like radiation or chemotherapy, aplastic anemia, alcohol abuse, infections, or autoimmune diseases may have biased outcome findings to the disfavor of thrombocytopenic patients.[14,23] Furthermore, interaction between APT and non-APT cannot be ruled out. Nevertheless, possible therapeutic consequences remain enigmatic, especially if there is a role of platelet transfusions for this specific subset of patients.

Despite the widespread use of platelet transfusions in bleeding disorders, substituting thrombocytes in ICH patients with platelet dysfunction, that is, concomitant APT, as done in the PATCH trial, did not reveal beneficial effects.[6] Whether the results of these trials are explained by imbalances of baseline characteristics alone or additional hazardous effects of platelet transfusion due to proinflammatory effects is not sufficiently elucidated. However, a beneficial effect on outcome in patients with ICH was not registered.[24] Notably, the trial excluded patients with thrombocytopenia (thrombocytes <100×10^9/L).

In light of our results, that is, thrombocytopenia not affecting HE and functional outcome neither among ICH patients under APT nor non-APT, the use of platelet transfusions should further prompt caution in regular application of platelet transfusion. However, given

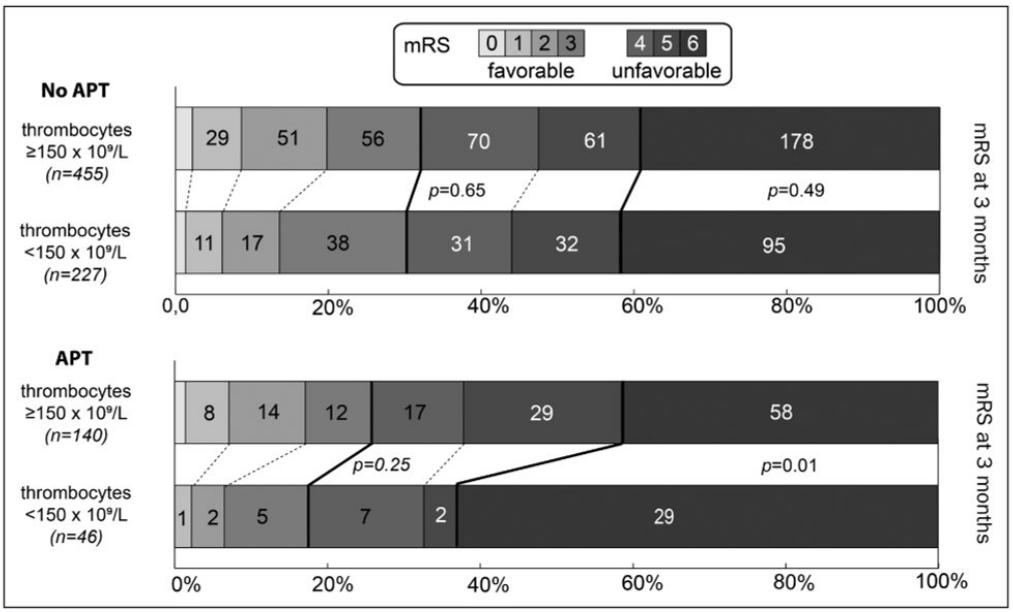

Figure 2. Functional outcome according to platelet count for matched antiplatelet therapy (APT) and non-APT intracerebral hemorrhage patients after 3 mo.

Functional outcome was assessed after 3 mo using the modified Rankin Scale (mRS). Six hundred eighty-two patients without platelet therapy (APT, 455 patients without and 227 patients with thrombocytopenia) were investigated for outcome analysis after PS matching. One hundred eighty-six patients with prior antiplatelet therapy (140 patients without and 46 patients with thrombocytopenia) were available for outcome analysis after PS matching. Dashed lines separate each score on the mRS. The thick lines illustrate the proportion of patients with unfavorable outcome and mortality, respectively. mRS score of 0 indicates no symptoms; mRS score 1, no significant disability; mRS score 2, slight disability and inability to carry out all prestroke activities; mRS score 3, moderate disability but able to walk without personal assistance or wheelchair; mRS score 4, moderate-to-severe disability, needs assistance to attend to own bodily needs, unable to walk without assistance; mRS score 5, severe disability, requires constant attention and care, bedridden; and mRS score 6, death.

an increased mortality in ICH patients with thrombocytopenia and previous APT, the significance of platelet transfusions for this specific subset of ICH patients should be established in future studies. Furthermore, especially patients with severe thrombocytopenia need further investigation of potential beneficial effects of platelet transfusions.

Limitations of our analysis include the mixture of data from the monocentric UKER cohort with data on oral anticoagulation–associated ICH obtained among the retrospective multicenter RETRACE program. With a relevant proportion of VKA patients within the APT and non-APT groups, the lack of reversal strategies, that is, blood pressure management, may represent a relevant confounder. Furthermore another limitation represents the low patient numbers, specifically to explore subanalyses among both non-APT and APT groups to address the significance of severe thrombocytopenia. The study design may thus have been prone to potential center effects not compensated in our adjustments. Similarly, though adjusting for oral anticoagulation, remaining effects on HE rates cannot be excluded. Further, residual bias due to missing data cannot be fully ruled out. Finally, solid data on platelet transfusions were not available why patients who indeed received platelet transfusions might have confounded our results.

Taken together, our study implies that thrombocytopenia does not affect occurrence of HE and is not related to functional outcome among ICH patients, neither in those with nor without prior APT. Given increased mortality rates, the clinical significance of platelet transfusions for the subset of ICH patients with thrombocytopenia and previous APT should be explored in future studies.

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Supplemental Materials

Tables I–III

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Influence of bundled care treatment on functional outcome in patients with intracerebral hemorrhage

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Background and aims: General guideline recommendations in patients with intracerebral hemorrhage (ICH) include blood pressure-, temperature- and glucose management. The therapeutic effect of such a "care bundle" (blood pressure lowering, glycemic control, and treatment of pyrexia) on clinical outcomes becomes increasingly established. For the present study, we aimed to investigate associations of strict bundled care treatment (BCT) with clinical outcomes and characterize associations with key outcome effectors such as hematoma enlargement (HE) and peak perihemorrhagic edema (PHE).

Methods: We screened consecutive ICH patients (n = 1,322) from the prospective UKER-ICH cohort study. BCT was defined as achieving and maintaining therapeutic ranges for systolic blood pressure (110–160 mmHg), glucose (80–180 mg/dL), and body temperature (35.5–37.5°C) over the first 72 h. The primary outcome was the functional outcome at 12 months (modified Rankin Scale (mRS) 0–3). Secondary outcomes included mortality at 12 months, the occurrence of hematoma enlargement, and the development of peak perihemorrhagic edema. Confounding was addressed by a doubly robust methodology to calculate the absolute treatment effect (ATE) and by calculating e-values.

Results: A total of 681 patients remained for analysis, and 182 patients fulfilled all three BCT criteria and were compared to 499 controls. The ATE of BCT to achieve the primary outcome was 9.3%, 95% CI (1.7 to 16.9), $p < 0.001$; e-value: 3.1, CI (1.8). Mortality at 12 months was significantly reduced by BCT [ATE: –12.8%, 95% CI (–19.8 to –5.7), $p < 0.001$; e-value: 3.8, CI (2.2)], and no association was observed for HE or peak PHE. Significant drivers of BCT effect on the primary outcome were systolic blood pressure control (ATE: 15.9%) and maintenance of normothermia (ATE: 10.9%).

Conclusion: Strict adherence to this "care bundle" over the first 72 h during acute hospital care in patients with ICH was independently associated with improved functional long-term outcome, driven by systolic blood pressure control and maintenance of normothermia. Our findings strongly warrant prospective validation to determine the generalizability especially in Western countries.

Clinical trial registration: ClinicalTrials.gov, identifier [ID: NCT03183167].

KEYWORDS
ICH, bundle, treatment, PHE, HE

Introduction

Intracerebral hemorrhage accounts for 11–22% of strokes and contributes to the burden of the disease with approximately 42% of the disability adjusted life-years due to the stroke (47 million life-years) (1, 2). Although the "one" breakthrough intervention improving functional outcome and mortality does not exist, a variety of treatment approaches possibly interacting with one another have been investigated (3). Baseline guideline-recommended interventions comprise an early and strict implementation of blood pressure, temperature, and glucose management (4). Over the last years, several large clinical trials and observational studies provided new evidence enhancing acute ICH care by investigating the potential benefit of single interventions (5–8). Nevertheless, the potential synergistic benefits of guideline-recommended treatments when combined remain elusive, especially in Western countries. Clustering interventions together as a care bundle lately revealed promising outcomes (9, 10). For example, Parry-Jones et al. focused on a "bundle" of treatments: reversal of coagulation status, referral to neurosurgery, blood pressure control, and admission to a neurological intensive care unit, and found a 6 to 12% absolute reduction in mortality (10). Most currently, the cluster-randomized INTERACT3 trial has been published demonstrating that implantation of a care bundle protocol in low- and middle-income countries without a previous standardized operating procedure for ICH patients resulted in improved functional outcome (11). This large trial ($n = 7.036$) included patients mainly from China and could document significant differences according to treatment allocation only for the parameter blood pressure, hence potentially driving the overall effect on the entire range of mRS estimates (common odds ratio 0.86; 95% CI: 0.76–0.97; $p = 0{\cdot}015$).

The present study investigated whether the consistent and effective implementation of bundled care treatment (BCT) targets for systolic blood pressure, glucose levels, and temperature improved patient functional long-term outcomes after intracerebral hemorrhage. In addition, we aim to evaluate the key components of a care bundle and characterize associations with hematoma enlargement (HE) and peak perihemorrhagic edema (PHE).

Methods

Study participants and study design

We included patient data from the prospective single-center UKER-ICH registry [patients with spontaneous ICH; from 1 January 2006 until 31 December 2015 (NCT03183167)]. Detailed information and methods have been published previously (12–15). The study was approved by the local ethics committee and institutional review boards based on the central votes from Friedrich-Alexander-University Erlangen-Nuremberg, Germany (Re.No-4409 & 30_16B, 115_17B: "Retrospective analysis of patients with intracerebral haemorrhage," approval date 20 June 2017) (12). Consent was obtained from patients or legal representatives. The procedures followed were in accordance with IRB ethical standards for human experimentation and the Helsinki Declaration of 1975. Patients with secondary ICH etiologies such as aneurysms, arteriovenous malformations, tumorous lesions, trauma, or coagulopathies other than oral anticoagulation were excluded (12–15). In addition, we excluded patients with symptom onset >8 h or withdrawal of therapy within 24 h according to previous studies (16) (Figure 1).

Data acquisition

Data collection included baseline data on demographics (age and sex), prior comorbidities (hypertension, coronary artery disease, prior stroke, and abnormal kidney or liver function), prior medication (oral anticoagulation and antiplatelet medication), timing measures (time from symptom onset to first and second CT and time from symptom onset to treatment), and neurological status assessed using the National Institutes of Health Stroke Scale (NIHSS) upon hospital admission. In addition, the premorbid modified Rankin Scale was assessed (17). We evaluated hematoma characteristics (ICH location, intraventricular hemorrhage, and ICH volume) by neuroradiologists (S.H., S.L. and T.E.) blinded to clinical information. Assessment of mortality and functional outcome (modified Rankin Scale [mRS]) at 12 months was obtained by independent personnel, as previously reported (12). We recorded all available bundled care treatment (BCT) parameters, that is, measurement of systolic blood pressure, temperature, and blood sugar levels within the first 72 h.

Definition of BCT

Patients with ICH were categorized into two groups: one group with patients fulfilling the BCT criteria over the first 72 h (BCT) and the control group of patients not fulfilling the criteria (non-BCT). The BCT criteria consisted of three target parameters: systolic blood pressure, temperature, and glucose management. We defined the following target ranges according to standard operating procedures at our institution in place over the study period: (1) systolic blood pressure between 110 mmHg and 160 mmHg, (2) temperature between 35.5°C and 37.5°C, and (3) blood sugar levels between 80 mg/dL and 180 mg/dL. We evaluated all available measurements, divided these into 6-h intervals, and recorded maximum and minimum values over each period for each BCT parameter. Patients were categorized into the BCT group, if less than 33.3% of maximum or minimum values of each interval (i.e., >4/12) were outside of the predefined range over all 6-h intervals. We selected the systolic blood pressure range of <160 mmHg according to an internal standard operating procedure at our institution in place before the publication of the INTERACT-II trial data (7). Since 2013 this has been modified to a target systolic level of <140 mmHg[7]. Body core temperature was measured using the tympanic or bladder

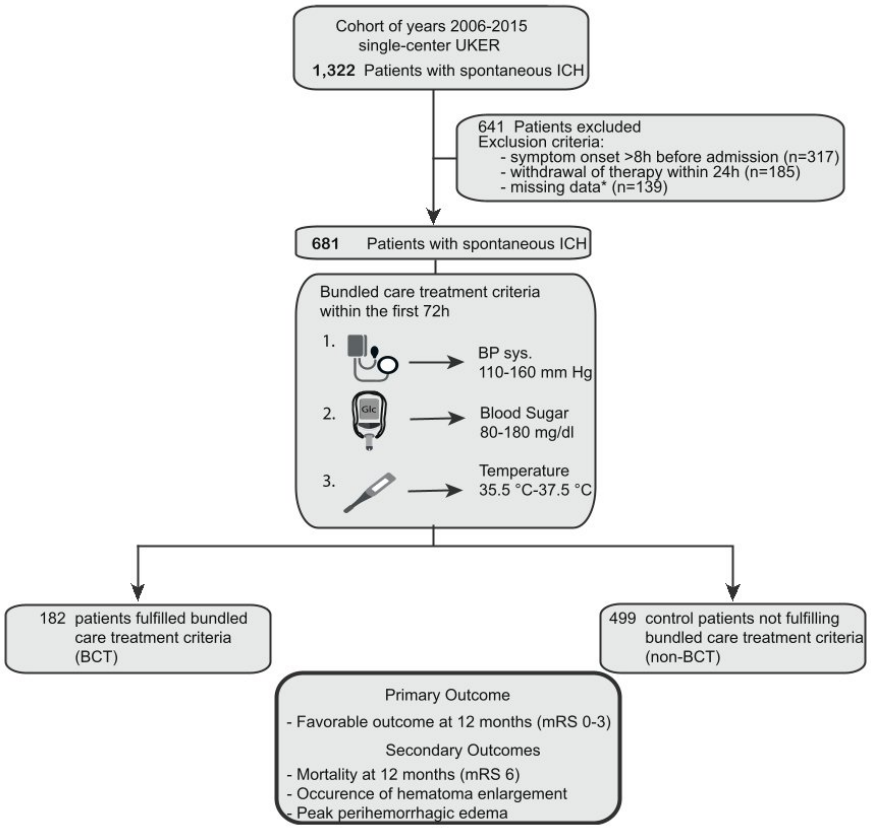

FIGURE 1
Flow chart of study participants. Overall, 1,322 patients with spontaneous ICH (years 2006–2015) were screened for analysis. 641 patients were excluded because of (i) symptom onset >8 h before admission ($n = 317$), (ii) withdrawal of therapy within the first 24 h ($n = 185$), and (iii) missing patient data ($n = 139$). 681 patients remained for primary and secondary outcome analyses. 182 fulfilled the bundle care treatment criteria, and 499 patients remained as controls. *Missing data consist of (i) more than 33.3% of maximum or minimum values of each BCT parameter over all 6-h intervals or (ii) follow-up imaging (dicom data for detailed analysis). BCT, bundled care treatment; ICH, intracerebral hemorrhage; UKER, Universitätsklinikum Erlangen Cohort of Patients With Spontaneous Intracerebral Hemorrhage.

temperature, and the chosen range was considered normothermia (35.5°C and 37.5°C) according to previous studies (5, 18, 19). Regarding blood sugar levels, we selected a conventional range of 80–180 mg/dL according to current AHA guideline which recommends treating hypo- and hyperglycemia to prevent adverse events (6, 20, 21).

Primary and secondary outcomes

The primary outcome measure was the functional outcome at 12 months assessed by the ordinal modified Rankin Scale (mRS; 0: no deficit, through 5: severe disability and 6: death). Functional outcome was grouped into favorable (mRS 0–3) and unfavorable (mRS 4–6) outcomes, as previously described (8). Secondary outcomes compromised (i) mortality at 12 months, (ii) occurrence of hematoma enlargement defined as an ICH volume increase of more than 33% (relative) or 6 mL from initial to follow-up imaging, and (iii) peak perihemorrhagic edema (PHE). We assessed PHE on all available CT scans using a validated semi-automated threshold-based algorithm with a threshold range of 5–33 Hounsfield units (22). Peak PHE was defined as the maximum PHE volume measured during hospitalization and dichotomized according to the median split method (22).

Statistical analysis

Statistical analyses were performed using STATA (Version 14·2) and R x64 3.2.0.[1] In general, confounders were considered relevant

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using a standardized mean difference larger than 20%. To address confounding, we used adjusted odds ratios (OR) and a doubly robust confounder-adjusted methodology to calculate adjusted absolute treatment effects, that is, augmented inverse probability weighting (AIPW) (23). These adjustments were applied in two ways: (A) identified confounders associated with an increased propensity for BCT and (B) validated confounders associated with primary and secondary endpoints; confounders were identified based on standardized mean differences (SMD). For exploratory analysis of the primary outcome, we used the aforementioned adjustment methodology. The categorization of non-dichotomous variables was split by the 50th percentile. Interactions of exploratory subgroup analyses were analyzed by the subgroup-defining variable (variable×intervention) and were considered significant for a p-value of <0.05. Sensitivity analyses compromised the evaluation of unmeasured confounding (e-values) (24). The average data missingness was approximately 7% per patient without difference between BCT and non-BCT patients. Missing functional outcome information was handled by multiple imputations by conditional specifications after assessment of missingness (25).

Results

Study population

We identified 681 patients from our prospective cohort study in spontaneous ICH ($n = 1{,}322$, Cohort of years 2006–2015 from UKER registry, Figure 1). A total of 182 patients (26.7%) fulfilled the strict BCT criteria and were compared to 499 controls (73.3%). We graphically displayed differences between these groups for all three BCT parameters over the first 72 h in Figure 2. Initial BCT measurements between groups were not significantly different (A, systolic blood pressure: 160 mmHg vs. 162 mmHg; B, temperature: 36.6°C vs. 36.7°C; blood sugar: 130 mg/dL vs. 132 mg/dL), and subsequent measurements over the 72-h time period significantly differed, that is, for systolic blood pressure in 92% (11/12, 6-h intervals), for temperature 75% (9/12, 6-h intervals), and for blood sugar levels 58% (7/12, 6-h intervals).

Sensitivity analyses of confounders

Baseline characteristics are shown in Table 1. We identified significant imbalances in BCT patients than in non-BCT patients, that is, more frequent prior diagnosis of hypertension [absolute difference (AD) 6.1, 95% CI (1.2 to 11.1) %; SMD 0.19], less frequent treatment with external ventricular drainage [AD −7.6, 95% CI (−15.4 to 0.1) %; SMD −0.16], more frequent lobar ICH location [AD 7.9, 95% CI (−0.4 to 16.2) %; SMD 0.16], and less frequent intraventricular hemorrhage [AD −10.5, 95% CI (−18.8 to −2.3) %; SMD −0.21]. For evaluation of confounding regarding the primary endpoint, sensitivity analysis was dichotomized according to functional outcome (mRS 0–3 at 12 months, Table 2). The results show that patients with mRS 0–3 at 12 months were younger [AD 7.1, 95% CI (5.2 to 8.9), years, %; SMD 0.58], had lower premRS [AD 1, 95% CI (0.8 to 1.2), SMD 0.64], had less comorbidity of prior stroke/TIA [AD 9.7, 95% CI (4.0 to 15.4), %; SMD 0.25], lower ICH volumes [AD 14.2, 95% CI (10.5 to 17.8), mL; SMD 0.67], lower NIHSS values [AD 9, 95% CI (7.6 to 10.4), SMD 0.84], more frequent rate of intraventricular hemorrhage [IVH, AD 23.9, 95% CI (16.7 to 31.2), %; SMD 0.50], and less frequent prior use of oral anticoagulation [AD 7.7 (2.2 to 13.2), %; SMD 0.21]. We accordingly performed sensitivity analyses for secondary outcomes: mortality at 12 months, occurence of hematoma enlargement and peak perihemorrhagic edema, dichotomized according to median split method (value 25 cm^3), for details please see Supplementary Tables S1–S3.

Analyses of the primary and secondary outcomes

The adjusted absolute treatment effect (ATE) of BCT to achieve a favorable functional outcome at 12 months was 9.3%, 95% CI (1.7 to 16.9), $p < 0{\cdot}001$ [adjusted OR, 1.86 (95% CI, 1.23–2.83), $p < 0.005$; (e-value, point estimate, 3.1, CI, 1.8)]. Among secondary outcomes, only mortality at 12 months was significantly reduced with an absolute treatment effect for BCT [ATE −12.8%, 95% CI (−19.8 to −5.7), $p < 0.001$; adjusted OR, 2.22 (95% CI, 1.40–3.53), $p < 0.005$; (e-value, point estimate, 3.8, CI, 2.2)]. There was no significant association of BCT regarding the occurrence of hematoma enlargement or peak perihemorrhagic edema [HE: ATE −0.1%, 95% CI (−6.8 to 7.8), $p = 0.89$; PHE: ATE −1.5%, 95% CI (−8.3 to 5.3, $p = 0.65$)] (Figure 3).

Exploratory subgroup analyses

For associations of BCT with the primary outcome according to predefined subgroups (Figure 4), significant ATE was found in younger patients aged 29–70 years, ATE 13.3%, 95% CI (2.8 to 23.8), in patients with higher NIHSS values, ATE 19.3%, 95% CI (8.8 to 29.7), in patients with larger ICH volumes (≥16.0 cm^3), ATE 17.6%, 95% CI (7.1 to 28.2) and larger peak edema volumes (≥25.0 cm^3), ATE 19.0%, 95% CI (8.1 to 30.0). In addition, significant ATE was found in patients with intraventricular hemorrhage, ATE 15.3%, 95% CI (4.1 to 26.5), and for patients without hematoma enlargement, ATE 16.1%, 95% CI (7.1 to 25.1). Significant interactions between treatment and subgroup categories were not detected (all $p > 0.05$).

Contribution of the components of BCT to the overall treatment

To assess the contribution of each component of BCT to the overall effect, we investigated the treatment effect separated for each component, that is, glucose, blood sugar, and systolic blood pressure management (Figure 3). Therefore, ICH patients were categorized according to the above-mentioned target parameters (see also Methods). Accordingly, we addressed confounding by sensitivity analyses and doubly robust methodology as aforementioned. Among the three components, blood sugar management revealed no significant treatment effects for primary and secondary endpoints. Both systolic blood pressure and temperature management revealed a significant absolute treatment effect regarding the primary endpoint and mortality at 12 months [BP: mRS 0–3: ATE 15.9%, 95% CI (9.2 to 22.6), $p < 0.001$; mRS 6: ATE −17.1%, 95% CI (−24.3 to −10.0),

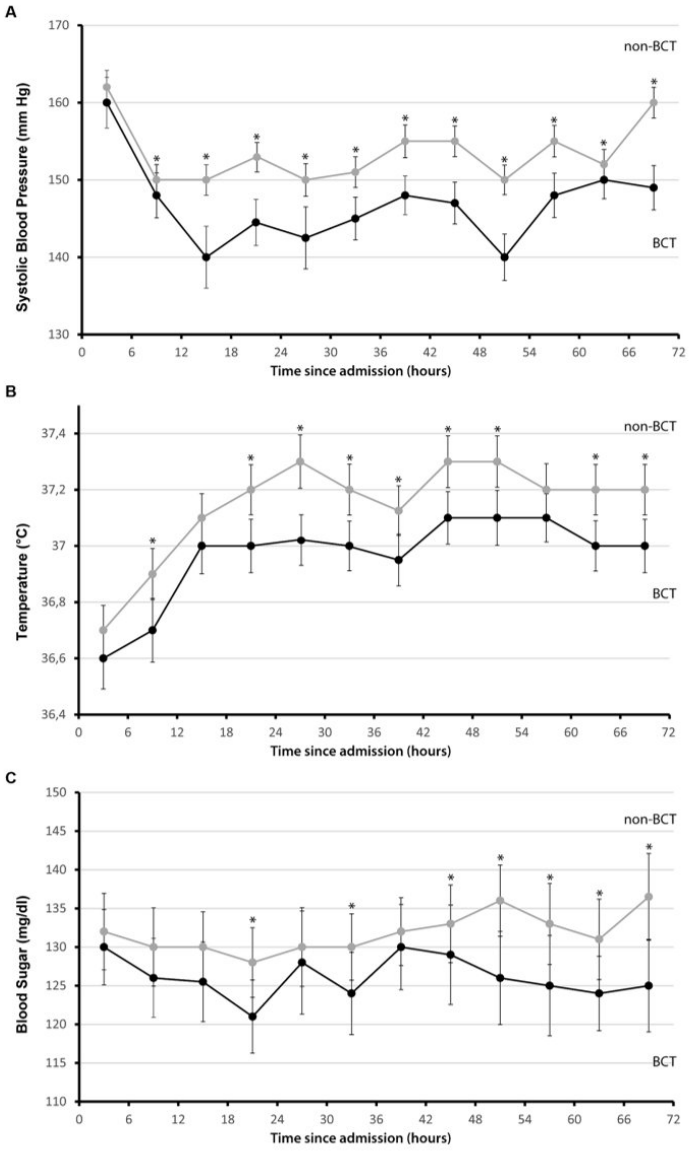

FIGURE 2
Systolic blood pressure, temperature, and glucose levels in 6-h intervals during the first 72 h mean values for **(A)** systolic blood pressure, mmHg, **(B)** temperature, °C, and **(C)** glucose levels, mg/dL measured in 6-h intervals since admission during the first 72 h separated for patients who fulfilled the bundle care treatment criteria (black) and for control patients (gray), maximum values were used. I bars indicated 95% confidence intervals. Asterisks mark significance $*p \leq 0.05$.

$p < 0.001$; temperature: mRS 0–3: ATE 10.9%, 95% CI (3.8 to 18.1), $p < 0.002$; mRS 6: ATE −10.4%, 95% CI (−17.5 to −3.3), $p < 0.001$]. Regarding the occurrence of hematoma enlargement, only systolic blood pressure showed a trend toward a treatment effect [ATE −6.9%, 95% CI (−14.0 to 0.2), $p = 0.06$]. Neither overall BCT, nor the separated components revealed a significant treatment effect on peak PHE.

TABLE 1 Baseline characteristics: comparison of BCT patients vs. non-BCT patients.

ICH patients (n = 681)	Non-BCT (n = 499)	BCT (n = 182)	Absolute difference (95% CI)	SMD
Age, mean (SD), years	69.7 (12.6)	69.0 (12.5)	−0.7 (−2.9 to 1.4)	−0.06
Female sex, no. (%)	212 (42.5%)	81 (44.5%)	2.0 (−6.4 to 10.4)	0.04
Pre-stroke mRS, median (IQR)	0 (0–2)	1 (0–2)	1 (0.6 to 1.4)	0.01
Medical history, no. (%)				
Hypertension	430 (86.2%)	168 (92.3%)	6.1 (1.2 to 11.1)	0.19
Diabetes mellitus	139 (27.9%)	46 (25.3%)	−2.6 (−10.0 to 4.9)	−0.06
Liver dysfunction	37 (7.4%)	14 (7.7%)	0.3 (−4.2 to 4.8)	0.01
Kidney dysfunction	73 (14.6%)	24 (13.2%)	−1.4 (−7.3 to 4.4)	−0.04
Hypercholesterolemia	199 (39.9%)	79 (43.4%)	3.5 (−4.9 to 11.9)	0.07
Coronary artery disease	113 (22.7%)	37 (20.3%)	−2.3 (−9.2 to 4.6)	−0.06
Prior stroke/TIA	98 (19.6%)	30 (16.5%)	−3.2 (−9.6 to 3.3)	−0.08
Prior oral anticoagulation	80 (16.0%)	33 (18.1%)	2.1 (−4.4 to 8.6)	0.06
Antiplatelet use	140 (28.1%)	51 (28.0%)	−0.0 (−7.7 to 7.6)	−0.00
Neurological status				
Glasgow Coma Scale[a], median (IQR)	13 (9–15)	13 (10–15)	0 (−0.8 to 0.8)	0.05
NIHSS[b], median (IQR)	13 (6–20)	13 (7–19)	0 (−2.0 to 2.0)	0.04
Max-ICH score[c], median (IQR)	4 (2–5)	4 (2–5)	0 (−0.7 to 0.7)	−0.07
Diagnostic imaging				
IVH, no. (%)	239 (47.9%)	68 (37.4%)	−10.5 (−18.8 to −2.3)	−0.21
Lobar ICH location, no. (%)	169 (33.9%)	76 (41.8%)	7.9 (−0.4 to 16.2)	0.16
Deep ICH location, no. (%)	259 (51.9%)	84 (46.2%)	−5.7 (−14.2 to 2.7)	−0.11
Infratentorial ICH location, no. (%)	68 (13.6%)	19 (10.4%)	−3.2 (−8.6 to 2.2)	−0.10
ICH volume, median (IQR), cm^3	13.5 (5.1–35.8)	15.8 (5.3–32.4)	2.4 (−2.1 to 6.8)	0.00
Follow-up imaging				
Hematoma enlargement[d], no. (%)	118 (23.7%)	45 (24.7%)	1.0 (−6.2 to 8.4)	0.03
Peak perihemorrhagic edema[e], median (IQR)	23.9 (9.7–48.1)	27.5 (9.8–49.8)	3.6 (−2.5 to 9.8)	0.07
Time windows				
Time onset to arrival, median (IQR), min	74 (28–224)	109 (46–208)	35 (−8.1 to 78.1)	0.09
Time first to second CT, median (IQR), h	21 (12–29)	20 (13–27)	−1 (−3.7 to 1.1)	−0.04
Inhospital measures				
EVD, no. (%)	178 (35.7%)	51 (28.0%)	−7.6 (−15.4 to 0.1)	−0.16
Surgical intervention, no (%)	40 (8.0%)	17 (9.3%)	1.3 (−3.5 to 5.1)	0.05
Ventilation, no (%)	231 (46.3%)	73 (40.1%)	−6.2 (−14.5 to 2.2)	−0.12
Ventilation duration, median (IQR), days	10 (3–21)	11 (3–19)	1 (−2.8 to 4.8)	−0.10

Absolute differences are presented in percent for frequency data and for scales or continuous variables as absolute differences according to the measurement unit (negative values indicate a decreased frequency or unit of measurement from the reference, that is, non-BCT). Standardized mean differences (SMDs) are presented to compare BCT patients vs. non-BCT patients. BCT, bundled care treatment; CI, confidence interval; EVD, extraventricular drainage; ICH, intracerebral hemorrhage; IQR, Interquartile range; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale, 0 no deficit to 6 death; no, number of patients; SD, standard deviation; SMD, standardized mean differences; TIA, transient ischemic attack.

[a]Glasgow Coma Scale (ranging from 3, comatose, to 15, alert).

[b]NIHSS, National Institutes of Health Stroke Scale (ranging from 0, no deficit, −40, severe neurological deficit; 40 is the maximum because in comatose ataxia is not scored).

[c]ICH score (ranging from 0 to 6, with higher scores indicating greater disability or fatal outcome (mRS 6) after ICH).

[d]Hematoma enlargement defined as an ICH volume increase of more than 33% (relative) or 6 mL from initial to follow-up imaging.

[e]Peak perihemorrhagic edema dichotomized according to median split (≥25 cm^3).

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TABLE 2 Baseline characteristics: comparison of patients who achieved the primary outcome (mRS 0–3) at 12 months vs. those who did not.

ICH patients (n = 681)	mRS 0–3 at 12 months (n = 288)	mRS 4–6 at 12 months (n = 393)	Absolute difference (95% CI)	SMD
Age, mean (SD), years	65.4 (12.5%)	72.5 (11.8%)	7.1 (5.2 to 8.9)	0.58
Female sex, no. (%)	119 (41.3%)	174 (44.3%)	3.0 (−4.6 to 10.5)	0.06
Pre-stroke mRS, median (IQR)	0 (0–1)	1 (0–2)	1 (0.8 to 1.2)	0.64
Medical history, no. (%)				
Hypertension	255 (88.5%)	343 (87.3%)	−1.3 (−6.2 to 3.7)	−0.04
Diabetes mellitus	83 (28.8%)	102 (26.0%)	−2.9 (−9.7 to 3.9)	−0.06
Liver dysfunction	18 (6.3%)	33 (8.4%)	2.1 (−1.8 to 6.0)	0.08
Kidney dysfunction	31 (10.8%)	66 (16.8%)	6.0 (0.9 to 11.2)	0.18
Hypercholesterolemia	140 (48.6%)	138 (35.1%)	−13.5 (−21.0 to −6.0)	−0.28
Coronary artery disease	57 (19.8%)	93 (23.7%)	3.9 (−2.4 to 10.1)	0.09
Prior stroke/TIA	38 (13.2%)	90 (22.9%)	9.7 (4.0 to 15.4)	0.25
Prior oral anticoagulation	35 (12.2%)	78 (19.9%)	7.7 (2.2 to 13.2)	0.21
Antiplatelet use	69 (24.0%)	122 (31.0%)	7.1 (0.4 to 13.8)	0.16
Neurological status				
Glasgow Coma Scale[a], median (IQR)	14 (12–15)	12 (6–14)	−2 (−2.7 to −1.3)	−0.67
NIHSS[b], median (IQR)	7 (4–14)	16 (10–25)	9 (7.6 to 10.4)	0.84
Max-ICH score[c], median (IQR)	2 (1–4)	5 (4–6)	3 (2.7 to 3.3)	1.32
Diagnostic imaging				
IVH, no. (%)	90 (31.3%)	217 (55.2%)	23.9 (16.7 to 31.2)	0.50
Lobar ICH location, no. (%)	105 (36.5%)	140 (35.6%)	−0.8 (−8.1 to 6.5)	−0.02
Deep ICH location, no. (%)	136 (47.2%)	207 (52.7%)	5.4 (−2.1 to 13.0)	0.11
Infratentorial ICH location, no. (%)	44 (15.3%)	43 (10.9%)	−4.3 (−9.5 to 0.8)	−0.13
ICH volume, median (IQR), cm^3	7.5 (2.3–17.9)	21.7 (8.6–45.1)	14.2 (10.5 to 17.8)	0.67
Follow-up imaging				
Hematoma enlargement[d], no (%)	51 (17.7%)	112 (28.5%)	10.8 (4.5 to 17.1)	−0.24
Peak perihemorrhagic edema[e], median (IQR)	14.8 (5.9–31.1)	34.6 (17.0–60.9)	19.9 (14.5 to 25.3)	0.64
Time windows				
Time onset to arrival, median (IQR), min	59 (30–181)	117 (29–247)	58 (22.1 to 93.6)	0.15
Time first to second CT, median (IQR), h	21 (14–33)	20 (12–27)	−1 (−3.6 to 0.6)	−0.22
Inhospital measures				
EVD, no. (%)	66 (22.9%)	163 (41.5%)	18.6 (11.7 to 25.4)	0.40
Surgical intervention, no (%)	21 (7.3%)	36 (9.2%)	1.8 (−2.3 to 6.0)	0.07
Ventilation, no (%)	78 (27.1%)	226 (57.5%)	30.4 (23.3 to 37.5)	0.64
Ventilation duration, median (IQR), days	8 (2–15)	11 (4–22)	3 (−0.9 to 6.9)	0.40

Absolute differences are presented in percent for frequency data and for scales or continuous variables as absolute differences according to the measurement unit (negative values indicate a decreased frequency or unit of measurement from the reference, that is, patients who achieved mRS 0–3). Standardized mean differences (SMD) are presented to compare patients who achieved the primary outcome vs those patients who did not.

CI, confidence interval; EVD, extraventricular drainage; ICH, intracerebral hemorrhage; IQR, Interquartile range; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale, 0 no deficit to 6 death; no, number of patients; SD, standard deviation; SMD, standardized mean differences; TIA, transient ischemic attack.

[a]Glasgow Coma Scale (ranging from 3, comatose, to 15, alert).

[b]NIHSS, National Institutes of Health Stroke Scale (ranging from 0, no deficit, −40, severe neurological deficit; 40 is the maximum because in comatose ataxia is not scored).

[c]ICH score (ranging from 0 to 6, with higher scores indicating greater disability or fatal outcome (mRS 6) after ICH).

[d]Hematoma enlargement defined as an ICH volume increase of more than 33% (relative) or 6 mL from initial to follow-up imaging.

[e]Peak perihemorrhagic edema dichotomized according to median split ($\geq$25 cm^3).

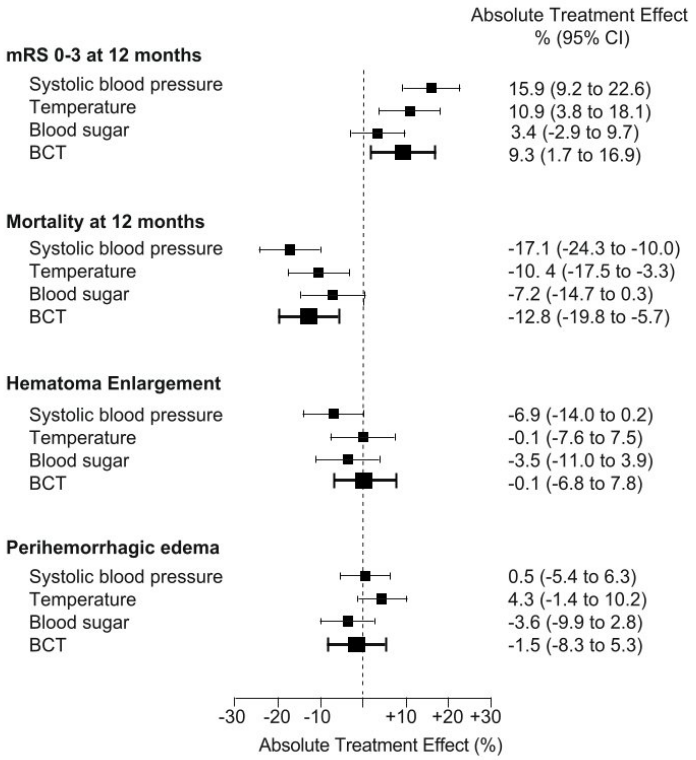

FIGURE 3
Associations of single BCT components to the absolute treatment effect. Results for the primary (modified Rankin Scale score 0–3 at 12 months) and secondary outcomes (mortality at 12 months), occurrence of hematoma enlargement, volume of peak perihemorrhagic edema, dichotomized according to median split (<25 cm^3) are shown as adjusted absolute treatment effects separated for each target parameter: systolic blood pressure, temperature, and blood sugar, as well as BCT effect for categorized outcomes (bold), $n = 681$. Abbreviations/scores: BCT: bundled care treatment; hematoma enlargement was defined as an ICH volume increase of more than 33% (relative) or 6 mL from initial to follow-up imaging; peak perihemorrhagic edema was defined as maximum perihemorrhagic edema volume measured during hospitalization and dichotomized according to the median split method.

Discussion

As key findings, we observed that a "care bundle" consisting of strict control of systolic blood pressure lowering, glucose levels, and normothermia over 72 h was related to improved functional long-term outcomes and survival in patients with intracerebral hemorrhage. Specifically, BCT showed larger treatment effects in younger but more severely affected ICH patients. Furthermore, we could identify that especially systolic blood pressure control and maintenance of normothermia contributed to the effectiveness of BCT. The questions arise, what may be the underlying mechanisms for this treatment effect of BCT and what is the contribution of each component to this overall effect?

Within analysis of the single components of BCT, we confirmed that lowering blood pressure contributed to a reduction of hematoma enlargement which consequently translated to improved functional outcomes. These results are, with respect to previous studies, not surprising (12, 26–28). Guidelines recommend a careful titration of blood pressure lowering to ensure continuous smooth and sustained control, avoiding peaks and large variability in SBP based on INTERACT-2 and Antihypertensive Treatment of Acute Cerebral Hemorrhage 2 (ATACH-2) for early intensive BP lowering (7, 8). It is important to note that blood pressure reduction also carries potential risks as highlighted by the ATACH-2 trial (8). Nevertheless, early treatment of blood pressure may reduce the risk of hematoma enlargement and improve functional outcomes which is supported by our analyses.

More interestingly, also maintenance of normothermia contributed to a significant improvement in functional outcomes which is controversially debated (5, 19, 29–31). Possible detrimental mechanisms of fever are hypothesized to contribute to the development of peak PHE (18, 31–33). In addition, in patients who develop hyperthermia, underlying infections may be present, which

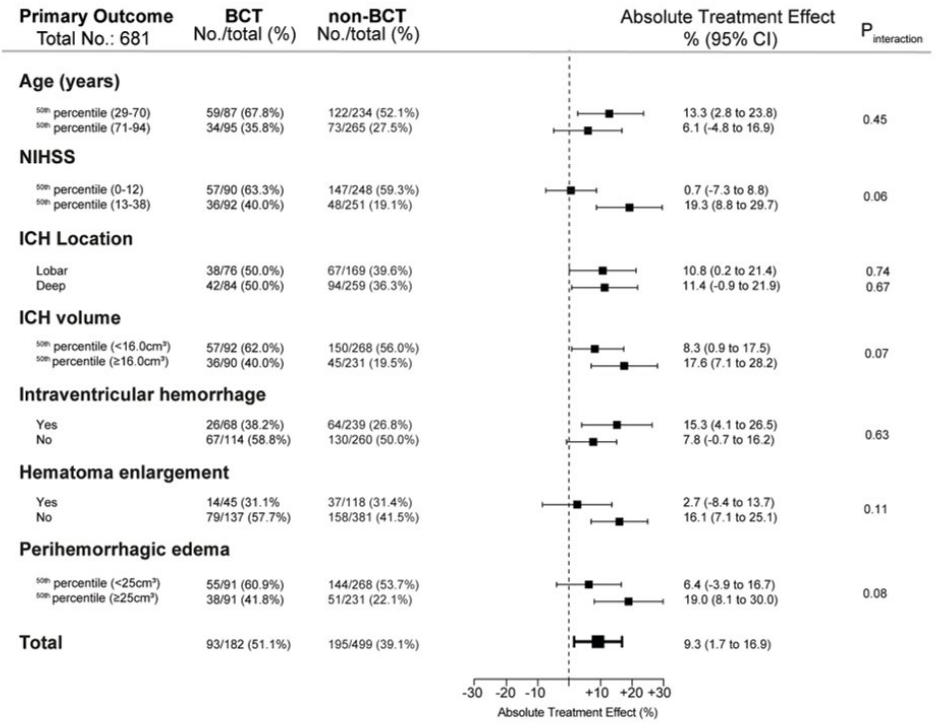

FIGURE 4
Exploratory subgroup analyses of the primary outcome. The results for the primary outcome (modified Rankin Scale score 0–3 at 12 months) are shown as crude frequency data and adjusted absolute treatment effects ($n = 681$). Interactions of exploratory subgroup analyses were analyzed by the subgroup-defining variable (variable×intervention) and were considered significant for $p < 0.05$. Abbreviations/scores: ICH: intracerebral hemorrhage; ICH volume was dichotomized according to median split (≥16.0 cm³). NIHSS, National Institutes of Health Stroke Scale. Hematoma enlargement defined as an ICH volume increase of more than 33% (relative) or 6 mL from initial to follow-up imaging; peak perihemorrhagic edema was defined as maximum perihemorrhagic edema volume measured during hospitalization and dichotomized according to the median split method (≥25.0cm³).

can negatively impact their outcomes. Nevertheless, we did not observe a statistically significant association with maintenance of normothermia and larger peak PHE, but we observed a statistical trend, ATE: 4.3 (−1.4 to 10.2) deserving further more in-depth investigations. Theoretically, this potential effect may vary over time, may be associated with the interventional time window (0–72 h), and may differ according to the time course of peak PHE development (34). Importantly, early PHE within 72 h has been reported as a predictor of peak PHE volume (31).

Targeted glucose management as the third part of our treatment bundle did not reveal any significant treatment effect. It is recommended that either hyperglycemia or hypoglycemia should be treated to prevent adverse events that may worsen outcomes (20, 21, 35–37). Previous studies do not indicate that strict targeted glucose management leads to improved outcomes in patients with ICH, which is also not supported by our results. In general, episodes with severe hypo- or hyperglycemia should be avoided during intensive care treatment, and randomized controlled data provided that severe hypoglycemic episodes were independently associated with increased mortality, yet without causal inference (6). From our data, we did not observe more frequent severe hypoglycemia episodes (<60 mg/dL) within the measured 72-h interval between both groups [2/182 (1%) BCT vs. 5/499 (1%) non-BCT; data not shown]. However, the extent to which strict implementation of specific glucose target values in the treatment of intracerebral hemorrhage affects clinical outcomes is still controversial.

Consequently, lowering blood pressure and managing temperature are substantial components of BCT to improve outcomes in intracerebral hemorrhage. Even if glucose management seems to have an inferior role, it is essential to prevent hypo- or hyperglycemia events to prevent adverse events.

However, the recently published cluster-randomized INTERACT3 trial revealed that implementing a novel care bundle protocol (early intensive blood pressure lowering, management algorithms for hyperglycemia, pyrexia, and abnormal anticoagulation) at hospitals without a prior standardized operating procedure improves functional outcome (11). The trial was undertaken mainly in low- and middle-income countries (contributing >99% of patients), and the authors

concluded that the incorporation of such a care bundle protocol resulted in improved functional outcomes and assumed that "the overall treatment effect seems to have been driven by intensive blood pressure lowering" (11). Importantly, the parameters of temperature and glucose management did not show significant inter-group differences, and therefore, the question of whether these parameters contribute to improved outcomes remains unanswered. Our study gives initial insights into the relevance of the individual bundle components and identifies blood pressure lowering and temperature management as drivers of this overall treatment effect. In addition, key outcome effectors such as hematoma enlargement and perihemorrhagic edema development including inflammatory processes seemed to be influenced and theoretically may be considered as mechanistically relevant to functional outcome. This assumption is supported by our observation that patients with more severe intracerebral hemorrhages (ICHs) and a higher incidence of intraventricular hemorrhage experienced a greater treatment effect.

Thereby, our study revealed that beneficial associations of BCT may exist when strictly controlled even in a hospital in Europe with existing SOPs executed at a dedicated neurological intensive care unit. INTERACT3 dominantly included patients with deep hypertensive ICH (88%), which was the effect-driving subgroup, as compared to data of this study with only 50% of patients with deep ICH. Hence, we provide data on the beneficial associations with strict BCT including all other ICH locations as non-trial selected real-world cohort.

Limitations of this study include low patient numbers in the BCT group, especially for exploratory analyses, and limitations inherent to the retrospective nature of this cohort study. In addition, data from this monocentric cohort may not be generalizable, and exact dosing and frequency of therapeutic medications were not part of this investigation. We cannot fully exclude that patients who stayed spontaneously within target ranges suffered less from major cerebrovascular and hemodynamic disruption as a consequence of the ICH. Therefore, we addressed confounding such as premorbid status, age, and ICH severity by robust statistical methodologies and sensitivity analyses. Furthermore, within the investigated time span (2005–2015), the guideline recommendation for systolic blood pressure lowering has changed following the publication of the INTERACT-II trial data (7). After 2013, this has been modified to a target systolic level of <140 mmHg at our institution. We did not observe bias over these differing treatment periods, that is, patients treated between 2013 and 2015 comprised 28% ($n = 191/681$) of the entire cohort, of which 25% ($n = 46/182$) were grouped into BCT compared to 29% ($n = 145/499$) grouped into non-BCT (data not shown). Potentially, we are missing stronger effects of more stringent blood pressure management due to the low proportion achieving less than 140 mmHg systolic according to current guideline recommendations. Bias due to confounding including also confounding by indication, residual bias, and unmeasured confounding cannot be fully ruled out but were addressed by robust statistical methodologies and sensitivity analyses.

Conclusion

Strict and consequent adherence to BCT consisting of systolic blood pressure lowering, treatment of pyrexia, and glucose management in patients with intracerebral hemorrhage was associated with improved functional outcomes at 12 months, specifically in younger patients with larger ICH volumes and larger edema volumes. Furthermore, we could identify that especially blood pressure lowering and treatment of pyrexia contributed to the beneficial associations of BCT whereas management of blood sugar seemed to have an inferior role. Future prospective studies are warranted to validate the effects of BCT and its components.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

The studies involving humans were approved by local ethics committee and institutional review boards based on the central votes from Friedrich-Alexander-University Erlangen-Nuremberg, Germany (Re.No-4409 & 30_16B, 115_17B: "Retrospective analysis of patients with intracerebral haemorrhage," approval date 20th June 2017). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AM: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Project administration, Validation. YS: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. VH: Data curation, Writing – review & editing. JS: Writing – review & editing. MS: Writing – review & editing. SH: Methodology, Writing – review & editing. SL: Methodology, Writing – review & editing. TE: Methodology, Writing – review & editing. BK: Writing – review & editing. BV: Methodology, Writing – review & editing. JK: Conceptualization, Project administration, Validation Writing – original draft, Writing – review & editing.

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Conflict of interest

AM reports personal fees from Alexion Pharma Germany GmbH, outside the submitted work. BV reports personal fees from Pfizer AG/ Bristol-Myers Squibb SA, personal fees from Bayer AG, grants from Institutional grant (Inselspital), personal fees from Ipsen Pharma, personal fees from CSL Behring, outside the submitted work. JK reports personal fees from Beohringer Ingelheim, personal fees from Biogen, personal fees from Boston Scientific, personal fees from

Sanofi, personal fees from Bayer AG, personal fees from Alexion, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1357815/full#supplementary-material

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Guideline-recommended basic parameter adherence in neurocritical care stroke patients: Observational multicenter individual participant data analysis

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Abstract

Introduction: Neurocritical care patients with neurovascular disease often face poor long-term outcomes, highlighting the pivotal role of evidence-based interventions. Although International Guidelines emphasize managing basic physiological parameters like temperature, blood glucose, blood pressure, and oxygen levels, physician adherence to these targets remains uncertain. This study aimed to assess adherence to guideline-based treatment targets for basic physiological parameters in neurocritical care.

Patients and Methods: This multicenter observational study was conducted across eight tertiary University Hospitals in Germany analyzed 474 patients requiring mechanical ventilation (between January 1st and December 31st, 2021). Adherence was defined as the rate of measurements within therapeutic ranges for systolic blood pressure (situation-adapted), mean blood pressure (MAP, 60–90 mmHg), glucose levels (80–180 mg/dl), body temperature (<37.5°C), partial arterial pressure of oxygen (PaO_2) 80–120 mmHg und partial arterial pressure of carbon dioxide ($PaCO_2$) 35–45 mmHg during the initial 96 h of hospitalization in 4 hour-intervals.

Results: Overall, 70.7% of all measurements were within the predetermined therapeutic ranges including SBP (71.3%), temperature (68.3%), MAP (71.4%), PaO_2 (65.2%), $PaCO_2$ (75.0%) and blood glucose (80.7%).

Discussion and Conclusion: This multicenter study demonstrates adherence to guideline-based treatment targets, underscoring the high standards maintained by neurological intensive care units. Our study offers valuable insights into

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adherence to guideline-based treatment targets for neurocritical care patients in Germany. To improve patient care and optimize therapeutic strategies in neurovascular diseases, further research is needed to examine the impact of these adherence parameters on long-term outcomes.

Keywords
NICU, bundle, adherence, ICH, AIS

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Introduction

Neurovascular disease patients in intensive care often face poor long-term outcomes due to factors like advanced age, comorbidities, and irreversible neuronal loss.[1,2] Given the scarcity of evidence-based treatments, it is crucial to prioritize interventions with strong evidence, such as decompressive surgery for acute ischemic stroke, reversal of anticoagulation in intracerebral hemorrhage, and early aneurysm closure in subarachnoid hemorrhage.[3–6] However, regardless of the disease type, managing "basic physiological parameters" such as temperature, glucose, blood pressure, and oxygen levels is fundamental in neurocritical care unit (NICU) treatment. Yet, evidence supporting adherence to recommended guidelines concerning long-term functional neurological outcomes in neurovascular neurocritical care patients is still lacking.[7–9]

Furthermore, there is currently growing interest in treatment bundles as evidence suggests that individual parameters alone may not suffice to significantly impact outcomes.[10] As currently demonstrated, the implementation of standard operating procedures (SOPs) to adhere to these basic parameters has been shown to improve outcomes for patients with intracerebral hemorrhage in low-income countries.[10] Yet, it is still uncertain (i) how stringently the recommended target values of basic parameters are adhered to in daily routine management and (ii) which factors are related to adherence.

Here, we performed a multicenter observational individual participant data analysis of patients with acute ischemic stroke (AIS), intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) treated at dedicated neurocritical care units in Germany. We aimed to (i) analyze the adherence to disease-specific guideline-recommendations for management of "basic NICU parameters" including systolic blood pressure (SBP), mean arterial blood pressure (MAP), temperature, blood glucose and blood oxygenation, including partial arterial pressure of oxygen (PaO_2) and partial arterial pressure of carbon dioxide ($PaCO_2$) and (ii) to evaluate factors associated with parameter-adherence.

Methods

Study design and population

We performed a retrospective observational multicenter study of neurointensive care patients requiring mechanical ventilation treated at eight dedicated neurocritical care units of tertiary University Hospitals in Germany. The study was approved by the institutional review boards and local ethics committees of all participating sites based on the central vote from Giessen University (AZ 177122). Data collection covered the period from 1st January until 31th December, 2021. Patients with the following inclusion criteria were enrolled: (i) age > 18 years; (ii) acute neurovascular disease, i.e. cerebral ischemia, intracerebral hemorrhage or subarachnoid hemorrhage (International Classification of diseases version 10, ICD10, i.e., 160.x, 161.x, I62.x, 163.x), (iii) neurocritical care admission due to intubation and controlled ventilation, and (iv) a hospital stay on NICU of a minimum of 4 days. Patients who received initial do-not-treat/do-not-resuscitate (DNT/DNR) orders as well as those who deceased within 24 h after admission were not enrolled. A priori we excluded all patients with missing data documentation (>33% missing data) or availability of the 4-hour measures during the first 96 h of treatment.

Clinical parameters

All obtained clinical parameters were extracted from institutional databases. These parameters were determined upon admission and every 4 h for the first 96 h of intensive care treatment. We assessed baseline demographic parameters (age, gender) as well as type of neurovascular disease including clinical parameters upon admission and pre-existing disability (measured using the modified Rankin Scale, mRS).[11] Specifically, we focused on the following parameters measures within 4 h intervals: (i) blood pressure, including systolic (SBP) and mean arterial blood pressure (MAP), (ii) temperature as obtained via bladder catheters, (iii) blood glucose, and (iv) blood oxygenation, including partial arterial pressure of oxygen (PaO_2) and partial arterial pressure of carbon dioxide ($PaCO_2$). Associated parameters consisted of duration of ventilation, duration of hospital stay, National Institute of Health Stroke Scale (NIHSS) score at discharge and in-hospital mortality and thrombolysis in cerebral infarction scale (TICI).[12–15] Patient parameters were anonymized upon entry into the pooled individual participant data sheet.

Outcomes

The primary endpoint was adherence to the guideline-based treatment-target recommendations, measured as

the rate of parameters within recommended ranges divided by all measurements of the respective parameter, i.e. as percentage. Specifically, for patients with cerebral ischemia, we adhered to the guidelines established by the German Society of Neurology, targeting a systolic blood pressure (SBP) range of 120–180 mmHg.[16] Following the recommendations of the European Stroke Organization (ESO) for acute ischemic stroke management, after successful thrombectomy (TICI 3), our SBP target range was adjusted to 110–160 mmHg.[17] In cases where acute reperfusion treatment was not implemented or was unsuccessful, SBP values exceeding 180 mmHg within the first 24 h were deemed acceptable. Additionally, the initial SBP measurement post-admission was considered "non-adherent" if it exhibited a reduction of >25% compared to the admission SBP.[17] Furthermore, our protocol included maintaining mean arterial pressure (MAP) between 60 and 90 mmHg, controlling temperature (<37.5°C), managing blood glucose levels (80–180 mg/dl), and ensuring arterial oxygen partial pressure (PaO_2) between 80 and 120 mmHg and carbon dioxide partial pressure ($PaCO_2$) between 35 and 45 mmHg.[16,18] For hemorrhagic stroke patients, our targeted parameters are: SBP (ICH: 110–140 mmHg; SAH: 110–180 mmHg), MAP (60–90 mmHg), temperature (<37.5°C), blood glucose (80–180 mg/dl) SAB,[7,10,17,19–21] as well as blood gases PaO_2 (80–120 mmHg) and $PaCO_2$ (35–45 mmHg) according to the recommendations of the European Society of Intensive Care Medicine.[18] Additionally, the initial SBP measurement post-admission was considered "non-adherent" if it exhibited a reduction of >90 mmHg compared to the admission SBP.[17]

Statistics

All statistical analyses were conducted using the SPSS software package version 29 (www.spss.com). The level of significance was set at alpha = 0.05. Continuously monitored data, including SBP measured via arterial lines, MAP, and temperature were recorded as discrete values at least once within each respective 4-hour interval. Discontinuously collected data, such as blood gas analyses and blood glucose measurements, were assigned to the nearest corresponding 4-hour time point. Data were presented as median and interquartile ranges as well as total counts with percentage. Adherence was measured as the rate of parameters within recommended ranges divided by all measurements of the respective parameter, that is, as percentage. To investigate patient characteristics associated with parameter adherence, we used multivariate regression analysis, adjusting for NIHSS, age, and sex with adherence as a median split binary variable.[22,23] To compare the respective center-specific adherence rates, we used a one-way ANOVA.

Results

Study population

Between January 1, 2021, and December 31, 2021, a comprehensive analysis was conducted on a total of 474 patients diagnosed with ischemic and hemorrhagic stroke across eight participating centers (Figure 1). Demographic and clinical characteristics of the study population are summarized in Table 1. The mean age of the cohort was 68.3 (SD 13.8) years, with 42.2% (200/474) being female. Upon admission, patients presented with a median NIHSS score of 19, and a significant portion (69.6% (330/474)) required preclinical intubation. Ischemic stroke was the predominant diagnosis, accounting for 69.8% (331/474) of cases, while hemorrhagic stroke constituted 30.2% (143/474), with intracerebral hemorrhage being the most prevalent subtype (24.1% or 114/474). In terms of interventions, intravenous thrombolysis was performed in 30.2% (100/331) of ischemic stroke cases, while 67.1% (223/331) underwent endovascular therapy. Among hemorrhagic stroke patients, external ventricular drains were utilized in 63.6% (91/143) of cases, and surgical hematoma evacuation was performed in 23.1% (33/143). Regarding outcomes, the median NIHSS score at discharge was 18. The in-hospital-mortality rate was 42.4% (201/474). All patients included in this study were mechanically ventilated during the observation period of 96 h. The median duration of ventilation was 235 h (IQR 137–378). We graphically displayed initial and subsequent measurements (median, interquartile range) over 96 h for SBP, MAP, temperature, blood glucose, PaO_2 and $PaCO_2$ (Figure 2, Supplemental Figure 1) within 4-hours intervals. With exception of initial median arterial PaO_2 (PaO_2 value, 123 mmHg (IQR, 89–173 mmHg)) the median values for all other parameters fall within their respective predefined target range (shaded in grey, Figure 2, Supplemental Figure 1). The interquartile range reveal variability, with outliers in ischemic stroke mostly falling within the lower blood pressure range and in hemorrhagic stroke in the upper range. For temperature, outliers are mainly in the upper range. In arterial blood gas measurements, $PaCO_2$ outliers appear both above and below the target range, with initial PaO_2 measurements trending towards hyperoxemia.

Adherence patterns to guideline-based treatment targets

We assessed adherence to guideline-based treatment-target recommendations within 4-hour intervals for key physiological parameters. Overall, 70.7% of all measurements were within the predetermined therapeutic ranges. Our findings indicate that out of 474 patients, 1 (0.2%) had adherence levels between 30% and 39%, 12 (2.5%) between

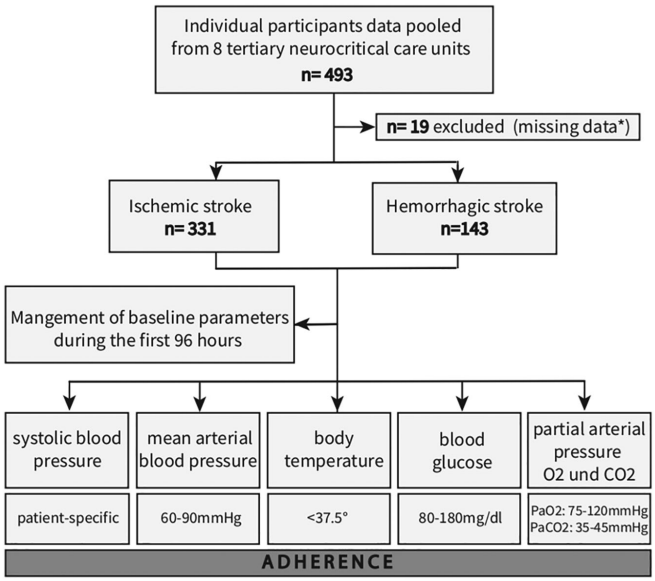

Figure 1. Flow chart of study participants.
A total of 493 neurocritical care patients from eight tertiary University Hospitals in Germany were investigated during the period from January 1st to December 31st, 2021. Nineteen patients were excluded because of missing data. Among the 474 patients remaining, 331 were diagnosed with ischemic stroke, while 143 had hemorrhagic stroke. Clinical parameters, including systolic blood pressure, mean arterial blood pressure, body temperature, blood glucose levels, and partial arterial pressure of oxygen and carbon dioxide, were recorded upon admission and every 4 h for the initial 96 h of intensive care treatment.
*Missing data consisted of: missing data documentation (>33% missing data) or availability of the 4-hour measures during the first 96 h of treatment.

40% and 49%, 46 (9.7%) between 50% and 59%, 132 (27.8%) between 60% and 69%, 217 (45.8%) between 70% and 79%, 64 (13.5%) between 80% and 89%, and 2 (0.4%) had adherence levels of 90% and 99%.

Table 2 and Figure 3 provide a comprehensive daily and 4 hour-interval analysis of adherence rates to guideline-based treatment targets over the initial 96 h of intensive care treatment. Our findings showed dynamic temporal adherence patterns across different parameters, with fluctuations observed during the first four days of treatment.

Adherence to SBP, MAP, blood glucose levels, PaO_2, and $PaCO_2$ generally improved from admission to the first day, indicating effective initial adjustments in treatment strategies. In contrast, adherence to temperature was notably high upon admission at 91.6%, but declined to 73.2% by day 1 and further to 64.0% by day 4. Overall, blood glucose levels consistently exhibited the highest adherence rates, followed by $PaCO_2$ and SBP. Initial adherence to PaO_2 was low, primarily due to hyperoxygenation with levels exceeding 120 mmHg.

Adherence associated parameters

Factors associated with high adherence to guideline-based treatment targets for physiological parameters in neurocritical care were comprehensively investigated using multivariate regression analysis. Among AIS and AHS we found no association regarding age, sex, NIHSS, pre-mRS, stroke subtype or TICI. The center-specific adherence rates ranged between 62.8% and 78.1% with significant difference between centers ($F = 15.49$, $p < 0.05$), see Supplemental Figure 2.

Discussion

This study represents the first comprehensive investigation of adherence to guideline-based treatment targets for neurocritical care patients with neurovascular disease in Germany, encompassing a broad representation of tertiary care centers. Our key findings reveal: (i) neurological intensive care units maintain high standards, yet there is

Table 1. Baseline characteristics and outcome parameters of the overall cohort.

	Cohort ($n = 474$)
Baseline characteristics	
Age,[a] years	68.3 (13.8)
Sex,[b] female	200 (42.2)
Admission status	
NIHSS at admission (0–42)[c]	19 (12–30)
Pre-mRS[c]	0 (0–2)
Prehospital intubation[b]	330 (69.6)
Diagnosis	
Ischemic stroke[b]	331 (69.8)
Hemorrhagic stroke[b]	143 (30.2)
ICH[b]	114 (24.1)
SAH[b]	29 (6.1)
Disease specific interventions	
EVT (Ischemic stroke)[b]	223/331 (67.1)
IVT (Ischemic stroke)[b]	100/331 (30.2)
Decompressive craniectomy (Ischemic stroke)[b]	11/331 (3.2)
Surgical hematoma evacuation (Hemorrhagic stroke)[b]	33/143 (23.1)
Coiling (Hemorrhagic stroke)[b]	22/143 (15.4)
Clipping (Hemorrhagic stroke)[b]	6/143 (3.5)
EVD (Hemorrhagic stroke)[b]	91/143 (63.6)
Lumbar drain (Hemorrhagic stroke)[b]	30/143 (21.0)
Outcome parameter	
NIHSS at discharge[c]	18 (9–25)
In-hospital mortality[b]	201 (42.4)
Duration of ventilation (h)[c]	234.5 (136.5–378)

EVD: external ventricular drain; EVT: endovascular therapy; IVT: intravenous thrombolysis; ICH: intracerebral haemorrhage; IQR: interquartile range; mRS: modified Rankin scale (0 no deficit to 6 death); NIHSS: National Institutes of Health Stroke Scale (ranging from 0, no deficit, –40, severe neurological deficit; 40 is the maximum because in comatose ataxia is not scored), applied for patients with ischemisch stroke and intracerebral haemorrhage; SAH: subarachnoidal haemorrhage.
[a]Mean ± SD.
[b]*n* (%).
[c]Median (interquartile range: 25th–75th percentile).

room for improvement; and (ii) adhering to strict temperature targets remains a significant challenge. While all other parameters rather improved in regard to their respective recommended thresholds during course of disease, temperature was the only parameter with decreasing adherence over time. Two aspects emerge from the data.

First, the adherence to certain thresholds in neurointensive care has been recommended for decades.[24–31] While this was initially based on pathophysiological considerations, several subsequent studies have provided varying levels of robust evidence supporting the recommended guidelines.[32–34] Nonetheless, the rationale for adhering to these recommended thresholds was also based on non-clinical outcomes, such as surrogate measures like cerebrovascular autoregulation, intracranial pressure, edema formation, and similar parameters.[35–39] Although, strictly speaking, evidence for adhering to the recommended guidelines with respect to long-term functional neurological outcome of neurovascular neurocritical care patients is still lacking, it is however highly likely that patients should benefit if adherence levels are rather high. Hence, our findings add knowledge to the field, as we here provide a first comprehensive analysis of the current situation across dedicated neurointensive care units in Germany. In essence, adherence levels appear acceptable, but need improvement. The latter seem achievable through interventions such as the establishment and implementation of straightforward Standard Operating Procedures (SOPs). As demonstrated in prior studies,[40] these might help further improve and increase average adherence levels. Furthermore, it should be noted that the evidence levels for different parameters vary, which should be considered when interpreting adherence in this study. While evidence on blood pressure management within the initial 24 h is robust, particularly for patients receiving reperfusion therapy for acute ischemic stroke and those with intracerebral hemorrhage (ICH), evidence for other parameters like temperature management or oxygenation targets varies and is often weak.[17,41] Notably, the INTERACT 3 trial serves as the pioneering randomized controlled trial (RCT) in patients with intracerebral hemorrhage (ICH) to unveil the advantages of a "bundle care" intervention.[10] However, it is noteworthy that this trial was conducted in low- and middle-income countries, thereby potentially limiting its applicability to high-income countries where adherence to standardized treatment protocols is more prevalent. The subsequent INTERACT 4 trial further contributes to this field by investigating the effects of prehospital blood-pressure reduction, which did not improve functional outcomes in a cohort of patients with undifferentiated acute stroke.[42] Our analysis of center-specific effects at established tertiary care centers in Germany, with adherence rates ranging from 62.8% to 78.1%, reveals certain differences in daily routine, most likely because of diverging SOPs. Hence, establishing strict protocols with teaching of the nursing and physician teams regarding monitor alarms and seem to indeed hold promise in enhancing overall adherence. Nevertheless, the value of adherence necessitates further enhancement and assessment in terms of its impact on relevant long-term functional clinical endpoints.

Second, interestingly variations in adherence were observed across different parameters. Parameters such as blood glucose and $PaCO_2$ levels demonstrated acceptable adherence, while blood pressure (both SBP and MAP) showed improvement over time but still require further enhancement. Temperature management emerged as a critical concern, as the initial measurement indicated mild hypothermia, yet adherence to this target declined which has been shown to have adverse effects.[41,43–46] The strong correlation between brain damage and fever increases

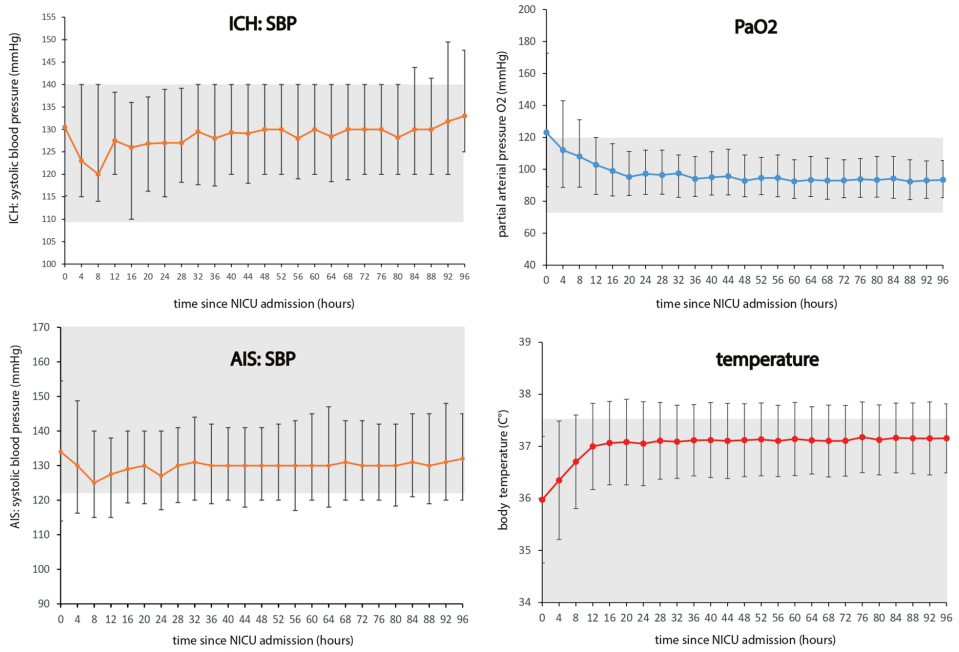

Figure 2. Median values of basic clinical parameters in 4-hours intervals during the first 96 h.
AIS: acute ischemic stroke; ICH: intracerebral hemorrhage; PaO_2: partial arterial pressure of oxygen; SBP: systolic blood pressure; NICU: neurointensive care unit.
Median values (IQR) for systolic blood pressure, mmHg separated for intracerebral hemorrhage and acute ischemic stroke, partial pressure of oxygen, mmHg and temperature, °C measured in 4-hours intervals since admission during the first 96 h.

Table 2. Adherence of NICU parameters from admission to day 4.

	Systolic blood pressure (%)	Mean arterial blood pressure (%)	Body temperature (%)	Glucose levels (%)	Partial arterial pressure O_2 (%)	Partial arterial pressure CO_2 (%)
Admission	58.7	50.6	91.6	74.4	30.6	58.2
Day 1	69.4	75.5	73.2	79.2	59.6	75.7
Day 2	72.6	73.7	66.0	82.2	68.7	76.1
Day 3	72.6	70.5	66.0	81.2	69.6	77.3
Day 4	72.8	69.3	64.0	81.0	68.9	77.5
Overall	71.3	71.4	68.3	80.7	65.2	75.0

Adherence to basic parameters is presented daily and cumulatively over a 96-hour period. Adherence is determined as the percentage (%) of measurements within the guideline-recommended range relative to the total measurements assessed upon admission, on a daily basis and overall.

notably within the first 24 h, potentially contributing to lower adherence observed, indicative that management may be inadequate when fever occurs.[43] One possible reason for the low level of adherence rates could be hesitancy due to the relatively high costs of devices, along with the need for deeper sedation to achieve the target of normothermia. Additionally, the lack of robust efficacy data, particularly in the context of ischemic stroke, may also contribute to the low adherence rates.

Furthermore, initial oxygenation performance was found to be the poorest, with only 30.6% adherence at admission. However, this is primarily due to excessive oxygen administration, which is known to be detrimental due to the production of free radicals, among other factors.[47]

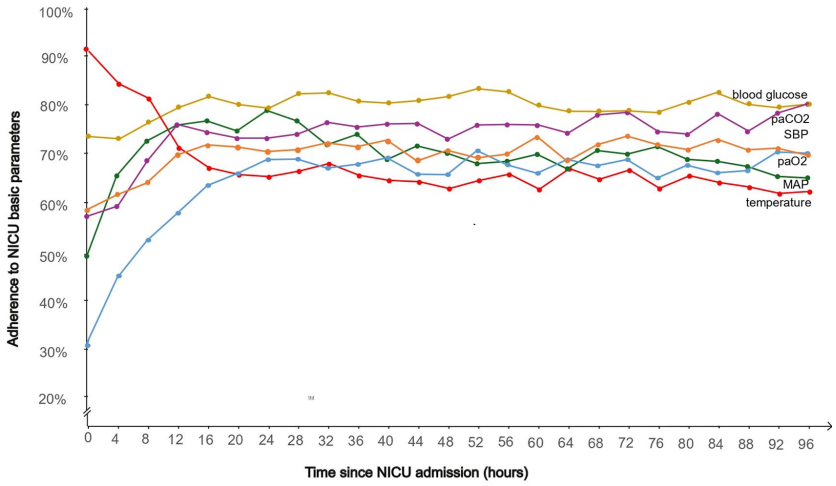

Figure 3. Adherence to guideline-based treatment targets in 4-hours intervals during the first 96 h of NICU.
SBP: systolic blood pressure; MAP: mean arterial pressure; PaO_2: partial arterial pressure of oxygen; $PaCO_2$: partial arterial pressure of carbon dioxide; NICU: neurointensive care unit.
Adherence to guideline-based treatment targets, that is, SPB, MAP, temperature, blood glucose, $PaCO_2$ and PaO_2 in 4-hours intervals during the first 96 h of neurocritical care treatment. Adherence is determined as the percentage (%) of measurements within the guideline-recommended range relative to the total measurements assessed within 4-hours intervals.

Therefore, simply aiming for oxygen levels above 80 mmHg is insufficient, as it often leads to excessively high values. Addressing this issue requires interventions to prevent hyperoxia and optimize oxygen therapy strategies.

While these data were collected from multiple centers, a limitation of the study is the small sample size for exploratory analyses and the inherent limitations associated with the retrospective nature of this cohort study. Additionally, the study design did not allow for a time-based assessment of adherence. Ideally, adherence would be defined as making a correction within a specific time interval after detecting a pathological value, an approach that should be addressed in future prospective studies. Furthermore, dosages and frequencies of therapeutic medications were not included in the investigations. Bias due to confounding cannot be fully ruled out. Another limitation is the lack of time-related data, such as time from symptom onset to admission, real-time variability of parameters and short-term drops of blood pressure or partial arterial oxygen pressure which was not recorded.[48] Additionally, critical aspects for preventing secondary brain injury, such as intracranial pressure monitoring, optimal timing for extubation decisions, and management strategies tailored to specific stroke subtypes, are not addressed in this study. While we focused on patient-specific characteristics that can influence adherence, there are many other factors, such as implementation strategies, clinical guidelines, and the broader environmental context, which future studies should explore in greater detail through prospective research. Furthermore, the study did not examine the impact of adherence on potential clinical outcomes, which should be addressed in future intervention studies, particularly in context of individualized therapy tailored on stroke subtype, etiology, and other relevant factors.[49] However, despite these limitations, the study effectively addresses the straightforward question of adherence, fulfilling the intention of the study.

In conclusion, our study provides valuable insights into adherence to guideline-based treatment targets for neurocritical care patients in Germany. Variations in adherence across parameters underscore the need for tailored interventions, particularly in temperature management and oxygen therapy strategies.

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Ethical approval

The study was approved by the Ethics Committee of the Medical University of the Justus-Liebig-University Giessen, Germany (No. AZ 177122).

Informed consent

Written informed consent was not necessary due to the retrospective and anonymous analyses and publication.

Guarantor

PS

Contributorship

Patrick Schramm, Hagen Huttner contributed to the study conception and design. Material preparation, data collection and analysis were performed by Omar Alhaj Omar, Angelika Alonso, Min Chen, Christian Claudi, Norma J Diel, Friedrich Erdlenbruch, Stefan Gerner, Benedikt Hiller, Benjamin Knier, Dominik Lehrieder, Hendrik Lesch, Dominik Michalski, Anne Mrochen, Hermann Neugebauer, Johann Pelz, Hauke Schneider, Silvia Schönenberger, Corinna Ringmaier, Henning Stetefeld, Andreas Totzeck and André Worm. Statistical analysis was performed by Anne Mrochen and Omar Alhaj Omar. The first draft of the manuscript was written by Anne Mrochen, Hagen Huttner and Omar Alhaj Omar. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Supplemental material

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Original Investigation | Neurology

Disability-Adjusted Life-Years Associated With Intracerebral Hemorrhage and Secondary Injury

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Abstract

IMPORTANCE Intracerebral hemorrhage (ICH) contributes significantly to the global burden of disease.

OBJECTIVE To examine the association of ICH and secondary injury with disability-adjusted life-years (DALYs) for the individual patient.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was conducted using data from the Universitätsklinikum Erlangen Cohort of Patients With Spontaneous Intracerebral Hemorrhage study. Consecutive patients admitted to a single tertiary care center from January 1, 2006, to December 31, 2015, were included. The sample comprised patients with oral anticoagulation–associated ICH (OAC-ICH) or primary spontaneous ICH (non-OAC-ICH). Statistical analysis was conducted from October 1 to December 31, 2020.

EXPOSURES ICH occurrence and secondary injury.

MAIN OUTCOMES AND MEASURES DALYs, years of life lost (YLL), and years lived with disability (YLD) were analyzed by hematoma location, ICH volume, and secondary injury (ie, hematoma expansion [HE], intraventricular hemorrhage [IVH], and perihemorrhagic edema [PHE]).

RESULTS Among 1322 patients with ICH, 615 (46.5%) were women and the mean (SD) age at hospital admission was 71 (13) years; ICH was associated with a mean (SD) of 9.46 (8.08) DALYs, 5.72 (8.29) YLL, and 3.74 (5.95) YLD. There were statistically significant differences in mean (SD) DALYs by extent of hematoma volume (< 10 mL ICH: 7.05 [6.79] DALYs; 10-30 mL ICH: 9.91 [8.35] DALYs; >30 mL ICH: 12.42 [8.47] DALYs; $P < .001$) and ICH location (deep location: 10.60 [8.35] DALYs; lobar location: 8.18 [7.63] DALYs; cerebellum: 8.14 [6.80] DALYs; brainstem: 12.63 [9.21] DALYs; $P < .001$). Regarding population-level disease burden of secondary injuries after ICH, there was a statistically significant difference in mean (SD) by injury type, with 0.94 (3.19) DALYs for HE, 2.45 (4.16) DALYs for IVH, and 1.96 (2.66) DALYs for PHE ($P < .001$) among the entire ICH cohort. Regarding individual-level exposure to secondary injuries after ICH, there were a mean (SD) 7.14 (6.62) DALYs for HE, 4.58 (4.75) DALYs for IVH, and 3.35 (3.28) DALYs for PHE among patients with ICH affected by secondary injuries.

CONCLUSIONS AND RELEVANCE These findings suggest that there is a high burden of disability associated with ICH and secondary injuries, and the findings may guide public health strategies. The study findings further suggest that IVH and PHE may be relevant for the overall outcome of patients with ICH, that DALYs may represent a viable outcome parameter for studies to evaluate treatment outcomes in ICH research, and that IVH and PHE may represent potential treatment targets.

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Key Points

Question What is the burden of intracerebral hemorrhage and secondary injury?

Findings In this cohort study of 1322 patients with intracerebral hemorrhage, the condition was associated with 9.46 disability-adjusted life-years, while perihemorrhagic edema and intraventricular hemorrhage were associated with increased disability compared with hematoma expansion in the overall cohort.

Meaning These findings suggest that intracerebral hemorrhage is associated with a high burden of disability, and these findings may guide public health strategies.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

The global burden of diseases is quantified at regular intervals using disability-adjusted life-years (DALYs).[1] These are defined as the combination of years of life lost (YLL) owing to premature mortality and years lived with disability (YLD).[1] Intracerebral hemorrhage (ICH) contributes significantly to the global burden of disease.[2,3] However, the association of a single ICH event with DALYs for the individual patient has not been specified so far.

Several randomized controlled trials[4-7] evaluated treatment options targeting secondary injury after ICH, such as hematoma expansion (HE), intraventricular hemorrhage (IVH), and perihemorrhagic edema (PHE). However, to our knowledge, these secondary injuries have never been compared against each other regarding their association with clinical outcomes. Therefore, it is still uncertain which parameter should be the primary treatment target in ICH research.

Functional outcome, quantified by the modified Rankin Scale (mRS), is usually defined as the primary end point in ICH studies.[4-7] So far, to our knowledge, no single randomized trial has reported a significant treatment association measured by the mRS among patients with ICH.[8] Given the disease severity and its enormous health care and economic implications, additional outcome parameters seem justified to identify and improve treatment options and decrease the burden of ICH disease. As a measure of disease burden, DALYs represent an obvious choice as alternative outcome parameter in ICH research. The purpose of the present study was to assess the association of ICH occurrence, hematoma location, and ICH volume with DALYs and to compare the association of secondary injury with DALYs by hematoma expansion, IVH, and PHE, thereby identifying the most relevant future treatment targets.

Methods

Written informed consent for this cohort study was obtained from patients or legal representatives, and the study was approved by the local institutional review board at Friedrich-Alexander-University Erlangen-Nuremberg in Germany (115_17B). The study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Detailed methods of the Universitätsklinikum Erlangen Cohort of Patients With Spontaneous Intracerebral Hemorrhage (UKER-ICH; NCT03183167) cohort study have been published previously.[9,10] In brief, consecutive patients with ICH admitted to the University Hospital Erlangen from January 1, 2006, to December 31, 2015, were included in a prospective, single-center institutional registry. Patients with ICH owing to secondary etiology, such as aneurysm, intratumoral hemorrhage, trauma, or arteriovenous malformation, were excluded. Analyses were conducted among patients with oral anticoagulation–associated ICH (OAC-ICH) and primary spontaneous ICH (non-OAC-ICH). Data on demographic characteristics, premorbid conditions, status at hospital admission, and laboratory and intrahospital parameters were assessed as previously published.[9,11] High burden of cardiovascular disease was defined as history of ischemic stroke or transient ischemic attack (TIA) and congestive heart failure. Low burden of cardiovascular disease was defined as history of ischemic stroke or TIA, history of congestive heart failure, or none of these.

Imaging

Hematoma characteristics and PHE were assessed on each imaging slice of all available imaging scans during patient hospital stays.[9,12] We calculated PHE using a semiautomatic volumetric algorithm and defined PHE as the maximum edema volume among available imaging scans.[13,14] Relative PHE was defined as the ratio of peak PHE volume to ICH surface area (calculated via the formula: ICH surface area = $\pi^{1/3} \times [6 \times \text{ICH volume}]^{2/3}$).[12,15] We calculated ICH volume using the ABC/2 method (A [greater hemorrhage diameter in the axial plane] times B [hemorrhage diameter at 90° to A in the axial plane] times C [number of computed tomography slices with hemorrhage], divided by 2) in case of round to ellipsoid ICH or ABC/3 method in case of irregularly shaped ICH.[16,17] Hematoma enlargement was

defined as a relative increase of more than 33% in ICH volume from initial imaging to follow-up imaging. Patients were divided into 3 groups by hematoma volume (ie, small ICH: <10 mL; medium ICH: 10-30 mL; and large ICH: >30 mL). The extent of IVH was assessed using the Graeb score; primary IVH was scored as deep ICH.[18]

Outcome Measures

We calculated DALYs for each patient with ICH as the sum of YLL owing to premature mortality and YLD as the consequence of ICH impairment according to the current World Health Organization classification (**Figure**).[1] We defined YLL as the difference between the patient's age-specific life expectancy and age at death and YLD as the number of years lived with disability multiplied by a disability-weighting factor. Specific weighting factors for each degree of the mRS have been previously published and were used in this study (eTable 1 in the Supplement).[19] For the UKER-ICH study, YLL and YLD were calculated using follow-up information on functional outcome and survival time. To perform accurate DALY assessment, YLD were specifically calculated for duration of hospital stay, from hospital discharge to 3 months after ICH diagnosis, from 3 months to 12 months after ICH diagnosis, and from 12 months after ICH diagnosis to death. The most recent functional status was applied for each time interval. In line with established methodology,[20] the calculation did not include premorbid status, age-weighting, or future discount.

Additionally, YLL and YLD were assessed for the UKER-ICH study based on follow-up at 3 months and life expectancies derived from Federal Statistical Office of Germany data using calculation models (eMethods and eTable 2 in the Supplement).[19,21-23] To investigate whether these previously published calculation models provided accurate DALY assessment, they were compared with the calculated values based on all available follow-up information (eMethods and eFigure 1 in the Supplement).

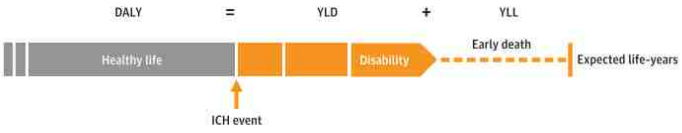
Data on functional outcome and mortality in the UKER-ICH study were assessed during hospital stay. These were evaluated by standardized mailed questionnaires or semistructured telephone interviews at 3 months and 12 months after the ICH event or retrieved from institutional databases in case of hospital readmission.[11,24]

Statistical Analysis

Statistical analyses were performed using SPSS statistical software version 24.0 (IBM) from October 1 to December 31, 2020. We used 2-sided statistical tests and set the significance level to $P = .05$. Frequency distribution was determined using the Kolmogorov-Smirnov test. Categorical variables were compared using the χ^2 test or Fisher exact test for proportions and given as total number and frequency in brackets. Continuous variables were compared using analysis of variance or Kurskal-Wallace test, respectively, and given as mean (SD).

For the calculation of YLL, YLD, and DALYs associated with secondary injury (attributable YLL [aYLL], attributable YLD [aYLD], and attributable DALYs [aDALYs] for extent of HE, IVH, and PHE), we multiplied attributable fractions by the overall YLL and YLD, respectively, for each secondary injury parameter. Attributable fractions were adjusted for relevant parameters associated with clinical outcomes after ICH (ie, age, National Institutes of Health Stroke Scale score, hematoma location, ICH volume, and secondary injury parameters [ie, HE volume, IVH extent, and PHE

Figure. Disability-Adjusted Life-Years (DALYs) After Intracerebral Hemorrhage (ICH)



Concept and calculation of years of life lost (YLL), years lived with disability (YLD), and DALYs are illustrated for patients with ICH. DALYs are defined as the sum of YLD and YLL owing to premature mortality as a result of the ICH event.

volume]).[25] Mortality at 3 months after ICH was used for aYLL estimation, and good functional outcome (ie, mRS 0-3 at 3 months after ICH) was used for aYLD estimation. Calculation of aYLL, aYLD, and aDALYs was performed for the overall cohort (ie, population-level disease burden of secondary injuries) and for the subgroup of patients affected by secondary injury (ie, individual-level exposure to secondary injuries). Patients who were affected were defined by the presence of HE, IVH, and relevant PHE (ie, relative PHE, or ratio of PHE to ICH surface, of >1.5). We calculated aDALYs as the sum of aYLL and aYLD (eMethods in the Supplement).[26]

Studies in cerebrovascular diseases focus on clinical outcomes within 3 months after the index event and rarely obtain long-term outcomes.[27] To evaluate, if DALYs may be determined in these studies, we compared DALY assessment (based on 3 months functional outcome only) with DALY calculation (based on information on long-term functional outcome and survival time, available for the UKER-ICH cohort).

Results

Among 1322 patients with ICH, 615 (46.5%) were women and the mean (SD) age at hospital admission was 71 (13) years (**Table 1**; eFigure 2 in the Supplement). There were 587 patients with deep hematoma location (44.4%), 574 patients with lobar ICH (43.4%), 100 patients with cerebellar ICH (7.6%), and 61 patients with brainstem ICH (4.6%). Information on missing data is provided in eMethods and eAppendix in the Supplement.

The Figure illustrates the concept and calculation of YLL, YLD, and DALYs for patients with ICH. Differences in outcome assessment between mRS and DALYs are outlined in examples of patients with ICH (**Table 2**). Conceptually, dichotomized end points of favorable outcome (eg, defined as mRS

Table 1. Clinical Characteristics of Patients by Hematoma Location

Characteristic	Patients, No. (%)				*P* value
	Deep location (n = 587)	Lobar location (n = 574)	Cerebellum (n = 100)	Brainstem (n = 61)	
Age, mean (SD), y	70 (12)	72 (13)	71 (12)	65 (14)	<.001
Women	247 (42.1)	281 (49.0)	56 (56.0)	31 (50.8)	.02
Men	340 (57.9)	293 (51.0)	44 (44.0)	30 (49.2)	.02
Prior comorbidities					
Hypertension	527 (89.8)	456 (79.4)	87 (87.0)	47 (77.0)	<.001
Prior ischemic stroke or TIA	133 (22.7)	96 (16.7)	24 (24.0)	9 (14.8)	.04
Prior hemorrhagic stroke or major bleeding	41 (7.0)	83 (14.5)	8 (8.0)	4 (6.6)	<.001
Congestive heart failure	91 (15.5)	70 (12.2)	12 (12.0)	6 (9.8)	.30
Admission status, median (IQR)					
NIHSS score	15 (8-28)	10 (4-21)	5 (3-24)	12 (5-29)	<.001
ICH score	2 (1-2)	1 (0-3)	2 (1-3)	2 (1-3)	<.001

Abbreviations: ICH, intracerebral hemorrhage; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Table 2. DALYs and mRS in Patient Examples

Patient No.	Age, y	ICH		HE	IVH	mRS at 3 mo	Favorable outcome (mRS 0-3)	YLD	YLL	DALYs
		Location	Volume, mL							
1	70	Lobar location	5	No	No	1	Yes	1.08	0.61	1.69
2	70	Lobar location	5	Yes	No	2	Yes	2.78	2.43	5.21
3	65	Deep location	30	No	No	3	Yes	4.20	4.50	8.70
4	65	Deep location	30	No	Yes	4	No	6.52	7.35	13.87
5	65	Deep location	30	Yes	Yes	5	No	10.97	6.45	17.42

Abbreviations: DALY, disability-adjusted life-year; HE, hematoma enlargement; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; YLD, years lived with disability; YLL, years of life lost.

0-3) did not account for the different clinical outcomes, while DALYs delineated these outcome differences.[28]

In the overall cohort, ICH was associated with a mean (SD) 5.72 (8.29) YLL, 3.74 (5.95) YLD, and 9.46 (8.08) DALYs. There were no statistically significant differences in DALYs between patients with non-OAC-ICH and those with OAC-ICH. There were more DALYs among patients with high burden of cardiovascular disease compared with patients with a low burden, although this increase was not statistically significant (eMethods and eAppendix in the Supplement).

Burden of ICH by Hematoma Location

There were statistically significant differences by hematoma location in mean (SD) DALYs (deep location: 10.60 [8.35] DALYs; lobar location: 8.18 [7.63] DALYs; cerebellum: 8.14 [6.80] DALYs; brainstem: 12.63 [9.21] DALYs; $P < .001$) and mean (SD) YLD (deep location: 4.72 [7.06] YLD; lobar location: 2.69 [4.43] YLD; cerebellum: 3.31 [4.74] YLD; brainstem: 5.03 [6.87] YLD; $P < .001$) (**Table 3**). There were increased YLL among patients with brainstem ICH, but there were no statistically significant differences in YLL by hematoma location.

Burden of ICH by Extent of Hematoma Volume

There were statistically significant differences in mean (SD) DALYs by hematoma volume (small ICH: 7.05 [6.79] DALYs; medium ICH: 9.91 [8.35] DALYs; large ICH: 12.42 [8.47] DALYs; $P < .001$). There were also statistically significant differences by hematoma volume in mean (SD) YLL (small ICH: 3.21 [6.55] YLL; medium ICH: 5.52 [8.40] YLL; large ICH: 9.42 [9.04] YLL; $P < .001$) and mean (SD) YLD (small ICH: 3.84 [4.96] YLD; medium ICH: 4.39 [6.54] YLD; large ICH: 3.00 [6.56] YLD; $P = .005$).

Burden of ICH Associated With Secondary Injury

The relevance of secondary injury pathways (ie, extent of HE, IVH and PHE) may be different for the individual patient with secondary injury vs the entire population, given that the frequency of these secondary injuries may vary substantially. We therefore analyzed the association between secondary injury and burden of ICH among patients who were affected (ie, had secondary injuries) and separately among the entire ICH cohort. The associations of secondary injury with DALYs, YLL, and YLD are provided in **Table 4**. Analyses were conducted among 720 patients with ICH and available PHE data. Patients with secondary injury were defined by presence of relevant HE (75 patients [10.4%]), IVH (386 patients [53.6%]), and relevant PHE (316 patients [43.9%]).

For mean (SD) aDALYs, there were statistically significant differences among all patients (HE: 0.94 [3.19] aDALYs; IVH: 2.45 [4.16] aDALYs; PHE: 1.96 [2.66] aDALYs; $P < .001$) and differences among patients who were affected (HE: 7.14 [6.62] DALYs; IVH: 4.58 [4.75] aDALYs; PHE: 3.35 [3.28] aDALYs). For mean (SD) aYLL, there were statistically significant differences among all patients (HE: 0.58 [2.62] aYLL; IVH: 1.33 [3.15] aYLL; PHE: 0.39 [0.76] aYLL; $P < .001$) and differences among patients who were affected (HE: 4.53 [6.37] aYLL; IVH: 2.49 [3.96] aYLL; PHE: 0.61 [1.05] aYLL). For mean (SD) aYLD, there were statistically significant differences among all patients (HE: 0.36 [1.82] aYLD; IVH: 1.12 [3.15] aYLD; PHE: 1.58 [2.74] aYLD; $P < .001$) and differences among patients who were affected (HE: 2.61 [4.87] aYLD; IVH: 2.09 [4.06] aYLD; PHE: 2.74 [3.55] aYLD).

Table 3. Burden of Intracerebral Hemorrhage by Hematoma Location

Outcome	Mean (SD)				*P* value
	Deep location	Lobar location	Cerebellum	Brainstem	
Patients, No.	587	574	100	61	NA
Years of life lost	5.89 (8.39)	5.45 (8.06)	4.83 (7.30)	7.60 (10.63)	.18
Years lived with disability	4.72 (7.06)	2.69 (4.43)	3.31 (4.74)	5.03 (6.87)	<.001
Disability-adjusted life-years	10.60 (8.35)	8.18 (7.63)	8.14 (6.80)	12.63 (9.21)	<.001

Abbreviation: NA, not applicable.

DALY Assessment Using Short-Term Functional Outcome

We compared DALY assessment (based on 3 months functional outcome only) with DALY calculation (based on information on long-term functional outcome and survival time, available for the UKER-ICH cohort). The mean (SD) difference between DALY calculation and formula assessment was −0.66 (3.37) DALYs, and the 95% limits of agreement were between −7.27 DALYs and 5.95 DALYs. (eFigure 1 in the Supplement).

Discussion

To our knowledge, this cohort study represents the first comprehensive assessment of DALYs associated with a single ICH event and secondary injury parameters. We found that ICH was associated with an increased burden of disability, notably in the subset of patients with brainstem and deep hematoma ICH location. We found that IVH and PHE, compared with HE, were outcome-relevant for most patients with ICH. The results of our study may guide public health strategies and improve the focus of ICH research toward the most relevant treatment targets. Furthermore, our findings suggest that DALYs may represent a viable outcome parameter that should be addressed by future ICH studies.

Defined as the combination of years of life lost owing to premature mortality and years lived with disability, DALYs appear to be the perfect measure of morbidity and mortality associated with intracerebral hemorrhage. However, the association of a single ICH event and DALYs for the individual patient have not been specified so far, to our knowledge, given that such individual patient data are not available for the Global Burden of Diseases Study.[1] We found that ICH occurrence was associated with 9.5 DALYs, substantially more than the 5.9 DALYs associated with severe ischemic stroke.[21] We found that DALYs increased with increased ICH volumes and were highest in the subset of patients with brainstem and deep hematoma ICH locations. Our findings suggest that public health strategies may reduce DALYs by 8.1 years for each cerebellar ICH, 8.2 years for each lobar ICH, 10.6 years for each deep ICH, and 12.6 years for each brainstem ICH prevented.

Table 4. Secondary Injury and Associated Burden of Intracerebral Hemorrhage

Patient group[a]	Mean (SD)[b]			*P* value
	HE	IVH	PHE	
aYLL				
Among patients who were affected	4.53 (6.37)	2.49 (3.96)	0.61 (1.05)	NA
Among overall patients	0.58 (2.62)	1.33 (3.15)	0.39 (0.76)	<.001
aYLD				
Among patients who were affected	2.61 (4.87)	2.09 (4.06)	2.74 (3.55)	NA
Among overall patients	0.36 (1.82)	1.12 (3.15)	1.58 (2.74)	<.001
aDALYs				
Among patients who were affected	7.14 (6.62)	4.58 (4.75)	3.35 (3.28)	NA
Among overall patients	0.94 (3.19)	2.45 (4.16)	1.96 (2.66)	<.001

Abbreviations: aDALY, attributable disability-adjusted life-year; aYLD, attributable years lived with disability; aYLL, attributable years of life lost; HE, hematoma enlargement; IVH, intraventricular hemorrhage; NA, not applicable; PHE, perihemorrhagic edema.

[a] Among 720 patients with secondary injury, patients who were affected were defined by the presence of relevant HE (ie, relative increase of intracerebral hemorrhage volume >30%; 75 patients [10.4%]), IVH (386 patients [53.6%]), or relevant PHE (ie, relative perihemorrhagic edema, or ratio of PHE to intracerebral hemorrhage surface, of >1.5; 316 patients [43.9%]).

[b] Analyses were adjusted for age, National Institutes of Health Stroke Scale score, deep intracerebral hemorrhage location, intracerebral hemorrhage volume, and secondary injury parameters (ie, HE volume, IVH extension [by Graeb score], and PHE volume).

Regarding secondary injury pathways, HE, IVH, and PHE have been independently associated with functional outcome and mortality.[9,13,18] However, to our knowledge, the extent of secondary injury by different parameters has never been sufficiently compared. Therefore, the most relevant parameter as primary treatment target remains unclear. We found that HE was associated with 7.1 DALYs among patients affected by HE. In contrast, among the overall cohort of patients with ICH, among whom relevant HE occurred in 10.4% of individuals, HE was associated with 0.9 DALYs, while IVH and PHE had more than 2-fold greater relevance for clinical outcomes in terms of DALYs. Additionally, PHE appeared most relevant for YLD among patients who were affected and patients with ICH overall. Our results may contribute to identifying the most relevant treatment targets in ICH research. Prevention of HE must be focused on patients with high risk of HE selected by radiological and clinical parameters.[9,29] However, to improve outcomes for most patients with ICH, our findings suggest that future research efforts should be aimed at treatment of IVH and PHE.[6,30,31]

Regarding outcome assessment, DALYs measure functional impairment during the remaining lifetime after ICH, while mRS measures functional status at a single time. Therefore, DALYs represent a continuous rather than a dichotomized or ordinal outcome variable with certain statistical advantages vs mRS.[28] We here found that DALYs delineated and accurately quantified clinical outcomes in ICH. We further found that DALYs could be calculated in ICH using mRS at 3 months after ICH event and life expectancies derived from Federal Statistical Office of Germany data. Therefore, our findings suggest that DALYs represent a viable outcome parameter in ICH research and could measure small treatment-associated outcomes even in underpowered studies, which may not be detected by mRS.[5-7,15,30,32-37] Future studies should include DALYs as a secondary outcome parameter to identify and improve treatment options and finally decrease the burden of ICH disease.

Limitations

Our study has several limitations. Relevant bias by patient selection may have influenced outcomes in our cohort given that patients with ICH due to secondary etiology, such as aneurysmal ICH, were excluded. Specific data on PHE were not available for the entire cohort, and we did not account for premorbid functional status. Although the applied method of attributable fraction assessment has been shown to provide estimation rather than precise calculation, the relevance of different secondary injury parameters should be sufficiently addressed and uncertainty remains.[26,38-41] The benefits of DALYs as an outcome parameter could be largely attributable to the combination of premature mortality and disability. However, the global burden of disease is defined by this combined outcome parameter, which may help to identify small treatment-associated outcomes in future ICH research.

Conclusions

This study provides data on DALYs among patients with ICH and secondary injury and may guide public health strategies. While we found that the occurrence of HE was associated with clinical outcomes among patients who were affected, IVH and PHE were associated with increased disability in the overall cohort compared with HE. These findings suggest that DALYs may represent a viable outcome parameter that may be applied in retrospective and prospective studies to evaluate treatment outcomes in ICH research.

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SUPPLEMENT.
eMethods.
eAppendix. Missing Data and Exploratory Analysis
eTable 1. Disability Weights for Modified Rankin Scale Levels
eTable 2. Annual Mortality After Intracerebral Hemorrhage and Ischemic and Hemorrhagic Stroke by Functional Status on Modified Rankin Scale
eFigure 1. Bland-Altman Analysis Comparing Disability-Adjusted Life-Years Measurement
eFigure 2. Patient Flowchart
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Stroke

CLINICAL AND POPULATION SCIENCES

Association of Intraventricular Fibrinolysis With Clinical Outcomes in Intracerebral Hemorrhage: An Individual Participant Data Meta-Analysis

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BACKGROUND: In patients with intracerebral hemorrhage (ICH), the presence of intraventricular hemorrhage constitutes a promising therapeutic target. Intraventricular fibrinolysis (IVF) reduces mortality, yet impact on functional disability remains unclear. Thus, we aimed to determine the influence of IVF on functional outcomes.

METHODS: This individual participant data meta-analysis pooled 1501 patients from 2 randomized trials and 7 observational studies enrolled during 2004 to 2015. We compared IVF versus standard of care (including placebo) in patients treated with external ventricular drainage due to acute hydrocephalus caused by ICH with intraventricular hemorrhage. The primary outcome was functional disability evaluated by the modified Rankin Scale (mRS; range: 0–6, lower scores indicating less disability) at 6 months, dichotomized into mRS score: 0 to 3 versus mRS: 4 to 6. Secondary outcomes included ordinal-shift analysis, all-cause mortality, and intracranial adverse events. Confounding and bias were adjusted by random effects and doubly robust models to calculate odds ratios and absolute treatment effects (ATE).

RESULTS: Comparing treatment of 596 with IVF to 905 with standard of care resulted in an ATE to achieve the primary outcome of 9.3% (95% CI, 4.4–14.1). IVF treatment showed a significant shift towards improved outcome across the entire range of mRS estimates, common odds ratio, 1.75 (95% CI, 1.39–2.17), reduced mortality, odds ratio, 0.47 (95% CI, 0.35–0.64), without increased adverse events, absolute difference, 1.0% (95% CI, −2.7 to 4.8). Exploratory analyses provided that early IVF treatment (≤48 hours) after symptom onset was associated with an ATE, 15.2% (95% CI, 8.6–21.8) to achieve the primary outcome.

CONCLUSIONS: As compared to standard of care, the administration of IVF in patients with acute hydrocephalus caused by intracerebral and intraventricular hemorrhage was significantly associated with improved functional outcome at 6 months. The treatment effect was linked to an early time window <48 hours, specifying a target population for future trials.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: fibrinolysis ■ hydrocephalus ■ intracerebral hemorrhage ■ mortality ■ standard of care

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Nonstandard Abbreviations and Acronyms

AD	absolute difference
ATE	absolute treatment effects
CLEAR III	Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III
ERICH	Ethnic/Racial Variations of Intracerebral Hemorrhage
GCS	Glasgow Coma Scale
ICH	intracerebral hemorrhage
IPD	individual participant data
IVF	intraventricular fibrinolysis
mRS	modified Rankin Scale
OR	odds ratio
RETRACE	German-Wide Multicenter Analysis of Oral Anticoagulation Associated Intracerebral Hemorrhage Study
SMD	standardized mean difference
SoC	standard of care
UKER	Observational Cohort Study Spontaneous ICH Conducted at the University Hospital Erlangen

Intraventricular fibrinolysis (IVF) is a treatment strategy in patients with intracerebral hemorrhage (ICH) and severe ventricular involvement (IVH).[1,2] Several studies demonstrated hastened intraventricular clot resolution by IVF and the randomized controlled CLEAR-III trial (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III) verified prior demonstration of safety (bleeding complications and infections) compared to placebo treatment in an ICH population with smaller parenchymal but larger intraventricular hemorrhage volumes.[3,4] Mortality rates were reduced, but the primary efficacy analysis for functional outcome was neutral.[3,5] Questions remain whether improved patient selection may provide functional benefit and establish this therapy with greater certainty.[3,6,7]

Two important subgroups have been identified from CLEAR-III, patients with intermediate-sized IVH volumes and time from symptom onset to randomization.[3] Hence, individualizing a treatment strategy suggests that threshold-based selection of lesion volumes and timing from symptom onset to IVF treatment may provide functional benefit. Only availability of a large sample with highly granular data would allow quantification of patient characteristics predictive of favorable functional outcome.[8–10] We thus conducted an individual participant data (IPD) meta-analysis integrating published studies on IVF and eligible ICH patients from large observational cohort studies.[11]

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request and after approval of the data coordinating centers of the participating trials and studies.

Search Strategy and Data Synthesis

We performed a systematic review searching the Cochrane Library, Pubmed, and Scopus databases, and international trial registries, without language restrictions for clinical studies from inception to July 30, 2019. For full details of search criteria for the systematic review, aggregate data meta-analysis, and statistical analysis plan, please see Supplemental Methods, Table S1, and Figure S1–S3. The systematic review identified 8 studies of which 3 fulfilled prespecified criteria for IPD contribution and after invitation 2 contributed IPD.[3,12,13] Hence, decision was made by the lead investigators (J.B.K., W.Z., S.T.G., S.S., D.F.H., H.B.H.) to complement the present analysis by integrating further IPD from existing large studies of general ICH populations with availability of highly granular data.[3,12,14–19] This decision was based on the fact that with these few available specific studies analytical methodology would have been limited by restricting appropriate adjustments for bias and confounding as well as leading to an inability to conduct sufficient exploratory analyses (Supplemental Methods). Identification of observational studies was performed by screening registries (ClinicalTrials.gov, European Clinical Trials Database), complemented by our systematic review, and by contacting established investigative teams. All findings are reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis of Individual Participant Data.[20]

The present IPD meta-analysis (Figure S1) incorporated 9 studies (Table S2): (1) the randomized controlled CLEAR-III trial (https://www.clinicaltrials.gov; Unique identifier: NCT00784134), (2) CLEAR-B phase-II trial (https://www.clinicaltrials.gov; Unique identifier: NCT00650858),[3,4] (3) the multicenter, prospective, case-control ERICH study (Ethnic/Racial Variations of Intracerebral Hemorrhage; https://www.clinicaltrials.gov; Unique identifier: NCT01202864),[15] (4 and 5) 2 multicenter cohorts from the German-wide multicenter analysis of oral anticoagulation associated intracerebral hemorrhage, RETRACE-study (German-Wide Multicenter Analysis of Oral Anticoagulation Associated Intracerebral Hemorrhage Study) part-I (https://www.clinicaltrials.gov; Unique identifier: NCT01829581)[14] and part-II (https://www.clinicaltrials.gov; Unique identifier: NCT03093233),[16,21] (6) the single-center observational cohort study (UKER [Observational Cohort Study Spontaneous ICH Conducted at the University Hospital Erlangen]) for primary spontaneous ICH conducted at the University Hospital Erlangen, Germany (https://www.clinicaltrials.gov; Unique identifier: NCT03183167),[17] (7) single-center observational cohort study in adult nontraumatic ICH patients conducted at the University of Tennessee Health Science Center,[18] (8) single-center observational cohort study in adult patients with spontaneous supratentorial ICH conducted at Beth Israel Deaconess Medical Center,[19] (9) single-center matched-pair cohort study conducted at University Hospital Heidelberg, Germany.[12] Informed consent was obtained from all participants or their legal representatives within each participating study if not waived by the respective ethical committees. Institutional review boards or ethical committees reviewed and approved all study protocols.

Data Extraction and Study Population

Eligibility for IPD inclusion comprised the following: (1) supratentorial primary ICH or IVH with IVH causing acute hydrocephalus treated with an external ventricular drainage, (2) patient age ≥18 years, (3) premorbid modified Rankin Scale (mRS) score ≤3, (4) >10 patients treated with IVF within each study framework, (5) no evidence of early care limitations or death within 48 hours after admission,[22] (6) no evidence of secondary ICH causes, (7) no other competing treatment intervention (eg, craniectomy, minimal invasive surgery), (8) use of validated methods for imaging assessment, (9) standardized scoring of neurological status (Glasgow Coma Scale [GCS] ranging from 3, comatose, to 15, alert), and (10) availability of standardized functional outcome assessed by the mRS (ranging from 0, no functional deficit to 6, death) recorded between 3 and 12 months after the index event. For methodology of data acquisition and description of included studies, please see Table S3. Complete data sets were available for patient identification; that is, the entire ICH cohort within each study framework was available for identification of patients eligible for IPD contribution according to the predefined eligibility criteria. Baseline data on demographics, prior comorbidities, prior medication exposures, timing measures, and neurological status upon hospital admission were obtained.[16] Imaging analyses were conducted at imaging cores within each study framework by investigators blinded to clinical information (Table S3). The IPD-set was compiled and centrally analyzed by the coordinating center (University Hospital Erlangen, Germany).[16]

Intervention and Outcomes

The investigated intervention (intraventricular fibrinolysis, IVF) consisted of the instillation of alteplase (1 mg/mL) through an external ventricular drainage until the stopping point was achieved. The stopping point was defined as radiographic opening of the third and fourth ventricles or relieved mass effect of IVH or reached maximum dose according to individual study protocols.[3,4,12] IVF was compared to either placebo treatment (CLEAR-III) or external ventricular drainage management according to American or European ICH guidelines, both referred to as standard of care (SoC) throughout the article.[23,24]

The primary outcome was predefined as the proportion of patients achieving favorable functional outcome at 6 months mRS score of 0 to 3 dichotomously compared with mRS score of 4 to 6. Secondary outcomes comprised (1) ordinal-shift analysis of mRS values at 6 months, (2) all-cause mortality at 6 months, and (3) adverse events defined as any intracranial bleeding complication or bacterial infection occurring within 30 days after ictus. Follow-up information was obtained according to individual study protocols by personnel blinded to clinical data (Table S3).

Risk of Bias Assessment

All included studies were evaluated for risk of bias using the ROBINS-I tool (Risk of Bias in Nonrandomized Studies of Interventions)[25] by consensus of the lead authors (Table S4).

Statistical Analysis

Full details of the prespecified statistical analysis plan of this IPD meta-analysis are provided Supplemental Methods. Each IPD-set was checked for completeness, consistency, and queries were resolved with participating investigators. We standardized coding, format, and units of measurement for scale or continuous variables to maximize data completeness.[26] Missing outcome information (5.4%, complete IPD-dataset) was handled by multiple imputations (Supplemental Methods; Table S4).[27] Sensitivity analyses involved interstudy variance of treatment effects across participating studies with clinical outcomes at 6 months, confounding due to excluded patients determined by interaction analysis (IVF×excluded patients), and evaluation of unmeasured confounding (*E* values).[9,28] Heterogeneity was evaluated by Cochran-Q testing, calculated I^2-values, considered significant $P<0.1$, and inconsistency of results were determined according to the GRADE-Handbook (Grading of Recommendations Assessment, Development and Evaluation).[29] Analyses for interactions of treatment effect (IVF×interaction term) were considered significant for $P<0.05$. All tests were 2-sided with significance level at $\alpha=0.05$. The systematic review and aggregate meta-analysis were conducted using RevMan (Version5.4) and IPD meta-analysis was conducted with STATA (version 14.2).

Statistical analyses of primary and secondary outcomes used pooled IPD (N=1501) comparing IVF treatment, as per-protocol basis, to SoC as reference. To rigorously address bias and confounding, we used 3 different confounder-adjusted methods conducted as one-stage approach to calculate adjusted odds ratios (OR) and adjusted absolute treatment effects (ATE). (1) Conventional OR-model calculated using generalized linear mixed-effect to analyze all studies simultaneously, accounting for clustering of treatment effects (between-study differences) across participating studies with random effects and adjustments for confounders associated with the investigated outcomes. (2) Doubly robust estimations to calculate ATE using logistic regression by a technique (augmented inverse probability weighting), which was identified as most conservative model after sensitivity analyses. Adjustments were performed in 2 ways (1) confounders associated with an increased propensity to receive IVF treatment, that is, oral anticoagulation, GCS, deep ICH location, ICH volume, IVH volume and (2) validated confounders associated with functional outcome and mortality, that is, age, prestroke mRS, oral anticoagulation, GCS, thalamic ICH location, ICH volume, IVH volume. (3) For graphical analyses only, we used a propensity-matched cohort (n=1150) using the aforementioned confounders associated with an increased treatment propensity, calculated by balanced, parallel (1:1) nearest neighbor approach (caliper. 0.2).[30] Analyses comprised the mRS distribution at 6 months and exploratory threshold regression analyses of nonlinear treatment effect modifiers (age, GCS, ICH volume and IVH volume, symptom onset to treatment) calculated using the multivariable fractional polynomials interaction approach with OR presented on a log-odds scale.[31]

In general, confounders were identified based on sensitivity analyses of each investigated outcome and considered relevant by a standardized mean difference larger than 10%. Primary and secondary outcome analyses comprised binary regression for the primary end point (mRS score of 0–3), mortality, and adverse events as well as ordinal-shift analyses (presented as common odds ratio, after checking the proportional odds assumption, as appropriate) across the entire mRS within generalized linear mixed-effect- and augmented inverse probability weighting modeling. Exploratory subgroup analyses followed

the same methodology. Subgroup categories of continuous or scale variables were grouped into tertiles or scored as present or absent and were tested for interactions (IVF×subgroup category) considered significant for $P<0.05$.

RESULTS

Systematic Review and Aggregate Data Meta-Analysis

The systematic review of published studies analyzing associations of IVF with mortality at discharge, mortality, and functional outcome at ≥3 months identified 2 trials and 6 observational cohort studies (Table S1 and Figure S1). Results provided significant heterogeneity and substantial data inconsistency for functional outcome (Figure S2). Risk of bias due to baseline confounding was judged high or unclear in 6 out of 8 studies (Figure S3).

Study Population of IPD Meta-Analysis

We screened 9 datasets with 8482 ICH patients for eligibility, pooling IPD data from one randomized controlled trial (CLEAR-III, including n=500), from one phase-II trial (CLEAR-B, including n=35), from one observational study (including n=52), and additionally integrated IPD from large observational cohort studies (ERICH, including n=388; RETRACE-I, including n=115; RETRACE-II, including n=144; UKER, including n=170; University of Tennessee Health Science Center, including n=80; Beth Israel Deaconess Medical Center, including n=17). Hence, the IPD study cohort consisted of 1501 patients of which 596 patients received IVF compared to 905 patients with SoC (Figure 1). Sensitivity analyses of excluded patients did not show significant interactions (Table S5).

Risk of Bias Assessment

Statistical heterogeneity was not significant and inconsistency of results across participating studies with respect to interstudy variance of treatment associations was determined low (I^2-fluctuation span, 0%–47%; Figure S4). Risk of bias was judged low to moderate risk across all participating studies (Figure S4 and Table S4).

IPD Meta-Analysis

Baseline characteristics are provided in the Table. Patients with IVF received the first dose at a median of 47.8 hours interquartile range (31.0–64.5) after symptom onset with a median cumulative dose of 5 mg alteplase interquartile range (3–8) and 95% CI (0–12). We identified significant imbalances in IVF treated patients compared to SoC, that is, less frequent prior use of oral anticoagulation (absolute difference [AD], 6.5% [95% CI, −10.7 to −2.2]), standardized mean difference [SMD], 0.16), more frequent deep ICH location (AD, 4.1% [95% CI, −0.1 to 8.2]; SMD, 0.10), less frequent higher GCS (values=13–15, AD, 6.0% [95% CI, −10.6 to −1.4]; SMD, −0.11), smaller ICH volumes (AD, −6.0 mL [95% CI, −7.9 to −4.1]; SMD, −0.54), and larger IVH volumes (AD, 6.0 mL [95% CI, 3.3–8.7]; SMD, 0.30). Sensitivity analyses dichotomized according to functional outcome (mRS score: 0–3 at 6 months; Table S6) showed more frequent IVF-use (AD, 12.2% [95% CI, 6.8–17.4]; SMD, 0.25), younger age (AD, −7.5 years [95% CI, −8.8 to −6.2]; SMD, −0.62), higher GCS values (AD, 3.0 [95% CI, 2.3–3.7]; SMD, 0.57), less frequent thalamic ICH (AD, −9.7% [95% CI, −15.3 to −4.1]; SMD, −0.19), lower ICH volumes (AD, −9.7 mL [95% CI, −11.5 to −8.0]; SMD, −0.59), and lower IVH volumes (AD, −8.0 mL [95% CI, −10.9 to −5.1], SMD, −0.45) in patients with favorable outcome. Sensitivity analyses according to adverse events showed more frequent prior oral anticoagulant use (AD, 9.2% [95% CI, 2.5–15.8]; SMD, 0.21) and larger IVH volumes (AD, 3.8 mL [95% CI, 0.2–7.4]; SMD, 0.10; Table S7).

Analyses of the Primary Outcome

The adjusted absolute treatment effect of IVF to achieve a favorable functional outcome at 6 months using the entire IPD cohort (N=1501) was 9.3% (95% CI, 4.4–14.1), $P<0.001$, according to the most conservative model identified by sensitivity analyses (all models, ATE-range, 9.3%–10.0%; Table S8). The adjusted-OR to achieve favorable functional outcome was 1.69 (95% CI, 1.26–2.23), $P<0.001$; (E values, point-estimate, 1.92, CI, 1.50) and the crude difference for the entire cohort (N=1501) was 42.1% (251/596) versus 30.5% (276/905). Graphical representation of the mRS distribution at 6 months using the propensity-matched cohort (N=1150) is shown in Figure 2A, with a difference in proportions of favorable functional outcome of 42.4% (244/575) versus 35.0% (201/575), for sensitivity analyses of the propensity-matched cohort (Table S9 and Figure S5).

Analyses of Secondary Outcomes

IVF treatment was associated with a significant shift towards improved functional outcome across the entire range of mRS, common-OR, 1.75 (95% CI, 1.39–2.17), $P<0.001$; (E values, point-estimate, 1.98, CI, 1.64). Mortality at 6 months was significantly reduced with IVF treatment compared with SoC, adjusted-OR, 0.47 (95% CI, 0.35–0.64), $P<0.001$; (E values, point-estimate, 2.28, CI, 1.81), with an ATE, −10.0% (95% CI, −14.5 to −5.4), $P<0.001$. Focusing on safety Figure 2B provides an overview of evaluated adverse events. In total 14.9% (89/596), adverse events in IVF treated patients were detected compared to 13.5% (122/905) in patients who received SoC, with an adjusted AD, 1.0% (95% CI,

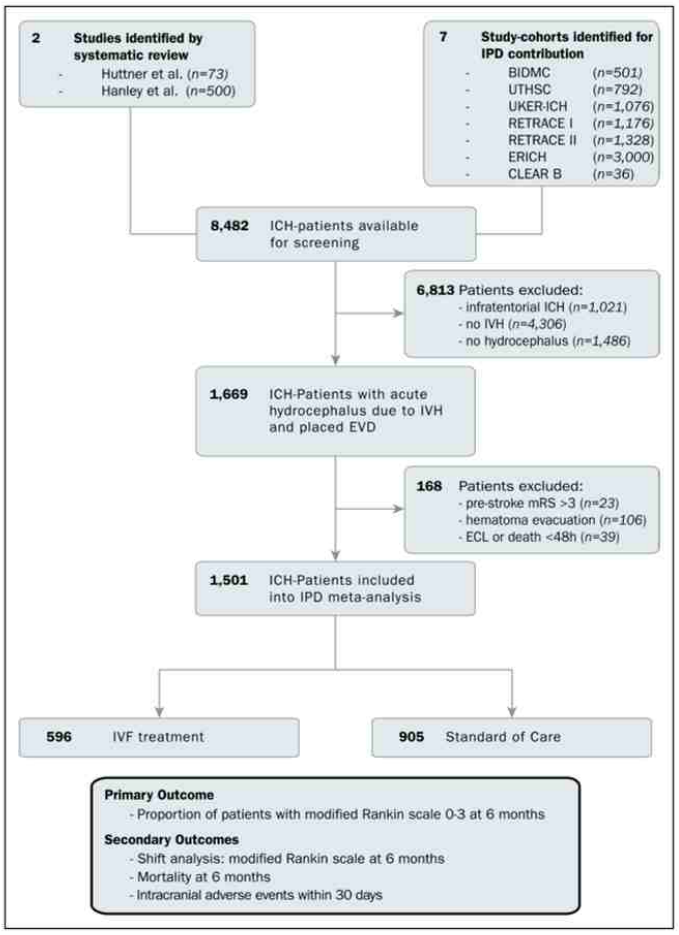

Figure 1. Flow diagram of study population and data analysis.
Flow diagram providing, screening, eligibility, exclusion, and generation of the study population available for individual participant data (IPD) contribution, based on the Preferred Reporting Items for Systematic Review and Meta-Analysis of Individual Participant Data guidelines. BIDMC indicates Beth Israel Deaconess Medical Center; CLEAR, Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage; ECL, early care limitations; ERICH, Ethnic/Racial Variations of Intracerebral Hemorrhage; EVD, external ventricular drainage; ICH, intracerebral hemorrhage; IVF, intraventricular fibrinolysis; IVH, intraventricular hemorrhage; RETRACE, German-Wide Multicenter Analysis of Oral Anticoagulation Associated Intracerebral Hemorrhage Study; UKER, Observational Cohort Study Spontaneous ICH Conducted at the University Hospital Erlangen; and UTHSC, University of Tennessee Health Science Center.

−2.7 to 4.8). New intracranial hemorrhagic complications were present in 8.6% (51/596) of IVF treated patients compared to 6.0% (54/905), a difference that was not statistically different, with an adjusted AD, 0.8% (95% CI, −2.3 to 3.0; Table S10).

Exploratory Subgroup Analyses

For associations of IVF with the primary outcome (Figure 3), significant ATE were found in younger patients aged 23 to 55 years, ATE, 13.4% (95% CI, 5.5–21.3), in patients with lower GCS (3–7) values, ATE, 12.1% (95% CI, 5.0–19.3), in nondeep ICH, ATE, 10.4% (95% CI, 0.8–23.1), or nonthalamic ICH, ATE, 12.6% (95% CI, 5.4–19.8), as well as in patients with larger ICH volumes (≥19.2 mL), ATE, 10.9% (95% CI, 2.8–19.0), and moderate IVH volumes (16.0–33.3 mL), ATE, 10.6% (95% CI, 3.0–18.2). The largest ATE was observed for symptom onset to treatment, especially in the earliest time window (treatment started within first tertile<29.9 hours after onset), ATE, 23.0% (95% CI, 12.8–33.2). The following time window (29.9–52.8 hours) remained significantly associated but revealed a lower ATE, 10.0% (95% CI, 1.3–18.7). Significant interactions between treatment and subgroup categories were not detected, all $P>0.05$. Similar associations were appreciated for the secondary outcomes (ordinal-shift analysis, mortality, and adverse events, Tables S11 through S13). Early IVF treatment (<29.9 hours) was associated with the largest shift towards improved functional outcomes, common-OR, 2.70 (95% CI, 1.67–4.35). Mortality reduction was most distinct in patients with GCS (3–7) values, ATE, −19.6% (95% CI, −26.9 to −12.2), and larger ICH volumes (≥19.2 mL) ATE, −19.3% (95% CI, −28.2 to −10.3). Upon exploratory analyses of IVF treatment with adverse events, the only significant association was observed in

Table. Baseline Characteristics Comparing Patients Treated With IVF Versus SoC

IPD cohort (N=1501)	IVF (n=596)	SoC (n=905)	Absolute difference, (95% CI)	SMD
Age, mean (SD), y	61.0 (12.4)	61.6 (12.9)	−0.5 (−1.9 to 0.7)	−0.05
Female sex, N (%)	246 (41.3%)	358 (39.6%)	1.7 (−3.4 to 6.7)	0.03
Medical history, N (%)				
Prestroke mRS [0–1]	539 (90.4%)	801 (88.5%)	1.9 (−1.2 to 5.1)	0.06
Hypertension	465 (78.0%)	737 (81.4%)	−3.4 (−7.6 to 0.7)	−0.08
Diabetes	116 (19.5%)	205 (22.7%)	−3.2 (−7.4 to 1.0)	−0.08
Coronary artery disease	47 (7.9%)	95 (10.5%)	−2.6 (−5.6 to 0.3)	−0.09
Prior stroke	87 (14.6%)	154 (17.0%)	−2.4 (−6.1 to 1.3)	−0.07
Prior oral anticoagulation	116 (19.5%)	235 (26.0%)	−6.5 (−10.7 to −2.2)	−0.16
Antiplatelet use	109 (18.3%)	158 (17.5%)	0.8 (−3.1 to 4.8)	0.02
Glasgow Coma Scale, median (IQR)	9 (6–13)	9 (6–13)	0.0 (−0.6 to 0.6)	−0.08
First tertile [GCS 3–7], N (%)	236 (39.6%)	332 (36.7%)	2.9 (−2.1 to 7.9)	−0.11
Second tertile [GCS 8–12], N (%)	211 (35.4%)	292 (32.3%)	3.1 (−1.7 to 8.0)	
Third tertile [GCS 13–15], N (%)	149 (25.0%)	281 (31.0%)	−6.0 (−10.6 to −1.4)	
Stability imaging, N (%)				
Primary IVH	51 (8.6%)	58 (6.4%)	2.1 (−0.6 to 4.9)	0.08
Deep ICH location	486 (81.5%)	701 (77.5%)	4.1 (−0.1 to 8.2)	0.10
Thalamic ICH location (n=1292)	276 (52.5%)	379 (49.5%)	3.0 (−2.6 to 8.5)	0.06
ICH volume, median (IQR), cm^3	8.5 (3.1–17.8)	14.5 (5.3–33.5)	−6.0 (−7.9 to −4.1)	−0.54
First tertile [0.0–6.3 cm^3], N (%)	250 (42.0%)	250 (27.6%)	14.3 (9.4 to 19.2)	−0.42
Second tertile [6.4–19.1 cm^3], N (%)	216 (36.2%)	284 (31.4%)	4.8 (0.0 to 9.7)	
Third tertile [≥19.2 cm^3], N (%)	130 (21.8%)	371 (41.0%)	−19.2 (−23.8 to −14.6)	
IVH volume, median (IQR), cm^3	26.6 (15.6–45.2)	20.6 (10.5–36.6)	6.0 (3.3–8.7)	0.30
First tertile [0.5–15.9 cm^3], N (%)	155 (26.1%)	347 (38.3%)	−12.3 (−17.1 to −7.6)	0.27
Second tertile [16.0–33.3 cm^3], N (%)	207 (34.7%)	292 (32.3%)	2.5 (−2.4 to 7.3)	
Third tertile [≥33.4 cm^3], N (%)	234 (39.3%)	266 (29.4%)	9.9 (4.9 to 14.7)	
Time windows (median [IQR], h, n=1303)				
Ictus to ED arrival	2.0 (1.0–4.5)	1.9 (1.0–4.3)	0.1 (−1.9 to 2.6)	0.05
Ictus to 1. CT scan	3.0 (1.6–6.8)	3.0 (1.6–7.0)	0.0 (−3.3 to 3.9)	0.06
Ictus to stability CT scan	30.2 (18.3–47.1)	30.0 (16.2–48.0)	0.2 (−2.9 to 3.3)	0.07
ED arrival to 1. CT scan	0.6 (0.3–1.0)	0.7 (0.4–1.2)	−0.1 (−0.2 to 0.0)	−0.09
1. CT scan to stability CT scan	23.3 (13.2–41.5)	23.3 (11.0–39.7)	−0.1 (−2.9 to 2.8)	−0.03

Comparison of patients who received IVF vs SoC presented for the entire IPD cohort. Absolute differences are provided in percent for frequency data and for scales or continuous variables as absolute differences according to the measurement unit (negative values indicate a decreased frequency or unit of measurement from the reference, that is, patients treated as SoC). CT indicates computed tomography; ED, emergency department; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IPD, individual participant data; IQR, interquartile range; IVF, intraventricular fibrinolysis; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; SMD, standardized mean difference; and SoC, standard of care.

patients with thalamic ICH, adjusted-OR, 1.74 (95% CI, 1.04–2.93), *P*=0.04 (Tables S11 through S13).

Threshold Analyses for the Primary Outcome

Exploratory threshold analysis of treatment effect modifiers with the primary outcome showed significant treatment effects of IVF almost across the entire range of age and GCS levels (Figure S6A and S6B) as well as for patients with intermediate-sized ICH (above 8–67 mL) and IVH (above 12–69 mL) volumes (Figure S6C and S6D). The most clear-cut threshold for treatment effects associated with favorable functional outcome was identified for the predictor: time from symptom onset to initiation of IVF treatment (Figure 4). Translating this threshold (IVF treatment received ≤48 hours compared with SoC) resulted in an ATE of 15.2% (95% CI, 8.6–21.8), *P*<0.001, to achieve the primary outcome (for the entire cohort analysis 78.5% (1179/1501) of patients were analyzed within the 48-hour time frame). Validating this time window threshold exclusively with CLEAR trial data resulted in an ATE of 13.3% (95% CI, 3.3–23.4), *P*=0.009 to achieve favorable functional outcome (for the CLEAR trial cohort analysis 68.4% [366/535] of patients were analyzed within the 48-hour time frame).

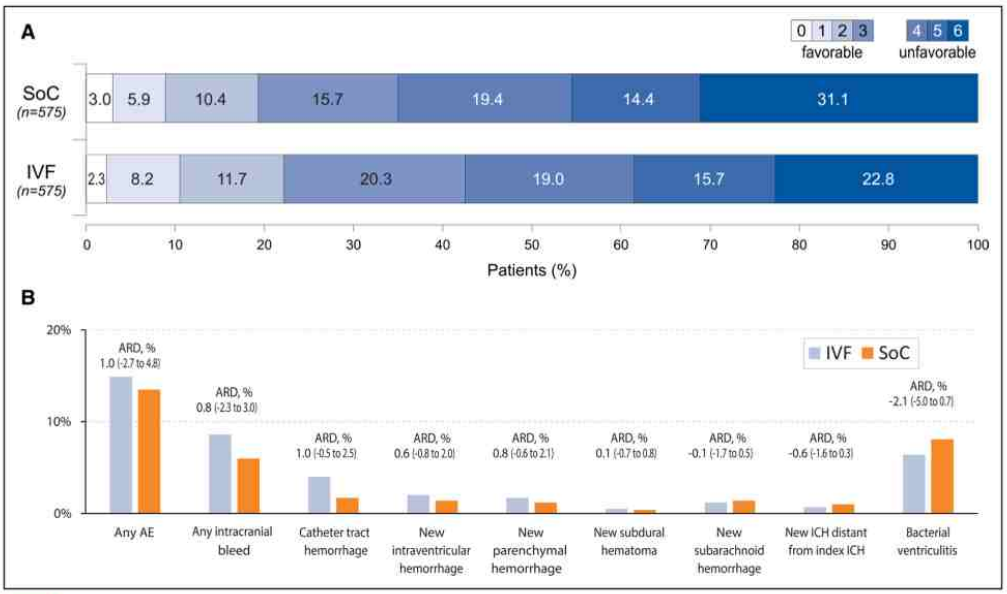

Figure 2. Modified Rankin Scale (mRS) distribution at 6 mo and intracranial adverse events.
A, Graphical comparison of the mRS distribution at 6 mo in patients who received intraventricular fibrinolysis (IVF) vs standard of care (SoC) presented for the propensity score-matched individual participant data (IPD) cohort (n=1150). For details of the matching procedure and balance, see Table S9 and Figure S5. **B**, Intracranial adverse events within 30 d of the ictus comparing IVF vs SoC presented for the entire IPD cohort (N=1501, Table S10). ARD indicates absolute risk difference; and ICH, intracerebral hemorrhage.

DISCUSSION

The present IPD meta-analysis incorporated trial and observational data and represents the largest analysis of patients treated with IVF to date. We provide that the use of IVF in this pooled analysis of 9 studies was related to improved functional outcome, specifically in an early time window <48 hours with an effect size of 15% using the IPD cohort, which was validated using only CLEAR trial data (effect size, 13%). Furthermore, we extend prior observations that the intervention is safe, feasible, and was significantly associated with improved survival.

What may be the reason that this analysis provided positive associations while a trial showed neutral results on functional outcome? Possible explanations refer to differences in patient selection and treatment characteristics among observational- compared with trial data. In observational studies, patient selection was most likely based upon expertise and individual protocols. A priori selection bias was rigorously addressed by sophisticated statistical means in this current study, yet important differences in patient selection compared to trial data were apparent. The latter involved more patients with thalamic ICH (59% versus 46%), a location with worse prognosis.[6] Trial inclusion criteria lead to significantly less patients treated with larger ICH volumes (≥19.2 mL) compared with nontrial patients (14% versus 44%) potentially associated with our results. Specifically, IVF treatment in these patients provided robust associations with reduced mortality (ATE, 19%) and increased favorable outcome (ATE, 11%). One general question refers to the conflict between internal versus external validity of randomized controlled trials.[32] CLEAR-III was aimed at addressing both as large international multicenter trial recruiting patients from 73 sites in 8 countries.[3] Yet, IVF represents a technical strategy disruptive to usual clinical practice and therefore not always fully applied in each clinical situation. We have learned from various randomized trials, for example, mechanical thrombectomy or carotid endarterectomy in ischemic stroke that hallmarks are crucial to demonstrate a clinical net benefit, such as patient selection, experience, and timing.[33] Similarly, our data suggest optimized patient selection, possibly higher center-experience, and most strikingly identified time from symptom onset to IVF as therapeutic window for treatment benefit up to 48 hours.

This hypothesis-generating analysis provides background evidence to justify exploring new questions. What may be the mechanistic concept behind rapid IVH resolution benefiting patients? Severe IVH leads to mass effect on ependymal, midbrain, and brain stem structures, along with obstructive hydrocephalus leading to direct damage and global brain hypoperfusion.[34,35] In various studies, IVH appears to exert independent effects on outcome beyond

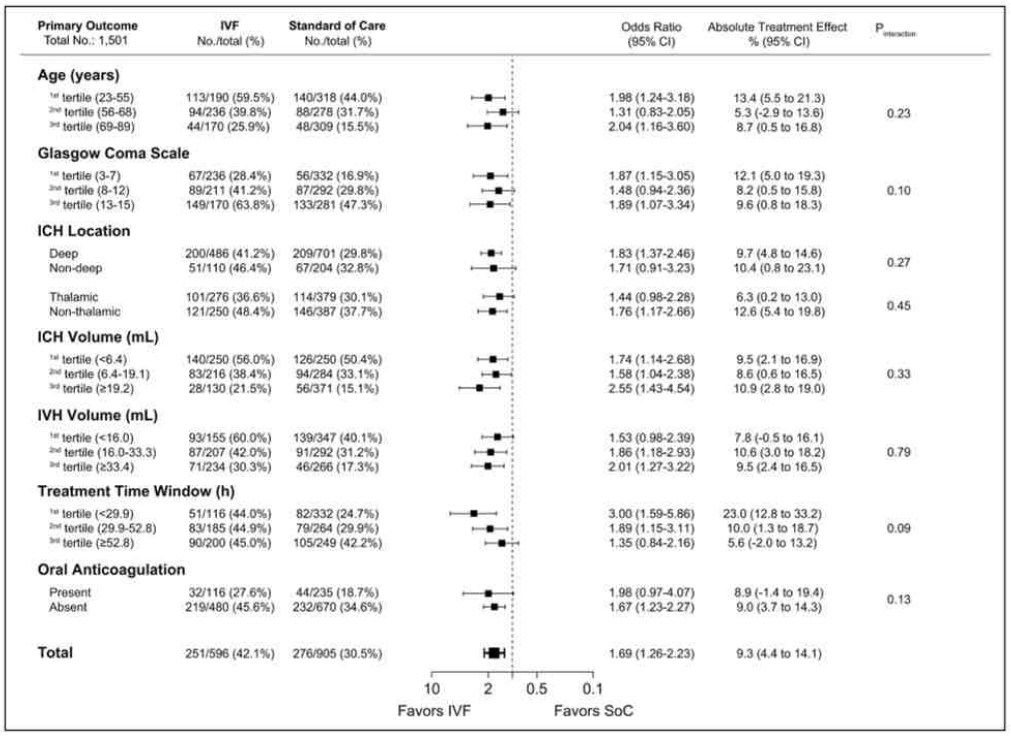

Figure 3. Exploratory subgroup analyses of the primary outcome.
Results for the primary outcome (modified Rankin Scale score 0–3) are presented as crude frequency data, adjusted odds ratios, and adjusted absolute treatment effects (for the entire cohort, N=1501). Adjusted models (generalized linear mixed-effect, augmented inverse probability weighting) were conducted as aforementioned. Interactions of exploratory subgroup analyses were tested using the subgroup-defining variable (variable×intervention) and were considered significant for $P<0.05$. ICH indicates intracerebral hemorrhage; IVF, intraventricular fibrinolysis; IVH, intraventricular hemorrhage; and SoC, standard of care.

ICH volume. Acute injury may be related to exaggerated neuroinflammation, yet causal relationships between outcome and acute inflammation, disturbed autoregulation, and the glymphatic system need to be determined.[36,37] Rapid clot removal by IVF limits exposure to blood-related toxins and harbors the potential to improve pathophysiology. However, IVF is not modifying parenchymal lesions suggesting that functional benefit may be driven by similar mechanisms influencing survival or otherwise by unknown factors which need to be elucidated. Specific analyses of CLEAR-III control group data suggest that instillation of saline only, that is, mechanical clot manipulation, neither led to rapid IVH resolution nor to a time-dependent association on clinical outcomes.[3] Hence, rapid clot removal achieved by alteplase is linked to improved functional outcome, presumably by multifactorial mechanisms stated above in a time-dependent manner. Regarding a subsequent randomized trial design, our findings support the evolving belief that "time is brain" not only in ischemic stroke. Current ICH trials have started to target early time windows (https://www.clinicaltrials.gov; Unique identifiers: NCT03385928, NCT03209258, NCT04434807).[38] Although time scales for ICH may be different than for ischemic stroke, our data suggest that early treatment with IVF is safe, feasible, and may positively influence outcomes.

Our results should be cautiously understood within the context of limitations pertaining to observational data (selection bias) from multiple cohorts as only 2 of 9 studies represented trials. Moreover, all observational studies were conducted by academic centers located in the United States and Germany with specialized neurointensive care units. The generalizability to hospitals without such capability is not addressed, but this may represent a potential avenue for quality improvement and implementation research. This study represents by far the largest investigation, tripling the size of the CLEAR-III, yet random sequence generation and allocation concealment were largely not present. Data derived from multiple cohorts required data harmonization to increase inferential equivalence.[26] Bias due to confounding was addressed by robust statistical methodologies and

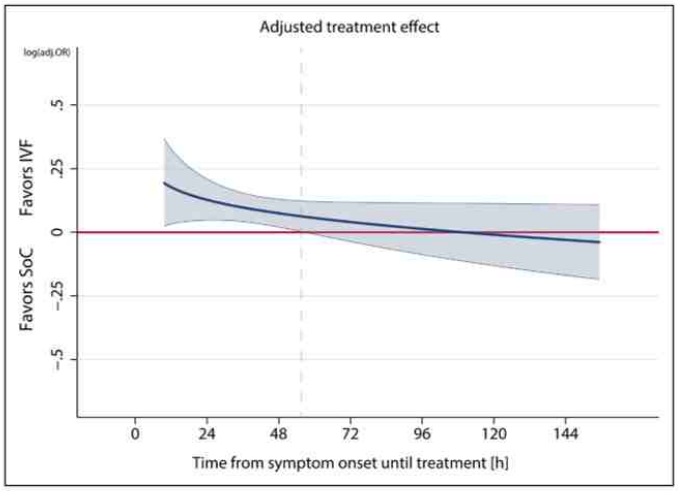

Figure 4. Threshold analysis for the primary outcome using the predictor (time from symptom onset to treatment).
Analysis was conducted as generalized linear mixed-effects model to analyze all studies simultaneously, accounting for clustering of treatment effects across participating studies with a random effect and adjustments for confounders associated with the primary outcome. Confounders comprised: age, prestroke modified Rankin Scale, oral anticoagulation, Glasgow Coma Scale, thalamic intracerebral hemorrhage (ICH) location, ICH volume, intraventricular hemorrhage volume. The adjusted odds ratio used fractional polynomials and was presented on a log-odds scale. IVF indicates intraventricular fibrinolysis; and SoC, standard of care.

sensitivity analyses included unmeasured confounding yet may not have completely compensated for this bias. Patients included into this study spanned a time frame from 2004 to 2015 with potential adaptations of ICH management. Imaging analysis was not centralized and lesion volume evaluation used validated but not standardized methodologies across all patients, which may have resulted in overestimation or underestimation. In addition, outcome was scored according to individual study protocols and may have been influenced by variability in time-point estimation or assessment methodology. We updated our systematic review search on May 25, 2021, which resulted in one more cohort study eligible for inclusion with a sample size of 80 patients representing a theoretical increase of 5% to the current investigation, and therefore, omission was considered sensible.[39]

CONCLUSIONS

As compared to SoC, the administration of IVF in patients with intracerebral and intraventricular hemorrhage was significantly associated with improved functional outcome at 6 months. The treatment effect was linked to an early time window of <48 hours, specifying a target population for future trials.

ARTICLE INFORMATION

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APPENDIX

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Invasiveness and Clinical Outcomes of Off-Hour Admissions in Patients with Intracerebral Hemorrhage

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Background: Whether time of hospital admission—during or outside regular working hours—affects functional outcome in intracerebral hemorrhage (ICH) is unestablished as previous analyses have focused on mortality only. We here investigate whether on- versus off-hour hospital admission in ICH is associated with levels of invasiveness and clinical outcomes. *Methods:* Based on the UKER registry (NCT03183167) we grouped ICH-patients according to on- versus off-hour hospital admission. Primary outcome measures was functional outcome after 3 months using the modified Rankin scale (mRS) dichotomized into favorable (mRS = 0-3) and unfavorable (mRS = 4-6). Multivariate regression analyses were used to adjust for baseline imbalances, and subgroup analyses were performed to explore associations of on- versus off-hour admission with invasiveness of therapeutic interventions. *Results:* A total of 438/1269 (34.5%) of ICH-patients were admitted during regular working hours. Mortality rates were not significantly different among patients with on- versus off-hour admission. On-hour patients showed a significantly larger proportion of patients with favorable outcome (on-hour: mRS = 0-3 after 3 months: 176/416 (42.3%) versus off-hour: 265/784 (33.8%); $P = .004$). Analysis of invasive therapeutic interventions revealed that likelihood of favorable outcome was significantly increased among on-hour admitted patients who did not require neurosurgical interventions (no external ventricular drain n = 349, OR: 1.67 [1.13-2.48], $P < .05$; no hematoma evacuation surgery n = 423, OR: 1.51[1.07-2.14], $P < .05$). *Conclusion:* This study verified an "off-hour effect" in ICH that relates to functional outcome, rather than mortality, and which may be linked to different levels of invasive therapeutic interventions in patients admitted during off-hour.

Key Words: Intracerebral hemorrhage—off-hour—off-hour effect—outcomes

Introduction

Hospital admission outside regular working hours influences clinical outcomes in a variety of disorders which coined the term "weekend effect" or "off-hour effect."[1] Regarding ischemic stroke, established treatment regimens and specialized comprehensive stroke centers may overcome this "weekend effect,"[2,3] however conflicting data exists in settings with increasing invasiveness, notably thrombectomy.[4]

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Previous studies on off-hour admissions in patients with intracerebral hemorrhage (ICH), possibly requiring invasive neurosurgical interventions, reported controversial findings: In INTERACT2 off-hour admission was not associated with increased mortality,[5] whereas other studies showed increased mortality rates at 7 and 30 days in off-hour admissions.[6,7] Furthermore, previous studies have mainly investigated the off-hour effects on mortality, whereas functional outcome so far was not considered. Consequently, it is essentially unestablished whether the invasiveness of therapeutic interventions, and functional outcome, is associated with on- versus off-hour admission in patients with ICH.

Methods

Patient Selection

We included consecutive ICH-patients of the UKER registry (NCT03183167, 2006-2014, n = 1269). As previously described, patients with secondary ICH were excluded.[2,3] The study was approved by the institutional review board and informed consent was obtained from patients or legal representatives.

Clinical Parameters and Procedures

Off-hour hospital admission was defined as admission outside regular working hours on weekdays (ie, 8:30 a.m.-4:30 p.m.), weekends and public holidays.[5] As described previously we retrieved demographics, pre-existing status, medication, clinical admission status, in-hospital parameters as well as laboratory data from medical records and institutional databases.[8,9] Diagnosis of ICH was made either by multislice computed tomography (Siemens SOMATOM Volume Zoom or Siemens Definition AS+) or 1.5 Tesla MRI (Siemens MAGNETOM Sonata or Siemens MAGNETOM Aera). Two neuroradiologists (H.L. and P.H.) blinded to clinical data classified hematoma characteristics (ie, location, volume, intraventricular hemorrhage). ICH volume was investigated using the ABC/2-method for ellipsoid and ABC/3-formula for irregularly shaped hematomas adjusted to imaging modality.[10-12]

Outcome Measures and Assessment

Primary outcome measures were functional outcome after 3 months using the modified Rankin Scale (mRS) dichotomized into favorable (mRS = 0-3) and unfavorable (mRS = 4-6). Secondary outcome measures included functional outcome at 12 months as well as mortality at 3 and 12 months after ICH onset.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0(SPSS Inc). The significance level was set at a = .05 and 2-sided statistical tests were performed. Baseline characteristics (on-hour versus off-hour) are presented as continuous (median and interquartile range, Mann-Whitney U test) or categorical variables (total number and frequency in brackets, compared using Person-chi-square and Fisher's exact tests). Multivariate regression analyses were calculated to determine the association between on-hour admission and favorable functional outcome. Odds ratios were adjusted for relevant ($P < .10$) differences in baseline parameters (age, premorbid mRS, GCS, initial ICH volume, initial intraventricular hemorrhage, deep hematoma location, and mechanical ventilation). Subgroup analysis were conducted regarding invasive therapeutic interventions and presented as forest plot to assess heterogeneity of on-hour on the primary outcome and delineate interactions.

Results

On-Hour Admission and Baseline Characteristics

The minority of ICH-patients 438/1269 (34.5%) were admitted during on-hours and presented with lower mean arterial blood pressure (114.7[103.3-129.9] vs 119 [103.3-134.7]; $P = .039$), lower NIHSS (11[3-23] vs 13[6-25]; $P = .002$), higher GCS Score (13[7-15] vs 13[6-15]; $P = .045$), and reduced rates of intraventricular hemorrhage (187 [42.7] vs 413[49.7]; $P = .017$) and deep location (172[39.2] vs. 390[46.9]; $P = .009$) as compared to off-hour patients. There were no significant differences among imaging characteristics or prior comorbidities (Table 1A).

Primary and Secondary Outcomes

On-hour admission was associated with a significantly higher proportion of ICH-patients with favorable outcome after 3 months (on-hour: mRS = 0-3 after 3 months: 176/416 (42.3%) versus off-hour: 265/784 (33.8%); $P = .004$), and after 12 months (on-hour: 174/392[44.4%] versus off-hour: 252/782[32.2%]; $P = .002$), respectively (Table 1C, Fig 1). Regarding mortality, there were no significant differences between on- and off-hour admission, neither at 3 months (130/416[31.3%] versus 285/784 [36.4]; $P = .08$) nor 12 months (159/392[40.6%] versus 332/728[45.6]; $P = .11$, Table 1C).

Differences in Invasiveness among ICH Patients with On-Hour Versus Off-Hour Admissions

There were significant differences in the frequency of applied invasive interventions (Table 1B): Patients admitted during on-hours received significantly less hematoma evacuation surgery (n=15/438(3.4%) vs. n=56/831(6.7%); p=.015) and placement of external ventricular drains (n = 89/438(20.3%) versus n = 229/831(27.6%); $P = .005$) compared to patients admitted outside regular working hours. The associations of these interventions for on-hour patients with the primary outcome according to treatment exposure are demonstrated in Figure 2. After adjustment

Table 1. *Clinical characteristics and outcomes of ICH patients (on-hours vs off-hour admission)*

	On-hour (n = 438)	Off-hour (n = 831)	*P*value
Age, y *(IQR)*	74 (65-81)	73 (63-80)	.13
Female sex, n *(%)*	210 (47.9)	388 (46.7)	.67
Prior comorbidities			
Hypertension, n *(%)*	374 (85.4)	703 (84.6)	.71
Diabetes mellitus, n *(%)*	132 (30.1)	219 (26.4)	.15
Prior ischemic/hemorrhagic stroke/TIA, n *(%)*	127 (29.0)	226 (27.2)	.50
Coronary artery disease, n *(%)*	96 (21.9)	210 (25.3)	.18
Congestive heart failure, n *(%)*	49 (11.2)	122 (14.7)	.08
Premorbid mRS, median *(IQR)*	1 (0-2)	1 (0-2)	.37
OAC, n *(%)*	80 (18.3)	166 (20.0)	.46
APT, n *(%)*	132 (30.1)	245 (29.5)	.80
Admission status, median (IQR)			
Mean arterial blood pressure, mmHg	**114.7 (103.3-129.9)**	**119.0 (103.3-134.7)**	**.039**
INR	1.0 (1.0-1.2)	1.0 (1.0-1.2)	.18
Hemoglobin, g/dL	13.8 (12.5-14.8)	13.7 (12.4-15.0)	.71
Leucocytes, $10^3/\mu L$	9.0 (7.0-11.7)	9.1 (7.2-11.8)	.66
GCS	**13 (7-15)**	**13 (6-15)**	**.045**
NIHSS	**11 (3-23)**	**13 (6-25)**	**.002**
CHADS VASc Score	3 (3-5)	3 (2-4)	.40
HAS Bled Score	3 (2-3)	2 (2-3)	.18
Imaging			
Initial ICH volume, cm^3, median (IQR)	13.2 (4.8-32.8)	13.6 (4.4-40.0)	.69
Hematoma enlargement (>33%), n *(%)*	48 (11.0)	95 (11.4)	.88
Intraventricular hemorrhage, n *(%)*	**187(42.7)**	**413(49.7)**	**.017**
Graeb score, median (IQR)	5 (2-8)	4 (2-7)	.06
Deep, n *(%)*	**172 (39.2)**	**390 (46.9)**	**.009**
Lobar, n *(%)*	**209 (47.7)**	**341 (41.0)**	**.022**
Infratentorial, n *(%)*	57 (13.0)	100 (12.0)	.61
B)			
Clinical parameters during hospital stay			
Mechanical ventilation, n *(%)*	151 (34.5)	329 (39.6)	.07
Duration of ventilation (d), median (IQR)	5.0 (1.0-16.3)	9.0 (2.0-19.0)	.05
OP evacuation, n *(%)*	**15 (3.4)**	**56 (6.7)**	**.015**
External ventricular drain, n *(%)*	**89 (20.3)**	**229 (27.6)**	**.005**
Symptom onset—admission (min), median (IQR)	**255.0 (109.5-817.5)**	**240.0 (91.0-515.0)**	**.028**
C)			
Primary and secondary outcomes, n (%)			
mRS 0-3 at 3 months	**176/416 (42.3)**	**265/784 (33.8)**	**.004**
mRS 0-3 at 12 months	**174/392 (44.4)**	**252/782 (32.2)**	**.002**
12-months mortality	159/392 (40.6)	332/728 (45.6)	.11
3-months mortality	130/416 (31.3)	285/784 (36.4)	.08
Early Care Limitation	70 (16.0)	102 (12.3)	.07
In-hospital mortality	105 (24.0)	200 (24.0)	.97

Abbreviations: APT, antiplatelet therapy; GCS, Glasgow Coma scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; TIA, transient ischemic attack.

Significant differences are now highlighted in bold. Significance Level was set at Alpha=0.05 both-sided

for baseline imbalances (age, mRS, GCS, initial ICH volume, initial intraventricular hemorrhage, deep localized ICH, and ventilation) there was a significant association between on-hour admission with favorable functional outcome (n = 438, OR: 1.51[1.08-2.12], p=.016), specifically in patients who did not require external ventricular drainage placement (n=349, OR: 1.67[1.13-2.48], p<.05) and no hematoma surgery (n = 423, OR: 1.51[1.07-2.14], $P < .05$), without significant heterogeneity between surgically and conservatively treated patients (Figure 2).

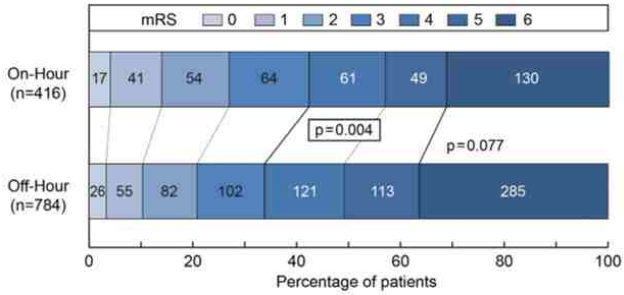

Figure 1. *Functional outcome at 3 months comparing patients with on-hour versus off-hour hospital admission. Distribution of functional outcome assessed at 3 months using the modified Rankin scale (mRS). Dashed lines separate each score on the mRS. The thick line separates the proportion of patients with favorable (mRS between 0 and 3) and unfavorable (mRS 4-6) outcome, and mortality, respectively.*

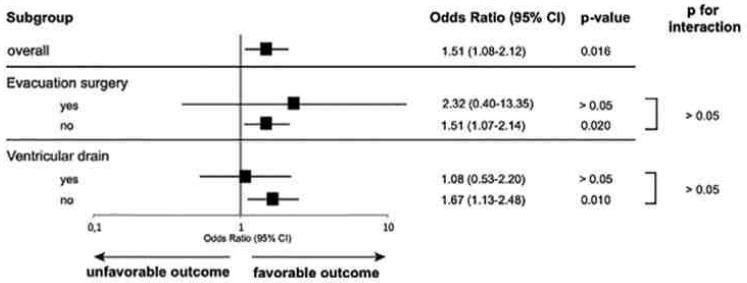

Figure 2. *Categorised subgroup analysis: association of on-hour admission and functional outcome. Regression analyses conducted within categorised subgroups for associations of on-admission with the primary outcome (favorable outcome [mRS 0-3 at 3 months] and unfavourable outcome [mRS 4-6 at 3 months]). Regression models were adjusted for baseline confounders (see methods section) and displayed as forestplots. Abbreviations: CI, confidence interval; OR, odds ratio.*

Discussion

To our knowledge we here for the first time demonstrate that on-hour admission in patients with ICH, although not affecting mortality, is related to better functional short- and long-term outcome, a finding possibly linked to invasiveness of neurosurgical interventions. Previous studies have mainly investigated the "off-hour effect" on mortality.[1,6,7,13,14] In INTERACT2 off-hour admission was not associated with increased mortality, similarly to our findings,[5] whereas other studies showed increased mortality rates at 7 and 30 days in off-hour admissions.[6,7] These uncertainties about a possible association of off-hour admission and mortality have been discussed in the context of different structural conditions and organization of stroke units, and implementations of standard operating procedures appear suitable to overcome "the weekend effect."[5]

The associations of off-hour admission with worse functional long-term outcomes were so far unestablished and the increased invasiveness of interventions during off-hours may in part account for these findings. Efforts seem warranted aiming at mitigating the unsteadiness of performing neurosurgical interventions during off-hours.[14,15] Further, our results may also indicate so far unexplained or unaccounted off-hour mechanisms which would require further in-depth analyses. One aspect to be considered may be the role of advanced imaging in stroke partially not being available during off-hours.[16-18]

Strengths of the present analysis include the large sample size with reliable clinical data. Nevertheless, it is a single-center study and the number of patients with surgical interventions is limited such that subanalyses create space for interpretation. In conclusion, this study reveals that hospital admission of ICH-patients during regular working hours is associated with less invasiveness of neurosurgical interventions, no mortality differences, and better functional outcome.

Author Contributions

A.M., M.I.S., and H.B.H. designed the study and wrote the manuscript. S.T.G., D.M., J.B.K., and S.S. obtained clinical data and critically revised the manuscript. P.H. and H.L. obtained and analysed imaging data. All authors approved submission of the final version of this article.

Conflict of Interest

None.

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5. ABKÜRZUNGSVERZEICHNIS

CAA	zerebrale Amyloidangiopathie
CI	Konfidenzintervall
DALY	disability adjusted life years
EVD	externe Ventrikeldrainage
ICB	intrazerebrale Blutung
MAP	arterieller Mitteldruck
mRS	modifizierte Rankin-Skala
OAK	orale Antikoagulation
OR	odds ratio
paO2	Sauerstoffpartialdruck
paCO2	Kohlendioxidpartialdruck
SBP	systolischer Blutdruck
SOP	standardized operating procedures
YLL	years of life lost
YLD	years lived with disability/disease

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