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Chapter 1

General introduction and thesis outline

"Different from all other medical specialties, save perhaps psychiatry, the neurologist is heavily dependent on listening to and interpreting what the patient tells us… If you don't know what is happening by the time you get to the feet you are in real trouble."

- Jerome M. Posner, 2013[1]

The skills involved in clinical neurology remain the cornerstone of the neurologist's profession.[2] Combining history, examination and localization into a differential diagnosis is truly an artform, leading to neurophobia in medical students, general practitioners, and hospital specialists.[3] Despite improvements in diagnostic investigations, clinical assessment cannot be replaced. When history, examination, and tests are joined together, they help establish the diagnosis at presentation in up to 90% of cases.[4]

Historically, neurology has been an outpatient specialty, but nowadays 10-20% of acute medical presentations are for neurological conditions.[5] Diagnostic neuroimaging has greatly advanced the field of acute neurology and the ability to treat acute neurological disorders has also rapidly expanded. For example, computed tomography angiography (CTA) and perfusion (CTP) are now easily accessible and widely applied techniques in the emergency department (ED) in patients with suspected acute ischemic stroke (AIS). When these scans confirm an occlusion of a cerebral artery, reperfusion therapies can be applied to restore blood flow. Surgical options have also increased, such as intracerebral pressure monitoring in patients with traumatic brain injury (TBI) or decompressive hemicraniectomy in patients with malignant cerebral infarction.

It is clear that over the past decades breakthroughs in technology and treatment have changed and expanded the role of the neurologist in the ED. With the ageing of the population, and neurological disorders disproportionately affecting older adults, the demand for and on neurologists in the ED is only expected to increase over time.[5,6] The expansion of diagnostic and treatment options inherently increases the number of decisions to be made. Which patients with TBI require (repeat) imaging or routine admission? What characteristics should make us wonder whether AIS is the right or only diagnosis? How do specific comorbidities affect risks and outcome of reperfusion therapy in patients with AIS? At the same time, many decisions in acute neurological disorders have to be made within narrow time frames. This frequently leads to clinical dilemmas that have to be figured out under pressure of a ticking clock.

MILD TRAUMATIC BRAIN INJURY

One of the most common reasons for neurological consultation in the ED is TBI.[7] Overall, the incidence of TBI is rising and it is a leading cause of death and long-term disability worldwide, associated with substantial economic consequences.[8]

TBI is categorized as mild, moderate or severe, based on the Glasgow Coma Scale (GCS) score.[9] Since its development in 1974 by University of Glasgow Professors Sir Graham Teasdale and Bryan Jennettto, this simple measurement has replaced previous inconsistent methods and has become an essential part of clinical practice and research worldwide. The scale, ranging from 3-15 points, assesses the level of consciousness of patients according to three aspects of responsiveness: eye-opening, motor, and verbal responses. Mild traumatic brain injury (mTBI) is defined as a GCS 13-15. In 2016, 38.200 patients with mTBI were presented to EDs across the Netherlands, representing approximately 80% of patients with TBI (Dutch Injury Surveillance System (LIS)[10]). The overall increase of patients with TBI is largely caused by a marked increase in elderly patients with mTBI caused by a fall,[11] but the emerging use of E-bikes amongst older adults also contributes to the rising number.[12] The absolute risk of intracranial complications after mTBI is low, but it is important to identify patients with relevant traumatic findings without performing a cranial computed tomography (CT) scan in every patient with head injury. Several clinical decision rules have been developed for this purpose, of which the CHIP rule walks this tightrope the best, with a sensitivity of 97% for potential neurosurgical lesions and a reduction of 21% CT scans compared to scanning every patient.[13] It includes - amongst other variables - vomiting, loss of consciousness, and amnesia.

The use of antiplatelet or anticoagulation therapy (low molecular heparin, vitamin K antagonists and direct oral anticoagulants) routinely warrants a cranial CT in patients with mTBI, with up to 29% of these patients having a traumatic intracranial hemorrhage (ICH).[14,15] Although a feared complication with high morbidity and mortality in case series, the risk of delayed ICH (traumatic ICH occurring after an initially normal CT in the absence of recurrent head trauma) is unclear and there is no consensus whether patients with mTBI on anticoagulation who have a normal initial cranial CT should be admitted for clinical observation and/or rescanned.[16] This knowledge gap is reflected by variations in national and international guidelines on the management of mTBI in patients on anticoagulants.[17-19] As anticoagulation use is increasing, particularly in the elderly,[19] bridging the knowledge gap might elucidate if admitting all patients with mTBI on anticoagulation therapy is necessary and cost-effective.

In summary, the incidence of patients with head trauma in general and of mTBI specifically is increasing. Clinical decision rules may be used as aid on which patients to scan, but knowledge gaps still remain on which patients to admit or rescan after an unremarkable cranial CT, such as patients with mTBI on anticoagulation therapy.

ACUTE ISCHEMIC STROKE

Another neurological disorder that is frequently encountered in the ED is stroke.[21] It is characterized by acute focal neurological deficits, caused by either a rupture (hemorrhagic stroke) or an occlusion (ischemic stroke) of a cerebral artery. Stroke ranks amongst the leading causes of death and long-term disability worldwide. Globally, there were 101 million prevalent cases of stroke in 2019.[22] In the Netherlands, 511.600 prevalent cases of stroke were reported in 2020, of which 38.300 were new patients: approximately 80% ischemic stroke and 20% hemorrhagic stroke.[21]

Most patients with acute ischemic stroke (AIS) have elevated blood pressure (BP) at presentation, which often declines spontaneously in the following days.[23] Previous research suggests that underlying stroke pathophysiology is reflected in initial BP values.[23-26] For example, patients with lacunar stroke often have a history of hypertension with increased arterial stiffness, which shifts the BP limits of cerebral autoregulation towards higher pressures.[26] Patients with large artery atherosclerosis may have compromised collateral circulation caused by diffuse stenotic lesions and may therefore require elevated BP levels to maintain blood flow to the ischemic penumbra.[24,25] In contrast, patients with cardio-embolic stroke without accompanying hypertension or atherosclerosis may need only moderate elevations in BP to ensure blood flow through a patent collateral circulation.[25]

Most studies assessing BP values in AIS found a U-shaped relationship between initial BP and functional recovery, with both lower and higher BP increasing the risk of poor outcome. [23,27,28] Subsequently, these studies focused on elevated BP, reporting an increased risk of symptomatic ICH[29] and edema,[30] but how low BP is associated with poor outcome and whether it should be treated remains unexplained.
The financial impact of stroke on society is substantial and highly dependent on functional outcome of patients. In stroke research, this is commonly assessed on the modified Rankin Scale (mRS). The mRS is a 7-point scale, which ranges from 0 (no symptoms) to 6 (death). Functional independence is defined as mRS 0-2 and indicates that a patient is at least "able to look after their own affairs without assistance, but unable to carry out all previous activities".[31]

To improve stroke outcome, a lot of research has been focused on acute stroke therapy. Currently, there are two main treatments for AIS: intravenous thrombolysis (IVT) and endovascular treatment (EVT). Both reperfusion therapies are aimed at removing the occluding thrombus from the cerebral artery to restore blood flow to the ischemic brain tissue. IVT tries to accomplish this goal by dissolving the thrombus with intravenously administered recombinant plasminogen activator (rt-PA). In EVT, the thrombus is mechanically removed from the cerebral artery with a stent retriever, introduced by groin puncture.

In 1995, IVT was first proven to have a beneficial effect on functional outcome in patients with AIS, notwithstanding an increase in symptomatic ICH.[32] IVT is administered in patients with a clinical diagnosis of stroke in the absence of ICH on the cranial CT scan. It is most effective when administered within 3 hours, but still safe and effective until 4.5 hours after stroke onset.[32,33] In selected cases with a wake-up stroke, time of onset/last-seen-well unknown or between 4.5 to 9 hours, IVT has also been proven beneficial beyond the standard time limits.[34,35]

Other neurological (for example migraine or seizures) and non-neurological (for example functional disorder or alcohol intoxication) disorders can present like stroke. These so-called stroke mimics (SM) represent 8% to 43% of patients presented to the ED with acute focal neurological deficits.[36] The narrow time window for treatment in patients with suspected stroke in the ED inevitably leads to some patients with a SM to be treated with IVT. Research has shown that IVT in patients with a SM is relatively safe, but patients with SMs are at increased risk for delayed diagnosis, over-investigation and unwarranted treatment or admission.[37] This is associated with substantial and unnecessary costs, which may be reduced when a correct diagnosis is made earlier.[38]

A well-known SM of posterior circulation stroke is acute alcohol intoxication. The fact that chronic alcohol abuse is a risk factor for stroke explains the fact that alcohol intoxication may be a SM, but also a concurrent diagnosis in stroke.[39] Unawareness amongst physicians, coupled with hesitancy of patients to disclose their alcohol consumption on their own accord, probably leads to reduced recognition of alcohol intoxication in the ED in patients with suspected stroke. How to distinguish between posterior circulation stroke and alcohol intoxication as a SM or concurrent diagnosis is unclear. However, these patients may be at greater risk of IVT-related complications than other SMs as ethanol impairs coagulation.[40] At the same time, there are also indications that alcohol consumption may cancel the beneficial effects of IVT in patients with stroke.[41] Additionally, little is known about how alcohol abuse affects treatment with secondary prophylaxis.

Between time constrictions and other contraindications, such as recent surgery, bleeding disorders and anticoagulation therapy, only 12 to 15% of patients with AIS are eligible for IVT.[42] Still, IVT remained the cornerstone of acute stroke therapy until 2015. In this year, several large trials, of which the Dutch MR CLEAN was the first to be published, demonstrated the safety and efficacy of EVT.[43] EVT is effective in patients with a large vessel occlusion which constitutes about a third of patients with AIS and represents the group with the most severe deficits and worst functional outcomes.[44] The standard time window is within 6 hours of stroke onset, but this has been extended to up to 24 hours in selected cases.[45,46] EVT has less contraindications than IVT, but again only 11-18% of patients with AIS are eligible.[47]

Multiple research efforts are aimed at increasing the number of patients meeting eligibility criteria for reperfusion therapy by further extending time windows for both IVT and EVT. In other studies, efficacy and safety is analyzed and proven in specific groups of patients, such as octogenarians.[48] A group that is of particular interest, is that of patients with cancer. With the improvement of cancer treatments, more patients will be living with cancer for longer periods of time and many cancers can be considered chronic. Therefore, as patients with cancer are at increased risk of AIS, neurologists will be confronted more often with them in the ED.[49,50] Comorbid cancer in AIS is associated with worse outcomes.[51] Although reperfusion therapy may improve outcome, IVT is often contraindicated due to surgery[52] or coagulopathy[53] and EVT has only been reported in case series and small-scale single-center studies.[54-58] It is important to keep in mind, that even if efficacy could be proven for EVT in patients with cancer and AIS, that it is an invasive and costly procedure. AIS in patients with cancer occurs most in more advanced stages.[59] Cancer care, and especially care towards the end of life, already takes up 6.7% of our total healthcare expenditure.[60] With healthcare costs in the Netherlands expanding rapidly and untenably,[61] one could question if EVT in patients with cancer and AIS is to be considered cost-effective. On the other hand, if proven effective, how justifiable is it from an ethical point of view to withhold a therapy that may add length and quality to the lives of patients with cancer? Cultural differences will also play a role in answering this question. In societies with a (historically) predominantly Christian tradition it is common to withhold or withdraw therapy deemed to prolong the dying process rather than save life.[62] This is much less accepted in an Islamic perspective: *"God has sent no disease, for which He has not sent treatment."*.[63]

In summary, patients with acute focal neurological deficits are frequently seen in the ED. Most have AIS, although SMs such as alcohol intoxication are common. In the first hours after onset reperfusion therapy can be administered. Therefore, a timely and correct diagnosis is important as costs, both personal and societal, are high. Low BP is

an uncommon find in patients with AIS, but its association with poor outcome remains to be elucidated. Reperfusion therapy, especially EVT, plays an important role in preserving favorable functional outcome, but its role has of yet not been studied in various groups of patients, such as patients with cancer.

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis is to provide guidance to neurologists in the ED on commonly occurring clinical dilemmas in acute neurological disorders. We hope that in doing so, we enable them to make more informed decisions. In **Chapter 2**, we focus on patients with mTBI on anticoagulation therapy. We examine the frequency of delayed ICH in these patients after an initial cranial CT scan without intracranial traumatic findings being reported. Special attention is paid to the development of ICH within 24 hours, to determine whether clinical observation is of additional value in these patients. In the subsequent chapters, we shift the focus to AIS. Alcohol intoxication is a common posterior circulation SM and can impede the decision for reperfusion therapy. In **Chapter 3**, we describe the frequency and clinical characteristics of patients with acute alcohol intoxication as a stroke mimic. Furthermore, we aim to describe patients with stroke and concurrent alcohol intoxication. Low blood pressure is uncommon in AIS, but it is unknown how it affects outcome. In **Chapter 4**, we explore the association between spontaneous low blood pressure and outcome after AIS. Stroke in patients with cancer is associated with worse outcomes, but EVT might benefit these patients. In **Chapter 5**, we assessed the clinical, imaging and safety outcomes of patients with AIS and active cancer who underwent EVT. Last, the results of this thesis and future directions are discussed in **Chapter 6**.

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Chapter 2

Evaluation of the yield of 24-hour close observation in patients with mild traumatic brain injury on anticoagulation therapy: a retrospective multicenter study and meta-analysis.

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ABSTRACT

Background/aims

Patients with mild traumatic brain injury (mTBI) on anticoagulants have an increased risk of intracranial hemorrhage (ICH). However, consensus is lacking on whether to admit them after normal initial cranial computed tomography (CT). We evaluated the yield of 24-hour neurological observation.

Methods

Retrospective multicenter study including adult patients admitted over a 5-year period with mTBI on anticoagulation (therapeutic dose heparin, direct oral anticoagulant, or vitamin K antagonist (VKA) with international normalized ratio (INR) ≥ 1.7) and reportedly normal cranial CT obtained within 24 hour after trauma. Primary endpoint was symptomatic ICH within 24 hours of injury. Literature on delayed ICH in patients with mTBI and anticoagulation use was reviewed.

Results

Of 17.643 mTBI patients, 905 met the inclusion criteria (median age 82 years). 97% used VKA (median INR 2.9). None developed delayed ICH within 24 hours. Nine patients deteriorated neurologically due to ICH, four within 24 hours (0.4%, 95% confidence interval (CI) 0.1–1.2) and five on day 2, 18, 22, 36 and 52, respectively. In six patients, including all four that developed symptoms within 24 hours, ICH was found upon reevaluation of initial imaging. The meta-analysis comprised of 9 studies with data from 2885 patients. The estimated pooled proportion of symptomatic delayed ICH or delayed diagnosis of ICH within 24 hours was 0.2% (95% CI 0.0–0.5).

Conclusions

Delayed (diagnosis of) ICH within 24 hours is very rare in mTBI patients on anticoagulants after reportedly normal initial CT. Routine hospitalization of these patients seems unwarranted when the initial cranial CT is scrupulously evaluated.

INTRODUCTION

Anticoagulation use is a risk factor for traumatic intracranial hemorrhage (ICH) in patients with mild traumatic brain injury (mTBI).[1-5] Therefore, clinical guidelines recommend routine cranial computed tomography (CT) in these patients.[3,4 6,7] Development of delayed ICH in patients whose initial CT did not show traumatic intracranial abnormalities has been reported in case reports and case series.[3,8,9] Although a feared complication, the risk of delayed ICH is unclear and there is no consensus whether patients with mTBI on anticoagulation with an unremarkable initial cranial CT should be admitted for clinical observation. This knowledge gap is reflected by variations in national and international guidelines on the management of mTBI in patients on anticoagulants. Italian guidelines recommend close observation including frequent measurement of Glasgow Coma Scale (GCS) during 24 hours and repeating a CT scan before discharge.[10] The European Federation of Neurological Societies advises 24-hour clinical observation including frequent GCS measurement, but no routine control imaging.[11] The guidelines of the Dutch Neurology Association state that clinical observation may not be warranted in all patients, but does not provide a recommendation on whether to admit these patients.[12]

Like many hospitals in The Netherlands, we routinely admit these patients for neurological observation until 24 hours after the trauma. We examined the frequency of delayed ICH in patients with mTBI on anticoagulants with an initial cranial CT scan without intracranial traumatic findings being reported by radiologist and/or neurologist, both in our own hospitals and in a meta-analysis of similar studies. We focused on the development of ICH within 24 hours, to determine whether clinical observation is of additional value in these patients.

METHODS

Study design and setting

We performed a retrospective observational multicenter study of patients admitted between January 1, 2010 and December 31, 2014. The study was approved by the ethical review boards of the Noordwest Ziekenhuisgroep Alkmaar and the Spaarne Gasthuis Haarlem. In addition, we performed a systematic review of the medical literature and a meta-analysis of the data found.

Patient selection

Data on patients with mTBI were retrieved by examining medical records with national hospital registration codes that could include mTBI patients (Supplementary Table I). Inclusion criteria were: age ≥ 16 years; mTBI; anticoagulation use (therapeutic dose heparin (LMWH), direct oral anticoagulant (DOAC), or vitamin K antagonist (VKA) and an international normalized ratio (INR) ≥ 1.7); cranial CT obtained within 24 hours of mTBI without intracranial traumatic findings being reported by radiologist and/or neurologist; hospital admission for clinical observation. Patients were excluded if the initial report of the CT scan revealed acute traumatic lesions, with the exception of skull fractures.

A non-contrast enhanced cranial CT scan was performed according to a standardized trauma protocol. In the emergency department the scan was interpreted in the Noordwest Ziekenhuisgroep by the neurology resident and the radiology resident and in the Spaarne Gasthuis by the neurologist on call. Patients with mTBI on anticoagulation therapy were routinely hospitalized. They received hourly examination of GCS and pupillary reactions for the first 6 hours and either every hour or every 2 hours thereafter until 24 hours after trauma. Vital signs were examined every 6 hours.

In one hospital anticoagulation treatment was not stopped or reversed if the CT was normal; in the other one dose of VKA was routinely skipped. CT imaging was repeated in patients who deteriorated clinically during observation (e.g., decrease in GCS, pupillary abnormalities, focal neurological deficits or seizures).

Outcome measures

The primary endpoint was the diagnosis of symptomatic delayed ICH within 24-hour observation after mTBI. We chose this endpoint to be able to determine the theoretical yield of 24-hour clinical observation in these patients. The secondary endpoint was the

establishment of symptomatic delayed ICH > 24 hours after trauma. Relevant clinical information was extracted from the medical records.

A neuroradiologist (E. A. E.) blinded for clinical information and follow-up imaging re-evaluated all cranial CT scans of patients who developed delayed ICH, combined with normal cranial CT scans in a 1:3 ratio.

Medical records of all departments after the clinical observation period were examined for clinical symptoms, readmission or death due to delayed ICH within 3 months after trauma. If no data were available in the medical records, the general practitioner was contacted to determine whether delayed ICH had occurred, or whether a patient had died from unknown causes within 3 months after mTBI.

Systematic review

For the systematic review, we searched Pubmed and Embase, using the following search terms: intracerebral/intracranial complication/hemorrhage/hematoma AND vitamin K antagonist /phenprocoumon/acenocoumarol/warfarin/anticoagulant/DOAC/ rivaroxaban/apixaban/dabigatran/edoxaban/heparinoids/fraxiparin/nadroparin/heparin AND head/brain/trauma/ injury. The primary search and study selection were performed by two independent assessors (M.A.V., M.S.M.B. (see Acknowledgements)). In case of disagreement a consensus was reached, with the possibility of consulting a third reviewer. Titles and abstracts were screened to identify potentially eligible studies, of which the references were screened subsequently. Then the full-length manuscripts were reviewed to assess if all of the following inclusion criteria were met: original data on patients with mTBI and anticoagulants, a routine cranial CT on presentation and the reporting of the frequency of delayed ICH. The study design, baseline clinical and imaging characteristics and outcome were extracted.

Statistical analysis

Data were analysed with SPSS (version 21; SPSS Inc, Chicago, IL, USA). For the meta-analysis, we calculated a pooled estimate of the incidence of delayed ICH (within and after 24 hours) using a mixed-effects Poisson regression with the number of patients in the study as an offset variable.

RESULTS

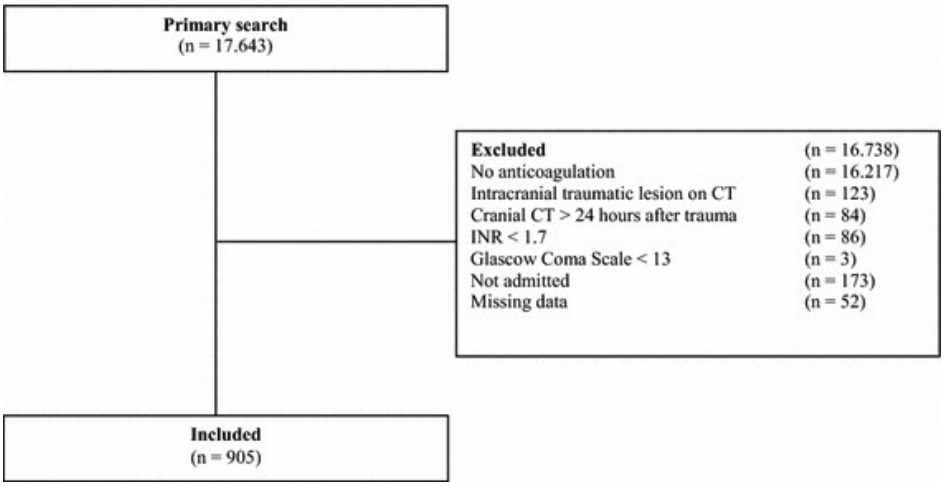
During the 5-year study period, 17.643 patients with a possible mTBI were presented in the two hospitals, of whom 1.426 used anticoagulants. We excluded 521 patients for the following reasons: intracranial traumatic lesions on initial report of CT scan (123), presentation > 24 hours after trauma (84), INR < 1.7 (86), GCS < 13 (3), not admitted (173), or missing data (52). A total of 905 patients were included in the analysis (Figure 1). Median age was 82 years (interquartile range (IQR) 74–87), 47% were men (Table 1). The majority of patients (97%) used a VKA, with a median INR of 2.9 (IQR 2.5–3.6). The primary indication for anticoagulation was atrial fibrillation (73%). The most common trauma mechanism was a ground-level fall (76%). Follow-up for a minimum of 3 months was available for 898/905 patients (99%).

Table 1. Baseline characteristics of total population.

	Total population, N = 905
Age in years - median (IQR)	82 (74–87)
Female:male - n (%)	484:421 (53:47)
Type of anticoagulation - n (%)	
VKA	874 (97)
LMWH	14 (2)
DOAC	17 (2)
Indication for anticoagulation - n (%)	
Atrial fibrillation	657 (73)
Mechanic heart valve	64 (7)
Thromboembolic disease	115 (13)
Other	69 (8)
INR - median (IQR)	2.9 (2.5-3.6)
Mechanism of injury - n (%)	
Ground-level fall	683 (75)
Fall from height	39 (4)
Motor vehicle accident	29 (3)
Bicycle accident	103 (11)
Direct blow	18 (2)
Other	33 (4)
Cranial fractures on CT - n (%)	43 (5)

Abbreviations: VKA vitamin K antagonist, LMWH low molecular weight heparin, DOAC direct oral anticoagulant, INR international normalized ratio, CT computed tomography

Figure 1. Flowchart of patient selection and inclusion.



None of our patients developed delayed ICH within 24 hours. Nine patients deteriorated neurologically due to ICH, four within 24 hours (0.4%, 95% confidence interval (CI) 0.1–1.2) and five on day 2, 18, 22, 36 and 52, respectively. In six patients, including all four that developed symptoms within 24 hours, ICH was found retrospectively upon reevaluation of the initial imaging. Of the nine patients with symptoms due to ICH, eight used a VKA for atrial fibrillation and six were men. Their median INR was 3.6 (IQR 2.8–4.3). One patient had a skull fracture. One patient had ICH as an incidental find on a scan conducted for symptoms due to an infarction in the other hemisphere. Their characteristics and outcomes are specified in Table 2. Their imaging is shown in Figure 2. With three cases of delayed ICH in our group of patients, our study was underpowered to analyze risk factors for delayed ICH.

Table 2. Characteristics and outcome of patients with symptoms due to intracranial hemorrhage.

Patient number	Sex M/F	Age (years)	Type of anti-coagulant	Indication for anti-coagulant	INR	Time to deterioration	Cranial CT	Retro-spective findings	Intervention	Outcome
1	M	68	VKA	AF	3.2	3h	SDH Contusion Skull fracture	+	VKA reversal	Full recovery
2	M	66	VKA	AF	4.1	4h	SDH	+	VKA reversal	Full recovery
3	F	81	LMWH	PE	NA	8h	Contusion	+	None[a]	Died
4	F	85	VKA	AF	8.2	22h	SDH Contusion	+	None[a]	Died
5	M	88	VKA	AF	3.4	2 days	Contusion	+	VKA reversal Burhole	Partial recovery
6	F	69	VKA	AF	2.7	18 days	SDH	-		Full recovery
7	M	83	VKA	AF	3.7	22 days	SDH (incidental) Infarction	+	None	Partial recovery
8	M	83	VKA	AF	2.7	36 days	SDH	-	VKA reversal Burhole	Partial recovery
9	M	87	VKA	AF	4.3	52 days	SDH	-	VKA reversal Burhole	Full recovery

Abbreviations: INR: international normalized ratio, M/F: male/female, VKA: vitamin K antagonist, LMWH: low molecular weight heparin, AF: atrial fibrillation, PE: pulmonary embolism, NA: non-applicable, SDH: subdural hematoma

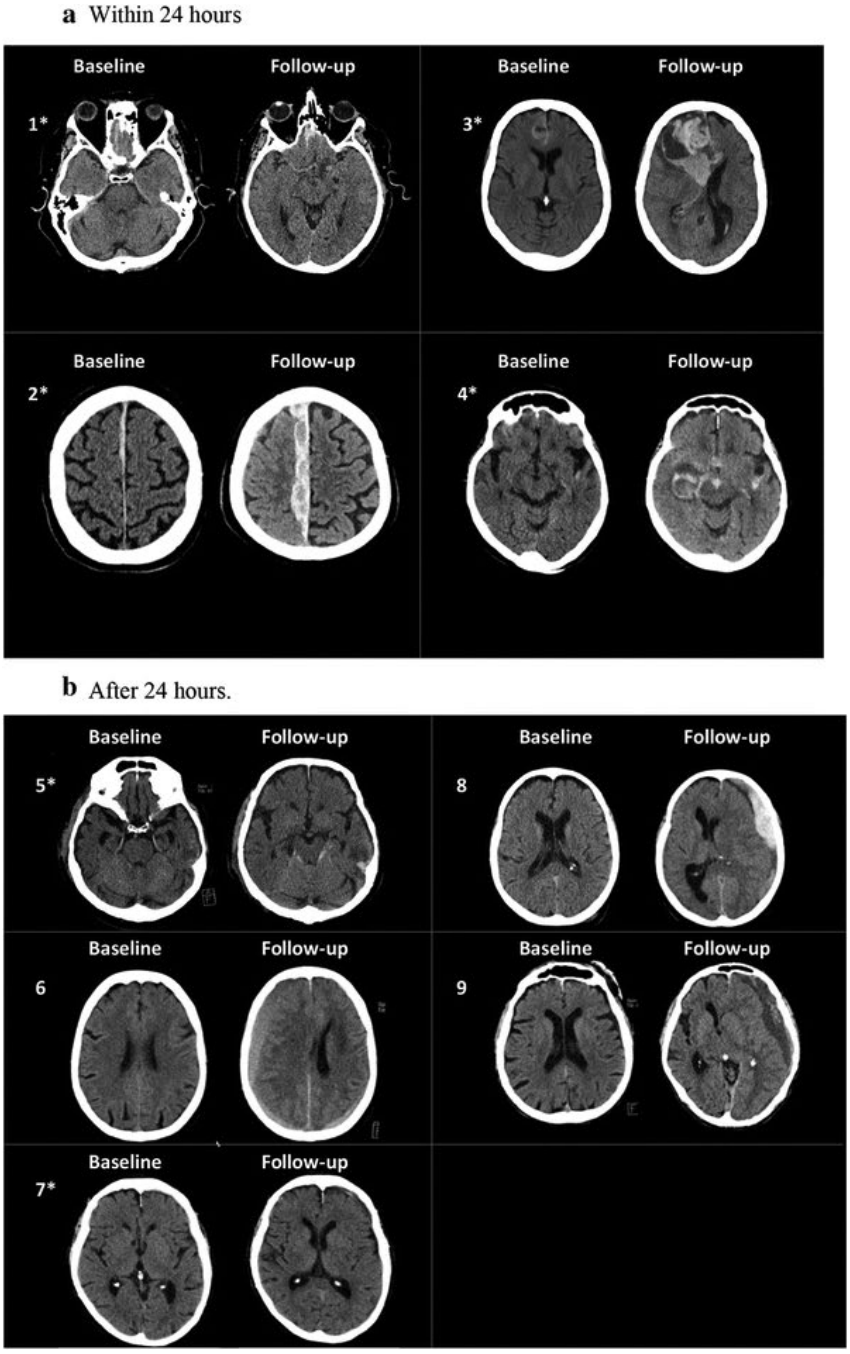
[a]Prognosis deemed futile

Table 3. Study characteristics and results.

References Study period	Design	N	Delayed (diagnosis of) ICH % (95%CI)	Symptomatic delayed (diagnosis of) ICH < 24 h % (95%CI)	Routine second CT	Reevaluation initial CT	Type of anticoagulant	Follow-up after 24 h
Kaen et al.[13] 2005-2006	PS	137	2 1.5 (0.3–5.7)	0 -	+	+	VKA (+AP)	-
Peck et al.[14] 2006-2009	RS	289	5 1.7 (0.6–4.2)	0 -	+	+	VKA (+AP)	+
Taylor et al.[19] 2010-2012	RM	59	1 1.7 (0.1–10.3)	1 1.7 (0.1–10.3)	+	-	VKA (+AP) LMWH	-
Menditto et al.[15] 2007-2010	PS	97	7 7.2 (3.2–14.8)	1 1.0 (0.1–6.4)	+	-	VKA	+
Nishijima et al.[16] 2009-2011	PM	687	4 0.6 (0.2–1.6)	0 -	-	-	VKA	+
Schoonman et al.[17] 2007-2011	RS	211	5 2.4 (0.9–5.8)	1 0.5 (0.0–3.0)	-	+	VKA	+
Lim et al.[21] Unknown	RS	295	1 0.3 (0.0–2.2)	0 -	-	-	VKA (+AP)	+
McCammack et al.[18] 2012-2013	RS	136	1 0.7 (0.0–4.6)	0 -	+	-	VKA DOAC	+
Uccella et al.[20] 2012-2013	RS	69	0 -	0 -	+	-	VKA	-
Present study	RM	905	9 1.0 (0.5–1.9)	4 0.4 (0.1–1.2)	-	+	VLA/LMWH/ DOAC	+
Total		2885	35 1.2 (0.6–2.2)	7 0.2 (0.0–0.5)				

Abbreviations: N: number, CI: confidence interval, CT: computed tomography P/R: prospective/retrospective, S/M: singlecenter/multicenter, ICH: intracranial hemorrhage, VKA: vitamin K antagonist, AP: antiplatelets, LMWH: low molecular weight heparin, DOAC: direct oral anticoagulant

Figure 2. Cranial CT of patients with symptomatic delayed (diagnosis of) ICH.



* retrospective findings on initial cranial CT

The literature search was conducted on October 17, 2016 (Supplementary Figure I). Of the 970 citations, 46 studies were retrieved for length review. Of these, nine fulfilled the selection criteria and were included in the final analysis.[13-21] Three studies were prospective and two studies were multicenter. The number of patients per study ranged from 59 to 687. All studies included patients on VKA therapy and two also included patients on DOACs or LMWH. In six studies a routine follow-up CT before discharge was performed. Three studies described reevaluation of the initial CT scans. None of the studies clearly differentiated between delayed ICH or delayed diagnosis of ICH after mTBI.

Meta-analysis of the nine studies from the systematic review and our study shows an overall pooled estimate for symptomatic delayed (diagnosis of) ICH within 24 hours of 0.2%; (95% CI 0.0–0.5). In retrospect 5/7 of these patients had traumatic findings visible on their initial cranial CT; reevaluation of the scans was not described for the other two patients.

Overall, 35 of 2885 patients (estimated pooled proportion 1.2%, 95% CI 0.6–2.2)) had delayed ICH or delayed diagnosis of ICH. ICH was found on routine follow-up scanning in 13 patients and by scanning because of neurological deterioration in 22 patients. A total of six patients required neurosurgical intervention and three patients were considered inoperable. Five patients died. The study characteristics and results are shown in Table 3.

DISCUSSION

Our study shows that the development of symptomatic delayed ICH in patients with mTBI on anticoagulation therapy with an unremarkable initial cranial CT scan is very rare. In fact, all four patients in our cohort who deteriorated within the 24-hour observation period retrospectively were found to have ICH present at baseline. Moreover, two of the five patients who deteriorated neurologically due to ICH after 24 hours also had ICH on the initial cranial CT scan.

Our study is in concordance with the findings of other groups, with overall frequencies of delayed ICH in anticoagulated mTBI patients ranging from 0 to 7%.[13-21] To our knowledge, the group we studied is the largest to date. Combined, our findings and those of the other studies indicate that only a small number of mTBI patients deteriorate within 24 hours due to delayed ICH. More importantly, most patients who develop neurological symptoms within 24 hours have a delayed diagnosis rather than delayed ICH: one patient in the study of Schoonman et al.[17] and four patients in our study.

The nine studies fulfilling the criteria for meta-analysis did not clearly differentiate between delayed ICH and delayed diagnosis of ICH after mTBI. Therefore, to be able to combine our data with those of the previously published studies, we included the three patients with delayed ICH as well as those six with delayed diagnosis of ICH in the analysis. Our meta-analysis pooled estimate showed a very low frequency of secondary deterioration (0.2%, 95% CI 0.0–0.5) due to delayed ICH or delayed diagnosis of ICH within 24 hours. Livingstone et al.[22] reported that in a prospective cohort of 2152 patients with mTBI who did not use anticoagulation, 19 patients (1.1%) retrospectively were found to have traumatic abnormalities on their cranial CT. The actual frequency of delayed ICH may be even lower when patients with delayed diagnosis of ICH rather than delayed ICH are excluded. This implies that these scans should be evaluated with the utmost care, preferably by an experienced (neuro)radiologist.

Hospital admission has its own risks. Most patients with mTBI on anticoagulation therapy are elderly patients. Studies show increased vulnerability with age for functional decline, due to hospitalization in itself and due to admission-related complications, such as urinary tract infections, delirium and pneumonia.[23-26] With the low frequency of delayed ICH, the possible benefit of admitting all patients with mTBI on anticoagulants might be outweighed by complications.

Due to the retrospective design of the study, follow-up neurological examination could not be obtained for every patient admitted. Nevertheless, our records did not reveal

readmission or death in any of these patients, suggesting there were no missed cases of delayed ICH.

Most patients used a VKA, and very few were treated with DOACs. Since the number of patients on DOACs is increasing, it could be questioned whether the results of our study can be extrapolated to patients on DOACs. As the risk of ICH is lower in patients using DOACs versus VKA,[27] this suggests the risk for developing ICH after mTBI may be even lower than in patients using VKAs. In conclusion, our findings indicate that the development of symptomatic ICH within 24 hours is very rare in patients with mTBI on anticoagulants when the initial cranial CT is normal. Routine hospitalization of these patients seems unwarranted, but scrupulous evaluation of the initial CT is mandatory.

ACKNOWLEDGEMENTS

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COMPLIANCE WITH ETHICAL STANDARDS

Integrity of research and reporting

The study was approved by the ethical review boards of the Noordwest Ziekenhuisgroep Alkmaar and the Spaarne Gasthuis Haarlem.

Conflicts of interest

The authors declare that they have no conflict of interest.

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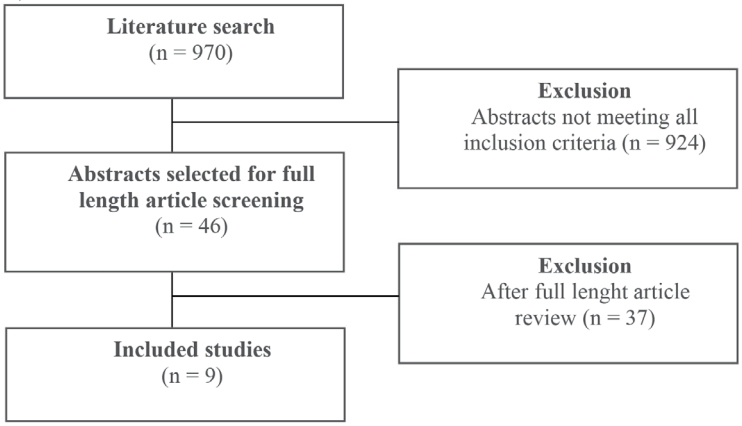
SUPPLEMENTAL MATERIAL

Table I. National hospital registration codes

1401 – Schedelfractuur (Skull fracture)
1402 – Commotio/ contusio cerebri (Brain concussion or contusion)
1409 – Overig letsel hoofd (Head injury, other)
1412 – Multitrauma SEH (Multitrauma emergency department)
1499 – Overig letsel, intoxicatie (Injury, other, intoxication)
1101 – Subarachnoidale bloeding
1102 – Intracerebrale bloeding
1103 – Intracraniële bloeding (sub- / epiduraal)

Figure I. Study selection



Chapter 3

Alcohol Intoxication as a Stroke Mimic and the Incidence of Acute Alcohol Intoxication in Stroke.

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*Shared first authorship

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ABSTRACT

Background/aims

Alcohol intoxication can be a posterior circulation stroke mimic (SM) as they share symptoms such as dysarthria, gait disturbances and nystagmus. We describe alcohol intoxication as a SM and the frequency of acute alcohol intoxication among stroke patients.

Methods

Prospective observational singlecenter study (2014-2017, Haga Ziekenhuis, the Hague). In all patients older than 16 years presenting as possible acute stroke less than 6 hours after onset, blood ethanol was measured; greater than 0.1‰ blood alcohol concentration (BAC) was considered elevated.

Results

In total 974 patients were included: 60 (6.2%) had elevated blood ethanol (mean: 1.3‰ BAC). In 180 of 974 patients (18.5%) a SM was diagnosed: 12 were due to alcohol intoxication (1.2% of total cohort, 6.7% of SMs, mean ethanol level: 2.2‰ BAC). Half of these patients denied or downplayed their alcohol consumption. Stroke and concurrent alcohol intoxication occurred in 38 of 794 strokes (4.8%, mean ethanol level: 1.1‰ BAC). Compared to other stroke patients, these 38 patients presented more often after working hours (mean 6.38pm versus 2.23pm) and received alteplase and endovascular treatment less often (23.7% versus 43.3%, p = 0.018 and 2.6% versus 8.9%, p = 0.145, respectively).

Conclusions

Of all patients presenting as possible acute stroke, 6.2% also drank alcohol. 18.5% of the whole cohort was diagnosed with a stroke mimic. Acute alcohol intoxication as sole diagnosis was diagnosed in 1.2% of the total cohort and 6.7% of stroke mimics, 50% denied or downplayed their alcohol consumption. 4.8% of all stroke patients also drank alcohol, they were significantly less likely to receive alteplase or endovascular treatment.

INTRODUCTION

Stroke remains a big burden to national health.[1] Rapid evaluation and treatment of patients with possible acute ischemic stroke in the Emergency Department (ED) reduces morbidity, mortality, and disability.[2-4] However, the need for fast door-to-needle and door-to-groin times presses for diagnosis within a short window of time.

Previous studies have shown that both neurological (for example migraine or seizures) and non-neurological (for example conversion disorder) diseases can present like stroke.[5-10] These so-called stroke mimics (SM) are reported to represent 8% up to 43% of patients admitted to the ED.[5-9] Therefore, patients with SM sometimes receive intravenous thrombolysis (IVT) or are admitted to a hospital ward. Although research has shown that these patients have very low risk of IVT-related complications,[11-17] there are still unnecessary costs involved with therapy and admission,[1,18] which may be reduced by swiftly identifying patients with SM.

Acute alcohol intoxication typically is a posterior circulation SM as these diagnoses share symptoms such as slurred speech, diplopia, gait disturbances, nausea, and nystagmus. The risks of IVT in patients with acute alcohol intoxication may be greater than in patients with other SM, because ethanol impairs fibrinolysis and increases platelet activation.[19,20]

Only few studies describe acute alcohol intoxication as a SM, but none of these provide details on these patients.[5,6,11-13] Furthermore, studies have shown that chronic alcohol abuse is a risk factor for stroke, both ischemic and hemorrhagic.[21-23] A study by Lemarchand et al. showed in a murine model that 6 week alcohol consumption worsens ischemic lesions and cancels the beneficial effects of IVT.[24] Acute alcohol intoxication and acute ischemic stroke may be concurrent and only little data has been published on outcome in these patients.[25,26]
The aim of this study is to describe the frequency and clinical characteristics of patients with acute alcohol intoxication as a SM. Furthermore, we aim to describe patients with stroke and concurrent alcohol intoxication.

METHODS

Study Design and Setting

This was a prospective observational single-center study in our large urban teaching hospital. The study protocol was approved by the regional ethics committee (METC Zuid

Holland). Due to the observational nature of our study, formal approval was waived. In all consecutive patients presented to the ED between January 2014 and December 2017, with a possible stroke who might be eligible for reperfusion therapy, the blood ethanol level was measured. According to our acute stroke protocol, these patients were evaluated by a stroke team, consisting of a neurologist, ED physician, ED nurse, and radiologist. All patients received a cranial computed tomography and blood examination. The neurologist, supported by the examination of imaging by the radiologist, determined whether the patient was eligible for IVT. Additional computed tomography-angiography was performed when ischemic stroke was diagnosed, to evaluate the possibility of endovascular treatment (EVT). Magnetic resonance
imaging (MRI) was available, but was not part of the routine workup.

Patient Selection and Data

We included all patients that were 16 years or older and presented within 6 hours after symptom onset. Patients were excluded in case of missing data on final diagnosis, blood ethanol level or time of onset. The final diagnosis was established by the treating neurologist after the complete workup in the ED and in case of admission at discharge. Blood ethanol level was routinely measured as part of the standardized blood examination of patients suspected of acute stroke. Blood was drawn immediately after arrival to the ED. An ethanol level greater than 0.1‰ blood alcohol concentration (BAC=10 mg/dL) was considered to be elevated. Relevant clinical data was extracted from the medical records. Vertebrobasilary symptoms were defined as follows: one or more of following symptoms: dysarthria, diplopia, ataxia, gait disturbances, and/or nystagmus.

Outcome Measures

Primary endpoint was the incidence of acute alcohol intoxication as SM. Secondary endpoints were the incidence of increased ethanol levels in all patients presented for possible reperfusion therapy and in patients with final diagnosis of stroke.

Statistical Analysis

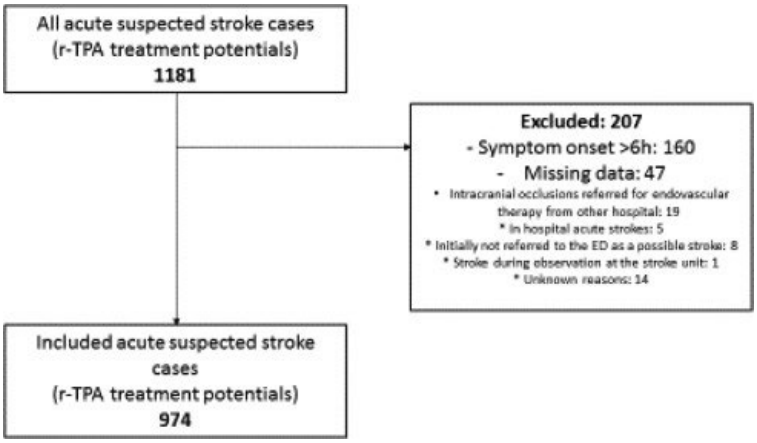
Data are represented as frequency (percentage), mean (standard deviation), and median (interquartile range (IQR)). We compared patients with and without increased ethanol values in the total cohort, in patients with final diagnosis of stroke and in SM. Furthermore, we describe characteristics of patients with final diagnosis of stroke versus patients with final diagnosis of SM, and of patients with a SM due to alcohol intoxication versus patients with stroke with concurrent alcohol intoxication and. Intergroup comparisons

were made with $\chi 2$ test, Fisher's exact test for discrete variables and with Mann-Whitney U test for continuous variables. All p values were two-sided and a value of less than 0.05 was considered to be statistically significant. Data were analyzed with SPSS (version 22, Armonk, NY: IBM Corp.).

RESULTS

Between 2014 and 2017, 1181 patients with a suspected acute stroke were presented for possible reperfusion therapy. We excluded 207 patients: 47 because of missing data on blood ethanol level (mostly because they were referred from another hospital for endovascular recanalization at our institution) and 160 because of symptom onset greater than 6 hours, see Figure 1. Therefore, a total of 974 patients were eligible: 496 (50.9%) males with a mean age of 70 years (±15 years).

Figure 1. Exclusions of patients



As shown in Table 1, 60 of the 974 patients (6.2%) had an elevated ethanol level with a mean value of 1.3‰ BAC (range 0.2-3.8‰). These patients were more often male (61.7% versus 50.2%, p = 0.109), were significantly younger (66 years versus 70 years, p = 0.010), had a lower systolic blood pressure (153 mm Hg versus 164 mm Hg, p = 0.003) and presented to the ED later than patients without an elevated blood ethanol level (time 6.45 pm versus 2.24 pm, p < 0.001).

Table 1. Characteristics of the Study Population (with Subgroups of All Strokes and All Stroke Mimics), Subdivided into without and with Elevated Ethanol Level.

	Total Cohort N = 974	Ethanol < 0.10‰ BAC n = 914 (93.8%)	Ethanol >0.10‰ BAC n = 60 (6.2%)	p-value	All Strokes n = 794 (81.5%)	Ethanol < 0.10‰ BAC n = 756 (95.2%)	Ethanol > 0.10‰ BAC n = 38 (4.8%)	p-value	All Stroke Mimics n = 180 (18.5%)	Ethanol < 0.10‰ BAC n = 158 (87.8%)	Ethanol > 0.10‰ BAC n = 22 (12.2%)	p-value
Male sex - n (%)	496 (50.9)	459 (50.2)	37 (61.7)	0.109	421 (53.0)	394 (52.1)	27 (71.1)	0.029	75 (41.7)	65 (41.1)	10 (45.5)	0.818
Age in years - mean ± SD	70 (±15)	70 (±15)	66 (±14)	0.010	72 (±14)	72 (±14)	65 (±15)	0.007	62 (±17)	61 (±17)	66 (±14)	0.350
Ethanol in ‰ BAC - mean (min-max)	-	-	1.3 (0.2-3.8)	-	-	-	1.1 (0.2-3.7)	-	-	-	1.6 (0.2-3.8)	-
Systolic BP in mmHg - mean ± SD	164 (±31)	164 (±31)	153 (±32)	0.003	166 (±31)	167 (±31)	156 (±31)	0.049	152 (±31)	154 (±31)	142 (±26)	0.169
Diastolic BP in mmHg- mean ± SD	87 (±18)	87 (±18)	82 (±19)	0.375	88 (±18)	88 (±18)	86 (±19)	0.963	83 (±19)	85 (±18)	76 (±21)	0.230
Time of presentation - median	2.33 pm	2.24 pm	6.45pm	0.001	2.28 pm	2.23 pm	6.38 pm	0.024	3.19 pm	2.45 pm	7.41 pm	0.027
Presented to ED at working hours - n (%)	502 (51.5)	491 (53.7)	11 (18.3)	0.000	418 (52.6)	410 (54.2)	8 (21.2)	<0.001	84 (46.7)	81 (51.3)	3 (13.6)	0.001
IVT - n (%)	349 (35.8)	339 (37.1)	10 (16.7)	0.001	336 (42.3)	327 (43.3)	9 (23.7)	0.018	13 (7.2)	12 (7.6)	1 (4.5)	1.000
EVT - n (%)	68 (7.0)	67 (7.3)	1 (1.7)	0.116	68 (8.6)	67 (8.9)	1 (2.6%)	0.145	-	-	-	-
Vertebrobasilary symptoms - n (%)	235 (24.1)	213 (23.3)	22 (36.7)	0.028	175 (22.0)	167 (22.1)	8 (21.1)	1.000	60 (33.3)	46 (29.1)	14 (63.6)	0.003

Abbreviatons: BAC: blood alcohol concentration, SD: standard deviation, BP: blood pressure, ED: emergency department, pm: after noon, IVT: intravenous thrombolysis, EVT: endovascular treatment

Table 2. Characteristics of the study population, subdivided into stroke and stroke mimic

	Total cohort N = 974	Stroke n = 794 (81.5%)	Stroke mimic n = 180 (18.5%)	p-value
Male sex - n (%)	497 (51.0)	421 (53.0)	75 (41.7)	0.006
Age in years - mean ± SD	70 (±15)	72 (±14)	62 (±17)	<0.001
Systolic BP in mmHg - mean ± SD	164 (±31)	166 (±31)	152 (±31)	<0.001
Diastolic BP in mmHg - mean ± SD	87 (±18)	88 (±18)	83 (±19)	0.094
Vertebrobasilary symptoms - n (%)	235 (24.1)	175 (22.0)	60 (33.3)	0.002
Time of presentation - median	2.33 pm	2.28 pm	3.19 pm	0.195

Abbreviatons: SD: standard deviation, BP: blood pressure, pm: after noon

Table 3. Total and frequency of all final diagnosis

Diagnosis	Total patients - n	% of stroke or stroke mimics	% of total cohort
Stroke	794	-	81.5
IS in posterior circulation	180	22.6	18.5
IS in anterior circulation	555	69.9	57.0
Hemorrhage in posterior circulation	9	1.1	0.9
Hemorrhage in anterior circulation	50	6.3	5.1
Stroke mimic	180	-	18.5
Somatoform	35	19.4	3.6
Peripheral vestibular disorder	27	15.0	2.8
Seizure	22	12.2	2.3
Othera	18	10.0	1.8
Migraine	15	8.3	1.5
Cardiac/collaps/orthostasis/syncope	15	8.3	1.5
Acute alcohol intoxication	12	6.7	1.2
Infection (brain or elsewhere)	9	5.0	0.9
No final diagnosis given	9	5.0	0.9
Intoxication, otherb	6	3.3	0.6
Malignancy	6	3.3	0.6
Hyperventilation	6	3.3	0.6

Abbreviatons: IS: ischemic stroke
aOther: transient global amnesia (n=3), subdural hematoma (n=1), local thrombosis in the arm (n=1), delirium (n=1), hypoperfusion (n=2), hypertensive encephalopathy (n=1), hyperglycemia (n=1), tiredness (n=3), amyloid spells (n=1), dementia (n=1), retention of the bladder (n=2), atrial flutter (n=1)
bOther intoxication included: cannabis oil (n=2), smoking cannabis (n=2), sedative-use (n=2)

Table 4. Alcohol intoxication only compared to stroke with concurrent alcohol intoxication

	Alcohol intoxication only n = 12	Stroke + alcohol intoxication n = 38	p-value
Male sex - n (%)	6 (50.0)	27 (71.1)	0.294
Age in years- mean ± SD	70 (±12)	65 (±15)	0.363
Ethanol in ‰ BAC – mean (min-max)	2.2 (1.0-3.8)	1.1 (0.2-3.7)	0.001
Systolic BP in mmHg - mean ± SD	143 (±33)	156 (±31)	0.289
Diastolic BP in mmHg - mean ± SD	67 (±24)	86 (±19)	0.034
Time of presentation - median	6.42 pm	6.38 pm	0.928
Working hours - n (%)	1 (8.3)	8 (21.1)	0.425
IVT - n (%)	-	9 (23.7)	-
EVT - n (%)	-	1 (2.6)	-
Vertebrobasilary symptoms - n (%)	11 (91.7)	8 (21.1)	<0.001
History of alcohol abuse - n (%)	4 (33.3)	18 (47.4)	0.512
Denial or downplay alcohol onsumption - n (%)	6 (50.0)	11 (28.9)	0.017
Nystagmus - n (%)	7 (63.6)	5 (13.2)	0.003

Abbreviations: SD: standard deviation, BAC: blood alcohol concentration, BP: blood pressure, IVT: intravenous thrombolysis, EVT: endovascular treatment

A total of 180 of 974 (18.5%) was diagnosed as a SM, they were more often female (58.3% versus 47.0%, p = 0.006), younger (62 years versus 72 years, p < 0.001) and had a lower mean systolic blood pressure (152 mm Hg versus 166 mm Hg, p < 0.001) compared to patients with a final diagnosis of stroke (see Table 2). Table 3 shows all different causes of SM. Somatoform disorder was diagnosed most often: 35 of 180 (19.4%), followed by peripheral vestibular disease (15.0%), seizure (12.2%) and migraine (8.3%). Acute ethanol intoxication was found in 6.7%. Other diagnoses were much less frequent and are listed in Table 3. Of all SMs 7.2% received IVT, no complications occurred.

As shown in Table 4, 12 patients had a final diagnosis of only alcohol intoxication, comprising 1.2% of the total cohort, 5.1% of patients with vertebrobasilary symptoms and 6.7% of SM. Compared to the 38 patients with stroke and concurrent alcohol intoxication, patients with only alcohol intoxication had a higher mean blood ethanol level: 2.2‰ BAC versus 1.1‰ BAC (p = 0.001). They more often had a nystagmus (63.6% versus 13.2%, p = 0.003) and other vertebrobasilary symptoms (91.7% versus 21.1%, p < 0.001): 9 of 12 patients had dysarthria, 10 of 12 had gait disturbances and 4 of 12 had either a difficulty finding words or incoherent speech. Only one patient did not experience vertebrobasilary symptoms: he was found by his neighbor in a state of confusion and had the inability to repeat a sentence or perform simple tasks. Of the patients that were diagnosed with a

SM due to alcohol intoxication, 50.0% denied or downplayed their alcohol intake versus 28.9% of the stroke patients with concurrent alcohol intoxication (p = 0.017). They were no differences in the time of presentation (p = 0.928). None of the patients diagnosed with only alcohol intoxication received IVT.

Stroke (either ischemic or hemorrhagic) was diagnosed in 794 of 974 (81.5%) patients. As shown in Table 1, 38 of 794 (4.8%) patients had a concurrent alcohol intoxication with a mean ethanol value of 1.1‰ BAC (range 0.2-3.7‰). The mean level of ethanol in SM due to alcohol intoxication was double compared to stroke patient with concurrent alcohol intoxication. 30 of 38 patients were diagnosed with a stroke in the anterior circulation and only 1 of these 30 patients experienced vertebrobasilary symptoms. Next to a paresis of the right arm and leg, neurologic examination showed a bidirectional nystagmus with a mean ethanol level of 2.0‰ BAC. Seven patients had a final diagnosis of ischemic stroke in the posterior circulation with comorbid alcohol intoxication; all these patients experienced vertebrobasilary symptoms. One of these 38 patients had a small hypertensive hemorrhage in the brainstem with mild hemiparesis on the left and vomiting. On average, patients with stroke and concurrent alcohol intoxication were 7 years younger than patients with a stroke without alcohol intoxication (p = 0.007). Their systolic and diastolic blood pressure were lower, 156 mm Hg versus 167 mm Hg, p = 0.049 and 86 mm Hg versus 88 mm Hg, p = 0.963, respectively. They were presented to the ED more often after working hours (79% versus 46%, p < 0.001) with a median time of presentation of 6.38 pm versus 2.23 pm (p = 0.024). Fewer patients with ischemic stroke and concurrent alcohol intoxication received IVT and EVT: 9 of 38 (23.7%) versus 327 of 756 (43.3%) (p = 0.018) and 1 of 38 (2.6%) versus 67 of 756 (8.9%) (p = 0.145), respectively (see Table 1). No complications of these procedures occurred in stroke patients with concurrent alcohol intoxication.

DISCUSSION

To our knowledge, we are the first study to measure blood ethanol consistently in every patient presented to the ED for possible reperfusion therapy. Kostulas et al. reported 8% of their stroke mimics to be alcohol intoxication which is in line with our result.[13] Others report lower percentages of alcohol intoxication: 1-4% of all SM.[5,6,11-13] As we also found that 34.0% of patients (and up to 50.0% of the patients with only alcohol intoxication) with an elevated ethanol level denied or downplayed their alcohol intake, it is possible that earlier studies that did not routinely measure ethanol level or ask about alcohol intake, have underdiagnosed alcohol intoxication as a SM. McClelland et al. reported in

their systematic review that 22% of all patients presented to the ER with a possible acute stroke are diagnosed with a SM which is comparable to our result.[9] Also consistent with previous studies is the younger age,[7-9,11-13,27] higher percentage of females,[8-12] and lower systolic blood pressure we report in patients with SM.[7,10,11-13]

Of all patients with a final diagnosis of stroke, 4.8% was also intoxicated with alcohol. Thirty of these 38 intoxicated patients with concurrent stroke were diagnosed with a stroke in the anterior circulation; only 1 of these 30 patients with a stroke in the anterior circulation experienced vertebrobasilary symptoms; a bidirectional nystagmus next to paresis of the right arm and leg. Seven patients had a final diagnosis of ischemic stroke in the posterior circulation with comorbid alcohol intoxication; all these patients experienced vertebrobasilary symptoms. Considering this last subgroup of patients, the diagnostic dilemma becomes greater, because their symptoms could be attributable to both stroke and intoxication. We could not find literature to confirm these findings. A blood ethanol level and/or a cranial MRI might, in these cases, help the clinicians in making an accurate diagnosis.

We showed that patients with a SM due to alcohol intoxication compared to patients with stroke and concurrent alcohol intoxication had higher mean ethanol levels and a 5 fold higher incidence of nystagmus. This is of particular importance, as our results show that significantly fewer patients with ischemic stroke and concurrent alcohol intoxication receive IVT and EVT in comparison to patients with an ischemic stroke without alcohol intoxication. Little has been published on this specific group of patients, but Gattringer et al. also found that patients with ischemic stroke and chronic or acute alcohol consumption have a decreased likelihood of receiving IVT.[25] A recent published article by Arokszallasi et al. describes 3 case reports that show that alcohol intoxication can even delay stroke diagnosis and therefore treatment.[26] Dubiety about the right diagnosis (only alcohol intoxication or comorbid ischemia in the posterior circulation) might be the explanation why in some cases reperfusion therapy is abandoned. Subsequently, clinicians might feel the concern of an increased risk of hemorrhage, even though the use of alcohol or acute alcohol intoxication is not a formal contraindication. Of all patients in our cohort with ischemic stroke and comorbid alcohol intoxication 10 received IVT and 1 EVT. No complications occurred, which is in line with the conclusion drawn by Gattringer et al. that IVT in patients with ischemic stroke with comorbid chronic or acute alcohol intoxication does not result in an increased risk for symptomatic intracranial hemorrhage.[25] However, a conclusive answer about safety of reperfusion therapy in patients with acute alcohol intoxication remains to be elucidated in larger studies. Even if IVT is safe in these patients, there are still unnecessary costs involved if acute alcohol intoxication as a SM is treated with IVT and submitted to a stroke ward.[18] Dawson et al. estimate that stroke unit bed

occupancy by SM could be reduced from 9.2% to 3.2% if MRI is performed upon suspicion and several studies have shown the feasibility of diffusion weighted imaging - only MR protocols in patients with SM in the ED.[6,28] However, cost effectiveness of this approach has not been tested. Moreover, MRI can be false-negative, especially in acute ischemic stroke of the posterior circulation.[29,31] In these patients, measurements of ethanol levels may be helpful in differentiating between a stroke and a SM.

Our results should be interpreted in the context of its strengths and limitations. To our knowledge, we are the first to explore patients (> 16 years) presenting with a possible acute stroke and concurrent alcohol intoxication systematically. Our results give an accurate account of alcohol intake in patients presenting to the ED for possible reperfusion therapy, as we measured ethanol levels in all consecutive patients and not only in patients clinically suspected of alcohol intoxication thereby limiting possible selection bias. In addition, our study was conducted in a large urban teaching hospital that services a large heterogeneous population comparable to many worldwide. Several limitations need warranting. First, although we are the first to report alcohol intake in consecutive patients with acute neurological symptoms over a 3-year period, the small number of patients with elevated ethanol levels restrict us from drawing strong conclusions on their distinguishing characteristics and since this is a single center study, the external validity may be limited. Second, future studies are needed to assess the risk of IVT in patients with concurrent alcohol intoxication and the long-term outcome. Last, final diagnoses are based on clinical expertise and are not routinely confirmed with cranial MRI. Therefore, it is possible that some patients were misdiagnosed. However, acute alcohol intoxication becomes very unlikely in case of symptoms lasting for several days.

SUMMARY AND CONCLUSION

In conclusion, this is the first cohort study to describe ethanol blood level in all patients presenting with possible acute stroke. Alcohol intoxication occurred in 6.2% of all patients presenting for possible reperfusion therapy. In our cohort, 18.5% was diagnosed with a SM and 1.2% is diagnosed with only alcohol intoxication. If only patients with vertebrobasilary symptoms are taken into account, this number rises to 5.1%. An interesting observation is that patients presenting to the ED with a possible acute stroke and elevated ethanol levels have a 2-fold increased risk of any SM. 4.8% of all patients with final diagnosis of stroke also drank alcohol. Patients with elevated ethanol levels in general and patients with only alcohol intoxication in particular most often present after working hours. They are not always forthcoming and truthful about their alcohol intake. Therefore, clinicians should consider measuring blood ethanol levels in the acute setting in patients with a possible stroke of the posterior circulation presenting after working hours. But since knowledge so far does not show an increased risk of symptomatic intracranial hemorrhage, these patients should not be withheld from IVT or EVT.

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Chapter 4

Association Between Low Blood Pressure and Clinical Outcomes in Patients With Acute Ischemic Stroke.

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ABSTRACT

Background and Purpose

Low blood pressure is uncommon in patients with acute ischemic stroke (AIS). We assessed the association between baseline low blood pressure and outcomes in patients with AIS.

Methods

Post hoc analysis of the PASS (Preventive Antibiotics in Stroke Study). We compared patients with AIS and low (< 10th percentile) baseline systolic blood pressure (SBP) to patients with normal SBP (≥ 10th percentile < 185 mm Hg). The first SBP measured at the Emergency Department was used. Outcomes included in-hospital mortality, major complications < 7 days of stroke onset, and functional outcome at 90 days (modified Rankin scale score). We used regression analysis to calculate (common) odds ratios and adjusted for predefined prognostic factors.

Results

Two thousand one hundred twenty-four out of 2538 patients had AIS. The cutoff for low SBP was 130 mm Hg (n=212; range, 70–129 mm Hg). One thousand four hundred forty patients had a normal SBP (range, 130–184 mm Hg). Low SBP was associated with an increased risk of in-hospital mortality (8.0% versus 4.2%; adjusted odds ratio (aOR), 1.58; 95% confidence interval (CI), 1.13–2.21) and complications (16.0% versus 6.5%; aOR, 2.56; 95% CI, 1.60–4.10). Specifically, heart failure (2.4% versus 0.1%; aOR, 17.85; 95% CI, 3.36–94.86), gastrointestinal bleeding (1.9% versus 0.1%; aOR, 26.04; 95% CI, 2.83–239.30), and sepsis (3.3% versus 0.5%; aOR, 5.53; 95% CI, 1.84–16.67) were more common in patients with low SBP. Functional outcome at 90 days did not differ (shift towards worse outcome: adjusted common odds ratio, 1.24; 95% CI, 0.95–1.61).

Conclusions

Whether it is cause or consequence, low SBP at presentation in patients with AIS was associated with an increased risk of in-hospital mortality and complications, specifically heart failure, gastrointestinal bleeding, and sepsis. Clinicians should be vigilant for potentially treatable complications.

INTRODUCTION

Most patients with acute ischemic stroke (AIS) have elevated blood pressure (BP) at presentation, which often declines spontaneously in the following days.[1] Several studies that examined the association between BP and outcome after AIS found a U-shaped relationship, with both lower and higher BP associated with an increased risk of poor outcome.[1–3] However, most of these studies mainly focused on high BP. Recently, the ENCHANTED trial (Enhanced Control of Hypertension and Thrombolysis Stroke Study) found that intensive BP lowering resulted in a lower risk of intracranial hemorrhage, but this did not translate into a better functional outcome at 90 days.[4] The association between spontaneous low BP and outcome after AIS has not been thoroughly assessed, which was the aim of our study.

METHODS

We included all patients with AIS from the PASS (Preventive Antibiotics in Stroke Study).[5] We used the first BP measured at the Emergency Department with an automatic BP monitor for all analyses. All patients or their legal representatives provided written informed consent. The study protocol was approved by the Institutional Review Board of the Academic Medical Center (Amsterdam, the Netherlands) and the research board of each participating center. Further details of the methods are provided in the Supplemental Material. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Outcomes of the study were in-hospital mortality, major complications within 7 days of stroke onset (defined as any thrombotic event, progressive stroke, symptomatic intracranial hemorrhage, major extracranial bleeding, sepsis, and heart failure; for definitions see the Supplemental Material) and functional outcome at 3 months (measured with the modified Rankin Scale score).

Statistical Analysis

After evaluation, systolic BP (SBP) showed the strongest association with functional outcome with a shift towards poor functional outcome for patients with an SBP lower and higher than 164 mm Hg: adjusted common odds ratio, 1.08 per 10 mm Hg decrease; 95% confidence interval (CI), 1.02–1.14 and adjusted common odds ratio, 1.05 per 10 mm Hg increase; 95% CI, 0.99–1.10. SBP was, therefore, used in all subsequent analyses (Figure

1 and Figures I and II in the Supplemental Material). We compared patients with low SBP (SBP < 10th percentile) versus normal SBP values (≥ 10th percentile < 185 mm Hg) versus high (SBP ≥ 185 mm Hg). The normal SBP group was used as reference group. The 10th percentile was chosen as it identifies a subgroup of patients with low SBP within the PASS study population. The 185 mm Hg was used as this is the upper threshold value for intravenous thrombolysis. An exploratory analysis of the lower second percentile was also conducted.

Intergroup comparisons were analyzed with $\chi 2$ test, independent T test, or Mann-Whitney U test. We used multivariable ordinal and logistic regression analysis to calculate (common) odds ratios for all outcomes and adjusted for predefined prognostic factors. When no event occurred in one of the groups, we added 0.5 to all 4 cells of the 2×2 table for the unadjusted analyses.[6]

RESULTS

Of 2538 patients included in PASS, 2124 had AIS and were included in the analyses. Two hundred and twelve patients were in the low SBP group (cutoff 130 mm Hg), 1440 (67.8%) in the normal SBP group, and 472 (22.2%) in the high SBP group (Figure III in the Supplemental Material). Patients in the low SBP group had higher National Institutes of Health Stroke Scale at baseline (median 6 versus 5; p = 0.001) and more often had cardioembolic stroke (33.0% versus 24.0%; p = 0.016), see Table I in the Supplemental Material.

In-hospital mortality was higher in the low SBP group (8.0% versus 4.2%; adjusted odds ratio (aOR), 1.58; 95% CI, 1.13–2.21; Table). Patients in the low SBP group also more often suffered from complications within 7 days after stroke onset (16.0% versus 6.5%; aOR, 2.56; 95% CI, 1.60–4.10). Specifically, patients with low SBP had a higher risk of heart failure (2.4% versus 0.1%; aOR, 17.85; 95% CI, 3.36–94.86), major extracranial bleeding (all gastrointestinal hemorrhages: 1.9% versus 0.1%; aOR, 26.04; 95% CI, 2.83–239.30), and sepsis (3.3% versus 0.5%; aOR, 5.53; 95% CI, 1.84–16.67). There was no difference in symptomatic intracranial hemorrhage between the groups.

After adjustment, there was a trend towards worse functional outcome at 90 days in patients with low SBP (adjusted common odds ratio, 1.24; 95% CI, 0.95–1.61; Figure 2). Outcomes of patients in the second percentile (SBP < 110 mm Hg) did not differ from those in the 10th percentile, except for a higher rate of heart failure (12.2% versus 2.4%; p

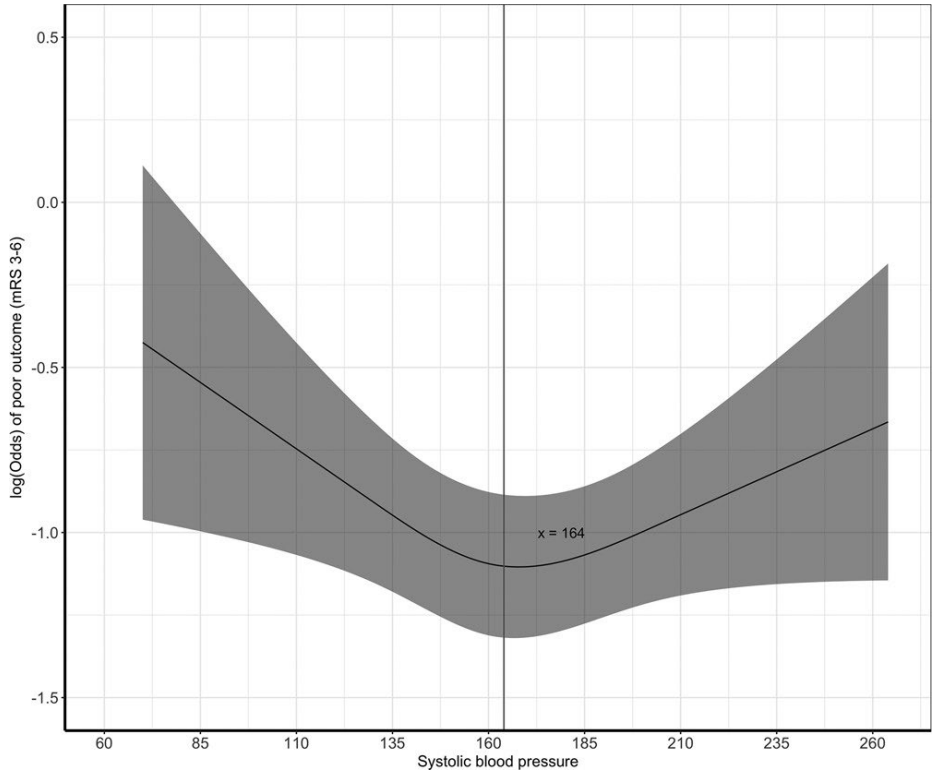
= 0.008, Table II in the Supplemental Material When patients in the high SBP group were compared with the normal SBP group, there were no statistically significant differences for any of our outcome measures (Table).

Table 1. Outcomes in SBP groups.

		Unadjusted OR (95%CI)	Adjusted OR (95%CI)
In-hospital mortality			
Low SBP	17/212(8.0)	1.97(1.13-3.44)	1.58(1.13-2.21)[a]
Normal SBP	61/1440(4.2)	1.0*	1.0*
High SBP	18/472(3.8)	0.90(0.52-1.53)	1.03(0.75-1.42)[a]
Cause of death			
Neurologic			
Low SBP	9/212(4.3)	1.78(0.84-3.76)	1.25(0.55-2.84)[b]
Normal SBP	35/1440(2.4)	1.0*	1.0*
High SBP	11/472(2.3)	0.96(0.48-1.90)	0.80(0.28-2.27)[b]
Septic			
Low SBP	5/212(2.4)	1.91(0.70-5.19)	1.61(0.57-4.54)[b]
Normal SBP	18/1440(1.3)	1.0*	1.0*
High SBP	4/472(0.8)	0.68(0.23-2.01)	1.74(0.41-7.41)[b]
Cardiac			
Low SBP	2/212(0.9)	1.95(0.40-9.45)	1.72(0.34-8.61)[b]
Normal SBP	7/1440(0.5)	1.0*	1.0*
High SBP	3/472(0.6)	1.31 0.34-5.08)	0.91(0.13-6.37)[b]
Other/unknown			
Low SBP	1/212(0.5)	6.82(0.43-109.45)	5.23(0.30-92.33)[b]
Normal SBP	1/1440(0.1)	1.0*	1.0*
High SBP	-	1.02(0.04-24.97)	-
Any complication within 7 days			
Low SBP	34/212(16.0)	2.77(1.81-4.22)	2.56(1.60-4.10)[a]
Normal SBP	93/1440(6.5)	1.0*	1.0*
High SBP	29/472(6.1)	0.95(0.62-1.46)	1.17(0.92-1.49)[a]
Thrombotic events[c]			
Low SBP	3/212(1.4)	2.28(0.62-8.50)	1.78(0.47-6.77)[b]
Normal SBP	9/1440(0.6)	1.0*	1.0*
High SBP	5/472(1.3)	1.70(0.57-5.11)	2.07(0.67-6.37)[b]
Progressive stroke			
Low SBP	14/212(6.6)	1.63(0.89-2.86)	1.26(0.67-2.36)[b]
Normal SBP	60/1440(4.2)	1.0*	1.0*
High SBP	18/472(3.8)	0.91(0.53-1.56)	1.13(0.65-1.98)[b]
Any major bleeding			
Low SBP	5/212(2.4)	2.29(0.83-6.38)	2.01(0.71-5.73)[b]
Normal SBP	15/1440(1.0)	1.0*	1.0*
High SBP	3/472(0.6)	0.61(0.18-2.11)	0.67(0.19-2.35)[b]

		Unadjusted OR (95%CI)	Adjusted OR (95%CI)
sICH			
Low SBP	1/212(0.5)	0.48(0.06-3.69)	0.40(0.05-3.14)[b]
Normal SBP	14/1440(1.0)	1.0*	1.0*
High SBP	3/472(0.6)	0.65(0.19-2.28)	0.74(0.21-2.62)[b]
Major extracranial bleeding[d]			
Low SBP	4/212(1.9)	27.67(3.08-248.80)	26.04(2.83-239.30)[a]
Normal SBP	1/1440(0.1)	1.0*	1.0*
High SBP	-	1.02(0.04-24.97)	-
Heart failure			
Low SBP	5/212(2.4)	17.37(3.35-90.10)	17.85(3.36-94.86)[b]
Normal SBP	2/1440(0.1)	1.0*	1.0*
High SBP	-	0.61(0.03-12.71)	-
Sepsis			
Low SBP	7/212(3.3)	6.99(2.43-20.13)	5.53(1.84-16.67)[b]
Normal SBP	7/1440(0.5)	1.0*	1.0*
High SBP	3/472(0.6)	1.31(0.34-5.08)	1.93(0.47-7.96)[b]

Figure 1. Association between SBP and log(odds) to achieve poor functional outcome at 90 days (mRS 3-6) estimated with multivariable logistic regression.



X-axis shows the SBP in mmHg, Y-axis shows the linear predictors of the regression model. The nadir is located at 164 mmHg SBP, and there was a shift towards poor functional outcome for patients with lower and higher SBP: acOR 1.08 per 10 mmHg decrease, 95%CI 1.02-1.14 and acOR 1.05 per 10 mmHg increase, 95%CI 0.99-1.10).

Figure 2. Functional outcome at 90 days (measured with modified Rankin Scale score).

Low vs. normal acOR 1.24, 95%CI 0.95-1.61. High vs. normal acOR 1.09, 95%CI 0.90-1.33. Missing values n=18.

DISCUSSION

We found that patients with AIS and low SBP had a higher risk of in-hospital mortality and major complications early after admission when compared with patients with normal SBP. Specifically, heart failure, gastrointestinal bleeding, and sepsis occurred more often in patients with low SBP. The higher rate of early complications did not translate into a statistically significant worse functional outcome at 90 days.

The prognostic value of BP in acute stroke has been previously evaluated. Many studies found U-shaped relationships between BP and outcomes, similar to our study.[1–3] However, the underlying mechanisms for these outcomes seem to differ between high and low BP. Most studies focused on high BP and identified edema and increased risk of symptomatic intracranial hemorrhage as causes for poor functional outcome in these patients.[1,3,7] We found significantly more major extracranial bleeding, heart failure, and sepsis in patients with low SBP. The observed association between low SBP and the risk of these complications, of course, does not necessarily indicate causality. The association could also be the other way around because low SBP could be a marker of these conditions developing. Moreover, patients with low SBP more often received intravenous thrombolysis, which may have contributed to the higher frequency of extracranial bleeding.

Our study has several limitations. First, the PASS was a randomized trial, which might have led to some selection bias in our patient cohort. Still, the inclusion criteria were broad and did not include any restrictions related to BP. Second, computed tomography angiography was not routinely conducted in our cohort. It is, therefore, possible that aortic or carotid dissections causing low BP were missed. Third, serial BP measurements would have been of value to study the association between low BP and outcome in more detail. Fourth, there is no clearly defined cutoff for low BP in patients with AIS. Previously identified nadirs of the tipping point in the U-shaped association between BP and outcome also vary between 120 and 180 mm Hg.[2,3] Because of this variability, we decided to use the lowest 10th percentile as a cutoff, which is also, of course, a somewhat arbitrary cutoff.

In conclusion, low SBP at presentation was associated with an increased risk of in-hospital mortality and complications in patients with AIS. Whether low SBP is a cause or consequence of these complications is unknown, but the presence of low SBP should prompt clinicians to look for these conditions.

SOURCES OF FUNDING

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DISCLOSURES

None.

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SUPPLEMENTAL MATERIAL

Preventive Antibiotics in Stroke Study (PASS)

PASS was a nationwide, multicenter, randomized, open-label trial with masked endpoint assessment conducted between 2010 and 2014[1]. In total, 2538 patients with acute stroke were enrolled. The primary aim was to evaluate the efficacy of preventive antibiotics in stroke patients. Patients with acute stroke (ischemic or hemorrhagic) were randomly assigned within 24 hours after symptom onset to either receive intravenous ceftriaxone at a daily dose of 2 grams during 4 days or standard stroke care. Exclusion criteria included clinical signs of infection on hospital admission requiring antibiotic treatment, pregnancy, hypersensitivity for cephalosporin's, subarachnoid hemorrhage, or imminent death. All clinician reported infections were also scored by a blinded adjudication committee according to modified Centers for Disease Control and Prevention criteria.[2] The trial protocol did not include restrictions on blood pressure (BP) values, or recommendations on when to administer antihypertensive treatment in participating patients.

Definition outcome measures

Mean arterial blood pressure (MAP) was calculated with the formula (2×diastolic BP (DBP)+systolic BP (SBP))/3. Stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[3] Stroke severity was quantified with the National Institutes of Health Stroke Scale (NIHSS).[4]

Any of the following events was scored as a major complication: any thrombotic event, defined as an acute vascular occlusion of an extremity or organ, documented by imaging, surgery, or autopsy[5]; progressive stroke, defined as an increase in NIHSS score of ≥ 4 points without underlying cause[6,] symptomatic intracranial hemorrhage (sICH) and major extracranial bleeding, defined according to the International Society on Thrombosis and Haemostasis criteria[7]; sepsis defined according to the Systemic Inflammatory Response Syndrome (SIRS) criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.[8]; heart failure, defined according to the European Society of Cardiology.[9]

Statistical analysis

BP as continuous variable

We evaluated the association between BP variables (SBP, DBP and MAP) and functional outcome by testing for non-linearity and comparing models with and without restricted cubic and quadratic splines using the Akaike Information Criterion (AIC). Using the AIC, systolic blood pressure had a better correlation with functional outcome than diastolic blood pressure and MAP. The association between SBP and functional outcome was non-linear (P-value likelihood ratio test < 0.001), with different effects in patients with BP under and over 164 mm Hg (Figure 1). For MAP a comparable, albeit more blunted, U-shape was found (Figure I). DBP was not associated with poor functional outcome (Figure II). We calculated adjusted common odds ratios for decreases and increases of 10 mm Hg below and above the nadir. We adjusted for age, sex, pre-stroke mRS, stroke severity (NIHSS), stroke etiology (TOAST), history of hypertension, atrial fibrillation, myocardial infarction, diabetes and prior stroke, and treatment with IVT.

BP as categorical variable

Categorical variables are presented as frequency and percentage, normally distributed continuous data as mean and standard deviation (SD), and non-normally distributed data as median and interquartile range (IQR).

In regression analyses, we adjusted for the following predefined prognostic factors: age, sex, pre-stroke mRS, stroke severity (NIHSS), stroke etiology (TOAST), history of hypertension, atrial fibrillation, myocardial infarction, diabetes, prior stroke, and treatment with IVT. To account for missing data in the regression analyses, we imputed missing values using the Multiple Imputation by Chained Equations method with five rounds of imputations.

A two-tailed *p*-value of <0.05 was considered to be statistically significant. The Statistical Package for Social Science (SPSS Inc.,version 22) and R software (Version 3.4.2, R Foundation) were used for statistical analyses.

SUPPLEMENTAL TABLES

Table I. Baseline characteristics

	Low SBP (70-129 mmHg) N=212	Normal SBP (130-184 mmHg) N=1440	High SBP (185-264 mmHg) N=472	P-value Low vs. normal	P-value High vs. normal
Median age (IQR)	72 (57-81)	73 (63-83)	77 (66-83)	0.073	<0.001
Male sex	119/212 (56.1)	858/1440 (59.6)	245/472 (51.9)	0.369	0.004
Median NIHSS (IQR)	6 (3-13)	5 (3-9)	4 (3-7)	0.001	0.008
Stroke etiology				0.016	<0.001
Cardio-embolic	70/212 (33.0)	346/1440 (24.0)	60/472 (12.7)		
Lacunar	35/212 (16.5)	325/1440 (22.6)	128/472 (27.1)		
Large artery	27/212 (12.7)	230/1440 (16.0)	86/472 (18.2)		
Other determined	3/212 (1.4)	5/1440 (0.3)	1/472 (0.2)		
Undetermined	77/212 (36.3)	534/1440 (37.1)	197/472 (41.7)		
Pre-stroke mRS				0.712	0.215
0	144/212 (67.9)	947/1440 (65.8)	323/472 (68.4)		
1	25/212 (11.8)	230/1440 (16.0)	69/472 (14.6)		
≥2	43/212 (20.3)	263/1440 (18.3)	80/472 (16.9)		
Mean BP mmHg±SD					
SBP	117±9	157±15	204±16	N/A	N/A
DBP	70±13	84±15	99±18	N/A	N/A
MAP	86±10	108±13	134±14	N/A	N/A
Medical history					
Hypertension	97/212 (45.8)	766/1440 (53.2)	301/472 (64.0)	0.043	<0.001
Previous stroke/TIA	78/212 (36.8)	481/1439 (33.4)	144/472 (30.6)	0.351	0.258
Diabetes mellitus	33/212 (15.6)	285/1440 (19.8)	107/472 (22.7)	0.162	0.189
Myocardial infarction	37/212 (17.5)	206/1439 (14.3)	47/472 (10.0)	0.254	0.015
Atrial fibrillation	45/212 (21.2)	233/1439 (16.2)	50/472 (10.6)	0.076	0.003
Peripheral artery disease	19/210 (9.0)	99/1435(6.9)	46/472 (9.8)	0.253	0.045
Medication					
Beta-blockers	87/211 (41.2)	509/1438 (35.4)	167/47 (35.5)	0.107	0.981
ACE inhibitors	56/212 (26.4)	369/1437 (25.7)	119/470 (25.3)	0.801	0.877
Anticoagulants	31/212 (14.6)	149/1439 (10.4)	39/472 (8.3)	0.076	0.212
Antiplatelet therapy	87/211 (41.2)	607/1439 (42.2)	181/472 (38.3)	0.823	0.146
IVT	100/212 (47.2)	595/1440 (41.3)	111 (23.5)	0.118	<0.001

Abbreviations: SBP: systolic blood pressure; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; BP: blood pressure; SD: standard deviation; DBP: diastolic blood pressure; MAP: mean arterial pressure; N/A: not applicable; TIA: transient ischemic attack; IVT: intravenous thrombolysis

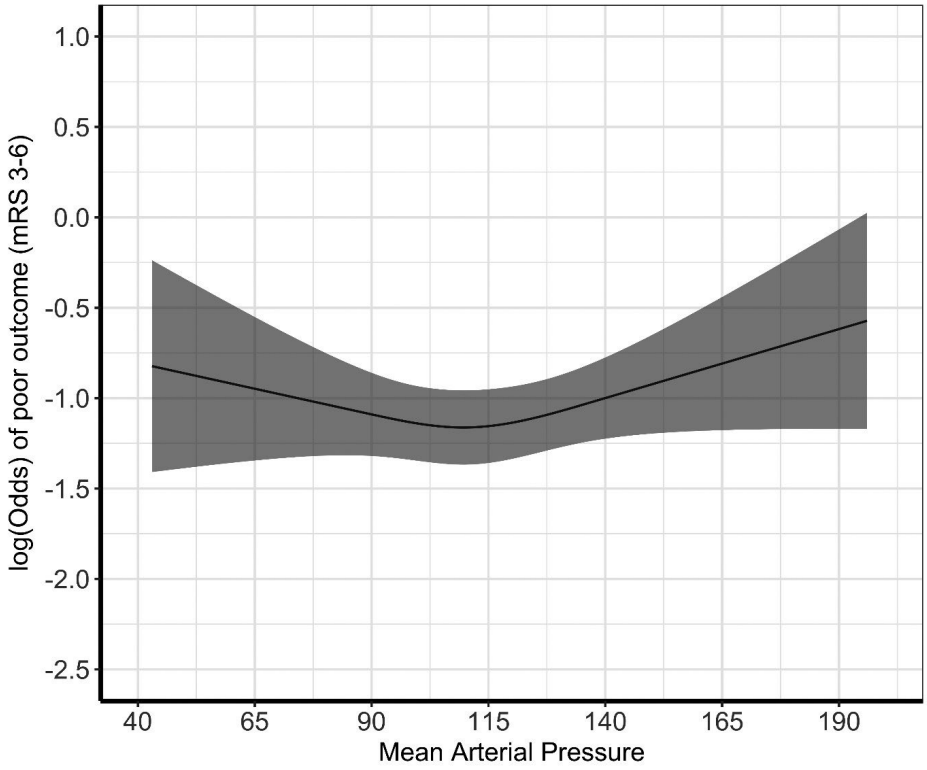
Table II. Outcomes of 2nd vs. 10th percentile

	2nd percentile (<110 mmHg) N=41	10th percentile (<130 mmHg) N=212	P value
In-hospital mortality	2/41 (4.9)	17/212 (8.0)	0.490
Cause of death			
Neurologic	0/41	9/212 (4.3)	0.354
Septic	1/41 (2.4)	5/212 (2.4)	0.975
Cardiac	1/41 (2.4)	2/212 (0.9)	0.435
Other/unknown	0/41	1/212 (0.5)	0.747
Any complication within 7 days	10/41 (24.4)	34/212 (16.0)	0.200
Thrombotic events	0/41	3/212 (1.4)	0.830
Progressive stroke	2/41 (4.9)	14/212 (6.6)	0.679
Any major bleeding	1/41 (2.4)	5/212 (2.4)	0.975
sICH	0/41	1/212 (0.5)	0.747
Major extracranial bleeding	1/41 (2.4)	4/212 (1.9)	0.817
Heart failure	5/41 (12.2)	5/212 (2.4)	0.008
Sepsis	2/41 (4.9)	7/212 (3.3)	0.620

sICH: symptomatic intracranial hemorrhage

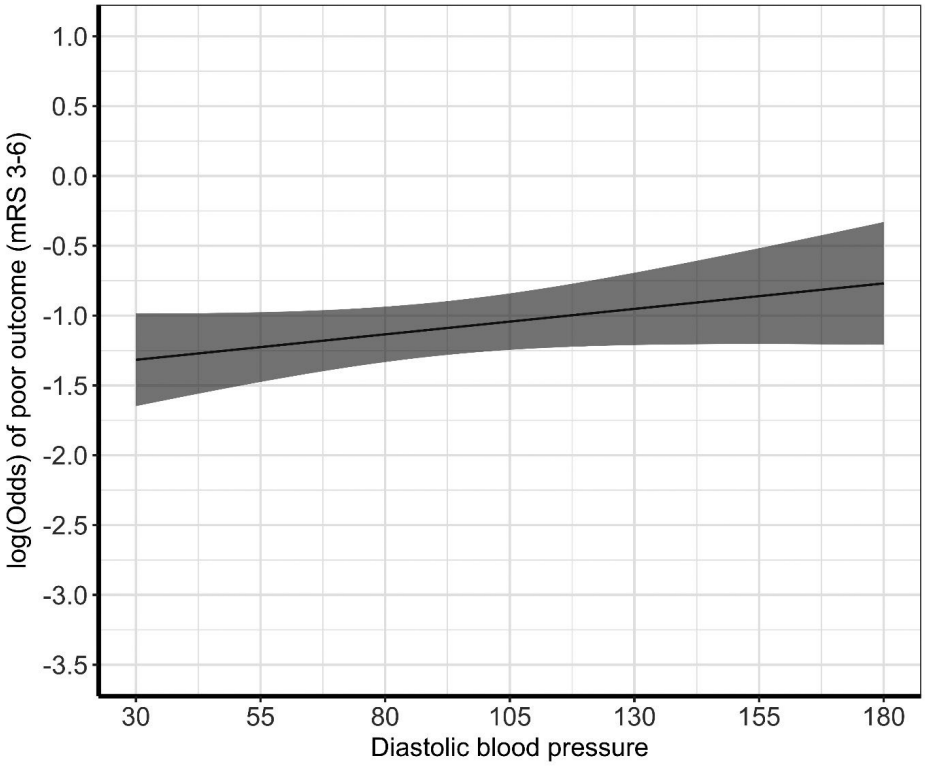
SUPPLEMENTAL FIGURES

Figure I. The association between Mean Arterial Pressure and the log(odds) to achieve a poor functional outcome at 90 days (defined as mRS 3-6) estimated with multivariable logistic regression.



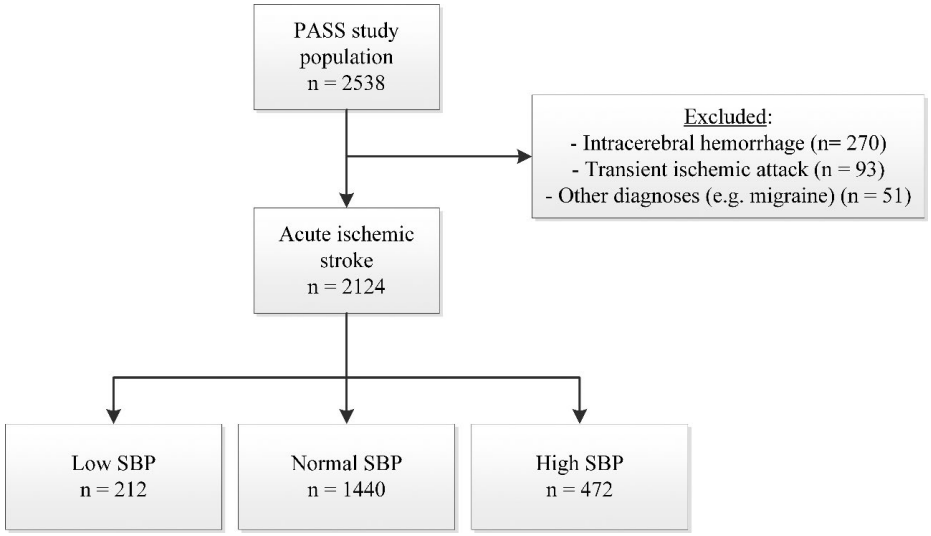
X-axis shows the MAP in mm Hg; Y-axis shows the linear predictors of the regression model. The nadir is located at 112 mm Hg. There was no statistically significant shift towards poor functional outcome for either values above and below the nadir (acOR 1.06 per 10 mm Hg increase in MAP, 95%CI 0.98-1.14 and acOR 1.04 per 10 mm Hg decrease in MAP, 95%CI 0.96-1.13, respectively).

Figure II. The association between diastolic blood pressure and the log(odds) to achieve a poor functional outcome at 90 days (defined as mRS 3-6) estimated with multivariable logistic regression.



X-axis shows the systolic blood pressure in mm Hg; Y-axis shows the linear predictors of the regression model. There was no statistically significant shift towards poor functional outcome (for every 10 mm Hg increase in DBP: acOR 1.03, 95%CI 0.99 – 1.08).

Figure III. Flowchart for patient selection



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Chapter 5

Clinical Outcome After Endovascular Treatment in Patients With Active Cancer and Ischemic Stroke: A MR CLEAN Registry Substudy.

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ABSTRACT

Background/aims

To explore clinical and safety outcomes of patients with acute ischemic stroke (AIS) and active cancer after endovascular treatment (EVT).

Methods

Using data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry, we compared patients with active cancer (defined as cancer diagnosed within 12 months before stroke, metastatic disease, or current cancer treatment) to patients without cancer. Outcomes were 90-day modified Rankin Scale (mRS) score, mortality, successful reperfusion (expanded Treatment in Cerebral Infarction score ≥2b), symptomatic intracranial hemorrhage (sICH), and recurrent stroke. Subgroup analyses were performed in patients with a prestroke mRS score of 0 or 1 and according to treatment setting (curative or palliative). Analyses were adjusted for prognostic variables.

Results

Of 2,583 patients who underwent EVT, 124 (4.8%) had active cancer. They more often had prestroke disability (mRS score ≥2: 34.1% vs 16.6%). The treatment setting was palliative in 25.3% of the patients. There was a shift toward worse functional outcome at 90 days in patients with active cancer (adjusted common odds ratio (acOR) 2.2, 95% confidence interval (CI) 1.5–3.2). At 90 days, patients with active cancer were less often independent (mRS score 0–2: 22.6% vs 42.0%, adjusted OR (aOR) 0.5, 95% CI 0.3–0.8) and more often dead (52.2% vs 26.5%, aOR 3.2, 95% CI 2.1–4.9). Successful reperfusion (67.8% vs 60.5%, aOR 1.4, 95% CI 1.0–2.1) and sICH rates (6.5% vs 5.9%, aOR 1.1, 95% CI 0.5–2.3) did not differ. Recurrent stroke within 90 days was more common in patients with active cancer (4.0% vs 1.3%, aOR 3.1, 95% CI 1.2–8.1). The sensitivity analysis of patients with a prestroke mRS score of 0 or 1 showed that patients with active cancer still had a worse outcome at 90 days (acOR 1.9, 95% CI 1.2–3.0). Patients with active cancer in a palliative treatment setting regained functional independence less often compared to patients in a curative setting (18.2% vs 32.1%), and mortality was higher (81.8% vs 39.3%).

Discussion

Despite similar technical success, patients with active cancer had significantly worse outcomes after EVT for AIS. Moreover, they had an increased risk of recurrent stroke. Nevertheless, about a quarter of the patients regained functional independence, and the risk of other complications, most notably sICH, was not increased.

INTRODUCTION

Patients with cancer are at increased risk of acute ischemic stroke (AIS), especially in the first months after diagnosis.[1,2] The stroke risk varies by cancer type and is generally higher in more advanced stages of the disease and in patients with adenocarcinomas.[3,4] About 10% of patients hospitalized with AIS are known to have cancer,[5,6] and 3% to 5% of patients are diagnosed with cancer within 2 years after stroke.[7] The most frequent types of cancer in patients with AIS are comparable to those in the general population, namely lung, gastrointestinal tract, and breast cancer.[8-11]

Previous studies have found that comorbid cancer is associated with increased stroke severity, stroke progression, and poor functional outcome.[11,12] In addition, the risk of stroke recurrence is 2- to 3-fold higher in these patients compared to patients without cancer.[8-10] Endovascular treatment (EVT) is often the only possible treatment modality in patients with AIS because patients with cancer regularly have contraindications for intravenous thrombolysis (IVT) such as recent surgery or coagulopathy.[11,13] However, except for case series and smallscale single-center studies, there are very few data on the short- and long-term outcomes after EVT in patients with stroke with cancer.[14-18]

The aim of our study was to compare the clinical, imaging, and safety outcomes of patients with AIS and active cancer who underwent EVT to those of patients without cancer.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

We used data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry, a prospective, observational cohort study of consecutive patients with ischemic stroke undergoing EVT in the Netherlands.[19] This registry started immediately after the final randomization in March 2014 for the MR CLEAN trial.[20] The 17 intervention centers that participated in the MR CLEAN trial prospectively collected data from consecutive patients with AIS treated with EVT. The medical ethics committee of the Erasmus University Medical Center in Rotterdam, the Netherlands approved the MR CLEAN Registry (MEC-2014-235). The research protocol was approved by the institutional review board of each participating center. The research boards waived the necessity of written informed consent.

Patients and Clinical Data

We included patients ≥18 years of age who were treated in a center that participated in the MR CLEAN trial with AIS of the anterior circulation for whom data on cancer status could be obtained from the discharge letters. Baseline characteristics, risk factors for stroke, imaging findings, and clinical outcomes were recorded with a standardized case record form. We distinguished 2 groups: patients with active cancer and patients without a history of cancer. Active cancer was defined as cancer diagnosis within 12 months before stroke, metastatic disease, or cancer treatment in the last 30 days. Patients who had declined cancer treatment were also considered to have active cancer. Patients with a history of cancer but not fulfilling the definition of active cancer were excluded from both groups. Noninvasive skin cancer (e.g., basal cell carcinoma), meningioma, myelodysplastic syndrome, and nonactive cancer diagnosed > 10 years before stroke were not registered as (history of) cancer. For patients with active cancer, the date of diagnosis, type of cancer, and details of treatment were extracted from the medical records.

Data Availability

Under Dutch law, source data cannot be made available because no patient approval was obtained for sharing (coded) individual data. However, on reasonable request to the corresponding author, detailed syntax and output files of statistical analyses will be made available.

Outcome Measures

The primary outcome was functional outcome at 90 days, measured with the modified Rankin Scale (mRS). The mRS is a 7-point scale that ranges from 0 (no symptoms) to 6 (death).[21] Secondary outcomes were functional independence (defined as mRS score 0–2), mortality at 90 days, in-hospital mortality, National Institutes of Health Stroke Scale (NIHSS) score at 24 to 48 hours, successful reperfusion (expanded Treatment in Cerebral Infarction scores ≥2b), symptomatic intracranial hemorrhage (sICH; defined as a decline in NIHSS score of ≥4 points and corresponding hemorrhage confirmed on imaging), recurrent stroke (defined as imaging of new brain infarction with corresponding clinical neurologic deficit), major extracranial bleeding (defined as any major bleeding as judged by local investigator), cardiac ischemia (defined as confirmed by ECG and release of appropriate biomarkers), and pneumonia (defined as an infection according to the Centers for Disease Control and Prevention National Healthcare Safety Network surveillance definition occurring within 7 days after the onset of stroke).[22]

Statistical Analysis

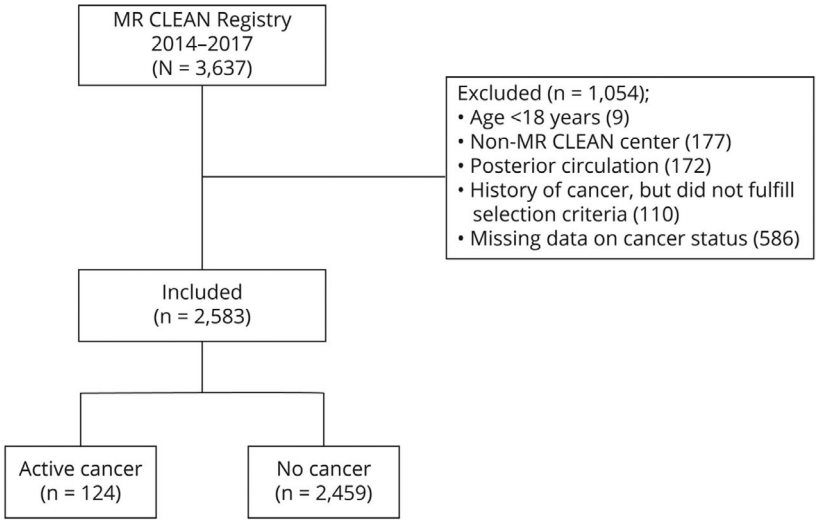
Intergroup comparisons were analyzed with the $\chi 2$ test, independent T test or Mann-Whitney U test as appropriate. The cumulative probability of survival during the 90-day follow-up period was estimated with the Kaplan-Meier method. Intergroup comparison was performed with the log-rank test. For regression analyses, missing variables were imputed with multivariate imputation by chained equations with 5 imputations. We used multivariable ordinal, logistic, and linear regression analysis to calculate adjusted odds ratios (aORs) or adjusted common odds ratios (acORs) and β coefficients for all outcomes and adjusted for the following predefined prognostic factors: age, prestroke mRS score, baseline NIHSS score, and onset-to-door time. In an exploratory analysis, we additionally adjusted for IVT because patients with cancer more often have contraindications for IVT.

When no event occurred in 1 of the groups, we added 0.5 to all 4 cells of the 2x2 table for the unadjusted analyses.[23] We performed a subgroup analysis for the primary outcome including only data from patients with a prestroke mRS score of 0 or 1 and a descriptive analysis of patients with a prestroke mRS score of 3 to 5. We also performed a descriptive subgroup analysis according to treatment setting (curative or palliative) for functional independence and mortality. All analyses were performed with R software (version 3.4.2, R Foundation, Vienna, Austria).

RESULTS

Between 2014 and 2017, 3,380 patients with AIS received EVT in the Netherlands. Of these, 797 were excluded from the present study, mostly because data on cancer status were missing (Figure 1). Of the 2,583 patients who were included in the analysis, 124 (4.8%) had active cancer. The most common types of cancer were digestive tract (31.1%) and lung cancer (25.0%) cancer, and 73.1% had metastatic disease (Table 1). In total, 84.8% of patients with active cancer had received cancer treatment in the last 30 days, including chemotherapy (22.2%), radiation therapy (15.2%), surgery (13.4%), or a combination of therapies (31.3%). The treatment setting was palliative in 25.3% of the patients.

Figure 1. Flowchart patient selection



Baseline Characteristics

Mean age and sex ratios were similar in both groups (Table 2). Patients with active cancer more often had prestroke functional disability (prestroke mRS score ≥2: 34.1% vs 16.6%, $p < 0.001$). Stroke severity was similar in patients with active cancer compared to patients without cancer (both median NIHSS score 16). Patients with active cancer more often used therapeutic anticoagulation (31.5% vs 17.6%, $p < 0.001$) and less often received IVT (56.6% vs 75.8%, $p < 0.001$). General anesthesia during EVT was applied more often in patients with active cancer (31.9% vs 21.1%, $p = 0.005$). Workflow times were comparable.

Table 1. Details of 124 patients with active cancer.

Type of cancer - n (%)	
Digestive tract	41/124 (33.1)
Lung	31/124 (25.0)
Urogenital	17/124 (13.7)
Breast	16/124 (12.9)
Gynecological	9/124 (7.3)
Hematological	3/124 (2.4)
Melanoma	3/124 (2.4)
Other[a]	4/124 (3.2)
Metastatic disease - n (%)	
Yes	68/93 (73.1)
No	25/93 (26.9)
Treatment in last 30 days – n (%)	
Chemotherapy	25/112 (22.2)
Radiation therapy	17/112 (15.2)
Surgery	15/112 (13.4)
Combination[b]	35/112 (31.3)
Other treatment	3/112 (2.7)
No current treatment	17/112 (13.7)
Treatment setting - n (%)	
Curative	65/87 (74.7)
Palliative	22/87 (25.3)

[a]metastases from unknown primary tumor (2), malignant tumor lower leg (histopathological findings not reported), sarcoma central pulmonary artery
[b]chemoradiation therapy (14), chemotherapy and surgery (12), radiation therapy and surgery (6), chemoradiation therapy and surgery (3)

Table 2. Baseline characteristics

	Active cancer n=124	No cancer n=2459	P-value
Age in years - mean ± SD	69±11	70±14	0.660
Male sex - n (%)	58/124 (46.8)	1277/2459 (51.9)	0.262
Pre-stroke mRS – n (%)			<0.001
0	64/123 (52.0)	1712/2421 (70.7)	
1	17/123 (13.8)	307/2421 (12.7)	
2	16/123 (13.0)	162/2421 (6.7)	
3	13/123 (10.6)	141/2421 (5.8)	
4	11/123 (8.9)	79/2421 (3.3)	
5	2/123 (1.6)	20/2421 (0.8)	
Pre-stroke mRS ≥ 2 - n (%)	42/123 (34.1)	402/2421 (16.6)	<0.001
NIHSS - median (IQR)[a]	16 (12-19)	16 (11-19)	0.275
Medical history - n (%)			
Hypertension	50/121 (41.3)	1262/2415 (52.3)	0.019
Previous stroke	17/122 (13.9)	408/2445 (16.7)	0.425
Diabetes mellitus	25/122 (20.5)	391/2446 (16.0)	0.187
Myocardial infarction	16/122 (13.1)	333/2422 (13.7)	0.843
Atrial fibrillation	32/122 (26.2)	582/2434 (23.9)	0.559
Hypercholesterolemia	32/120 (26.7)	696/2360 (29.5)	0.507
Peripheral arterial disease	14/122 (11.5)	232/2418 (9.6)	0.493
Smoking	36/121 (29.8)	531/2441 (21.8)	0.001
Medication - n (%)			
Blood pressure medication	62/121 (51.2)	1311/2418 (54.2)	0.521
Statins	37/120 (30.8)	844/2413 (35.0)	0.352
Therapeutic anticoagulation[b]	39/124 (31.5)	434/2459 (17.6)	<0.001
Antiplatelet therapy	38/122 (31.1)	743/2432 (30.6)	0.889
Mean blood pressure - mmHg ± SD			
Systolic[c]	145±25	150±25	0.026
Diastolic[d]	80±16	82±16	0.164
Lab results - mean ± SD			
Glucose[e]	7.4±2.5	7.5±2.3	0.826
INR[f]	1.23±0.40	1.18±0.42	0.227
Thrombocyte count[g]	272±120	249±83	0.006
IVT - n (%)	69/123 (56.6)	1862/2457 (75.8)	<0.001
Procedure - n (%)			
General anesthesia	38/119 (31.9)	490/2324 (21.1)	0.005
Balloon guiding	59/86 (68.6)	1227/1848 (66.4)	0.671
EVT performed	110/124 (88.7)	2083/2459 (84.7)	0.608

	Active cancer n=124	No cancer n=2459	P-value
Time in minutes - median (IQR)			
Onset-to-door[h]	64 (40-113)	57 (39-105)	0.296
Onset-to-groin[i]	203 (155-258)	200 (153-260)	0.897
Onset-to-reperfusion[j]	255 (203-335)	256 (204-320)	0.817
Door-to-needle[k]	25 (19-40)	24 (18-32)	0.199
Door-to-groin[l]	119 (85-152)	121 (88-157)	0.495
Duration of procedure[m]	56 (40-78)	60 (38-85)	0.717
ASPECTS - median (IQR)[n]	9 (8-10)	9 (7-10)	0.094
Occlusion location - n (%)			0.568
Intracranial ICA	5/117 (4.3)	130/2348 (5.5)	
ICA-T	26/117 (22.2)	487/2348 (20.7)	
M1	73/117 (62.4)	1350/2348 (57.5)	
M2	12/117 (10.3)	364/2348 (15.5)	
Other[o]	1/117 (0.9)	17/2348 (0.7)	

Abbreviatons: SD: standard deviation, NIHSS: National Institutes of Health Stroke Scale, IQR: interquartile range, mRS: modified Rankin Scale, INR: international normalized ratio, IVT: intravenous thrombolysis, EVT: endovascular treatment, ASPECTS: Alberta Stroke Program Early CT Score, ICA: internal carotid artery, ICA-T: internal carotid artery terminus, M1/M2/M3: middle cerebral artery, A1/A2: anterior cerebral artery.
Number of missing values: [a]3 (2.4%) vs. 26 (1.1%), [c]5 (4.0%) vs. 33 (1.3%), [d]5 (4.0%) vs. 41 (1.7%) , [e]11 (8.9%) vs. 284 (11.5%), [f]26 (21.0%) vs. 451 (18.3%), [g]14 (11.3%) vs. 339 (13.8%) , [h]22 (17.7%) vs. 398 (16.1%), [i]1 (0.8%) vs. 8 (0.3%), [j]9 (7.3%) vs. 144 (5.9%), [k]12 (9.7%) vs. 364 (14.8%), [l]38 (30.6%) vs. 551 (22.4%), [m]12 (9.7%) vs. 210 8.5%) [n]1 (0.8%) vs. 81 (3.3%).
[b]Vitamin K antagonist (missing=16), low molecular weight heparin (missing=32), direct oral anticoagulant (missing=34). [o]M3, A1 or A2

Outcomes

Patients with active cancer had worse functional outcome at 90 days compared to those without cancer (acOR for a shift on mRS score toward worse outcome 2.2, 95% confidence interval (CI) 1.5–3.2, Figure 2). The frequency of functional independence at 90 days was lower (22.6% vs 42.0%, aOR 0.5, 95% CI 0.3–0.8) and the mortality was higher (52.2% vs 26.5%, aOR 3.2, 95% CI 2.1–4.9, Table 3 and Figure 3) in patients with active cancer. The in-hospital mortality was also higher in patients with active cancer (25.2% vs 15.2%, aOR 2.1, 95% CI 1.3–3.2). Successful reperfusion (67.8% vs 60.5%, aOR 1.4, 95% CI 1.0–2.1), median NIHSS score at 24 to 48 hours (12 vs 10, β coefficient 0.02, 95% CI −0.8 to 2.3), and sICH rates (6.5% vs 5.9%, aOR 1.1, 95% CI 0.5–2.3) did not differ between groups. Recurrent stroke within 90 days was ≈3 times more common in patients with active cancer (4.0% vs 1.3%, aOR 3.1, 95% CI 1.2–8.1). The risk of other complications was comparable between patients with active cancer and those without cancer. Additionally adjusting the multivariable analyses for IVT had no material effect on the strength of the association between cancer and outcome (acOR for a shift on the mRS toward worse outcome at 90 days 2.1, 95% CI 1.5–3.1, aOR for functional independence at 90 days 0.5, 95% CI 0.3–0.8, and aOR for mortality at 90 days 3.2, 95% CI 2.1–4.8).

Figure 2. mRS scores at 90 days.
Comparison of 90-day mRS score in patients with active cancer (n=115) vs. no cancer (n=2318). There was a shift towards worse outcome for patients with active cancer (acOR 2.17, 95% CI 1.48-3.16).

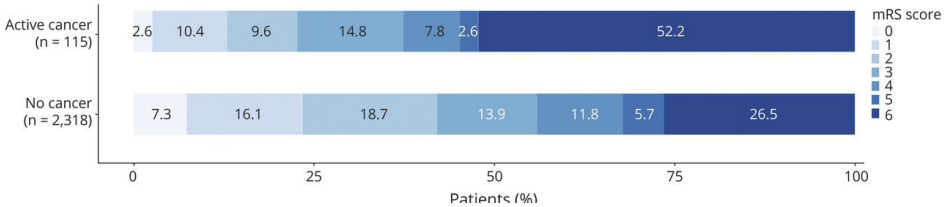


Table 3. Outcomes after 90 days

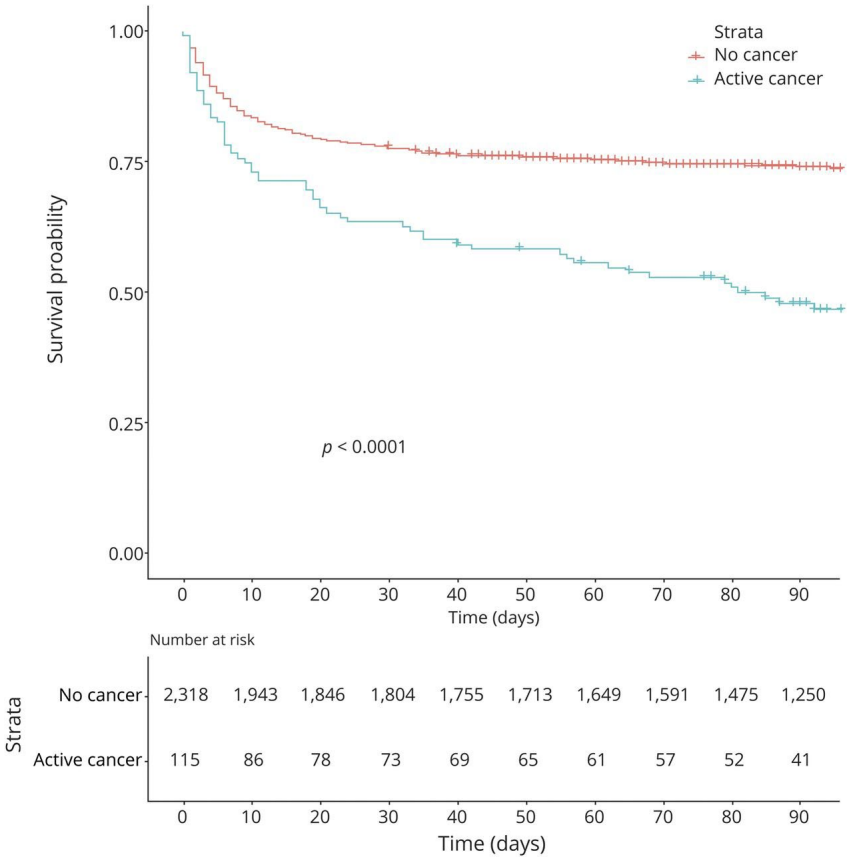
	Active cancer n=124	No cancer* n=2459	Unadjusted Beta/OR (95%CI)	Adjusted Beta/ OR (95%CI)
mRS at 90 days - median (IQR)[a]	6 (3-6)	3 (2-6)	2.50 (1.76-3.54)	2.17 (1.48-3.16)[c]
Functional independence at 90 days (mRS 0-2) - n (%)	26/115 (22.6)	976/2318 (42.1)	0.42 (0.27-0.65)	0.50 (0.31-0.81)[c]
Mortality at 90 days - n (%)	60/115 (52.2)	614/2318 (26.5)	2.87 (1.96-4.17)	3.17 (2.07-4.85)[c]
In-hospital mortality - n (%)	29/115 (25.2)	353/2318 (15.2)	2.03 (1.34-3.06)	2.05 (1.32-3.18)[c]
NIHSS at 24-48 hours - median (IQR)[b]	12 (5-18)	10 (4-17)	0.04 (-0.21-2.98)	0.02 (-0.75-2.32)[c]
eTICI≥2B - n (%)	82/121 (67.8)	1451/2397 (60.5)	1.35 (0.92-1.99)	1.40 (0.95-2.07)[c]
0	14/121 (11.6)	410/2397 (17.1)		
1	3/121 (2.5)	78/2397 (3.3)		
2A	22/121 (18.2)	458/2397 (19.1)		
2B	27/121 (22.3)	518/2397 (21.6)		
2C	18/121 (14.9)	251/2397 (10.5)		
3	37/121 (30.6)	682/2397 (28.5)		
sICH - n (%)	8/124 (6.5)	146/2459 (5.9)	1.09 (0.52-2.28)	1.12 (0.53-2.34)[d]
Recurrent stroke - n (%)	5/124 (4.0)	33/2459 (1.3)	3.10 (1.18-8.06)	3.06 (1.16-8.06)[d]
Extracranial hemorrhage - n (%)	4/124 (3.2)	48/2459 (2.0)	1.68 (0.59-4.74)	1.54 (0.54-4.39)[d]
Pneumonia - n (%)	11/124 (8.9)	261/2459 (10.7)	0.82 (0.44-1.54)	0.74 (0.39-1.40)[d]
Cardiac ischemia - n (%)	2/124 (1.6)	11/2459 (0.4)	3.65 (0.80-16.67)	3.56 (0.77-16.67)[d]

*Reference category.
Abbreviations: mRS: modified Rankin scale, NIHSS: National Institutes of Health Stroke Scale, IQR: interquartile range, OR: odds ratio, eTICI: expanded treatment in cerebral infarction, sICH: symptomatic intracranial hemorrhage.
Number of missing values: [a]9 (7.3%) vs. 141 (5.7%), [b]9 (7.3%) vs. 200 (8.1%)
[c]Adjusted for: age, pre-stroke mRS, baseline NIHSS and onset-to-door time
[d]Adjusted for: baseline NIHSS and anticoagulation

In the sensitivity analysis using only data from patients with a prestroke mRS score of 0 or 1, patients with active cancer still had a worse outcome at 90 days (acOR 1.9, 95% CI 1.2–3.0, Supplementary Figure Ia). For the subgroup of patients with a prestroke mRS score of 3 to 5, similar results were seen in patients with active cancer compared to patients without cancer (functional independence 3.8% vs 10.0% and mortality 65.4% vs 54.1%, Supplementary Figure Ib). The subgroup analyses according to treatment setting showed that patients with active cancer in a palliative treatment setting regained functional independence less often compared to patients in a curative setting (18.2% vs 32.1%) and that mortality was also higher (81.8% vs 39.3%).

This study provides Class I evidence that patients with active cancer undergoing EVT for AIS have worse functional outcomes at 90 days compared to those without active cancer.

Figure 3. Kaplan-Meier survival curve of cumulative mortality during the 90-day follow-up period in patients with active cancer vs. no cancer.



DISCUSSION

Comorbid active cancer was associated with a worse functional outcome and increased mortality in patients with AIS who received EVT compared to patients without cancer. Approximately half of the patients with active cancer died within 90 days after undergoing EVT, and among patients who were in a palliative setting, this proportion increased to 80%. The risk of recurrent stroke was also 3 times higher in patients with active cancer. The association between active cancer and poor outcome persisted in patientswho had no prestroke disability. Still, a quarter of the patients with active cancer regained functional independence at 90 days, and other complication rates, most notably sICH, were not increased in patients with active cancer.

Our results are in line with 3 smaller previous studies focusing on patients with cancer with AIS treated with EVT, with good functional outcome rates between 15% and 36% and mortality between 30% and 60%, despite achieving successful reperfusion in 63% to 89% of cases.16-18 None of these studies reported recurrent stroke, but other studies on AIS in patients with cancer found an increased risk similar to that in the present study.[8-10]

A number of factors may explain the increased risk of stroke in patients with cancer.[1,2] First, cancer may cause hypercoagulability, for example, due to increased levels of procoagulant factors and tumor-secreted microparticles triggering thrombosis.[24,25] Second, cancer and stroke share risk factors, in particular smoking and obesity.[2,3,26] Third, chemotherapy may enhance thrombin generation; radiotherapymay cause vasculopathy; and immune checkpoint inhibitors may cause cardiac events, which can also result in stroke.[27-29] Unfortunately, detailed information on use of immune checkpoint inhibitors was not available for the patients in our cohort.

Approximately 1 of every 4 patients with active cancer regained functional independence at 90 days after EVT. This percentage is only slightly higher than what was achieved in the (non-EVT) control arm of the MR CLEAN trial (19%).[20] It is also quite similar to the frequency of functional independence achieved by octogenarians after EVT.[30] Whether this proportion is considered to be worthwhile probably varies both among physicians and patients. On one hand, some would argue that a good outcome rate of one-quarter is insufficient to warrant an invasive and costly procedure such as EVT. On the other hand, one could also argue that this proportion is worth the effort of EVT, especially because the complication rate was not increased and because, if one refrains from EVT, the outcome of these patients is almost certainly invariably poor.[12] Our results cannot give a definitive answer on the efficacy and safety of EVT in the specific subgroup of patients with AIS

and active cancer, but by providing detailed data, we hope that physicians and patients are better equipped to make an informed decision.

Our study has a number of limitations. First, the cause of death was not assessed in the MR CLEAN Registry, and it is therefore unknown whether patients with active cancer died of stroke-related or cancer-related causes. Other studies on cancer and AIS, not targeted at EVT, reported overall mortality similar to that in our study.[12,26] Two previous studies focusing on EVT in patients with cancer with AIS reported vascular disease as the cause of death in 5 of 12 (41.7%) and stroke-related death in 5 of 8 (62.5%), respectively.[16,17] Second, there might have been a bias in the selection of patients with cancer who received EVT. In some patients, local physicians may have decided to refrain from EVT because of a poor prognosis. Because the MR CLEAN Registry collects data of only patients who actually received EVT (not of patients who were potentially eligible for EVT), we cannot be certain how often this situation occurred. On the other hand, it is also possible that bias occurred after EVT. Patients with cancer who developed AIS might have decided not to have complications treated, not to undergo extensive stroke rehabilitation, or to cease treatment for cancer. This might have contributed to worse functional outcomes. Third, not all details about cancer status could be obtained. A more detailed database would have allowed us to further explore possible heterogeneity among patients with cancer.

Despite similar technical success, patients with active cancer had significantly worse outcomes after EVT for AIS, even when their prestroke functioning was favorable (mRS score 0–1). Moreover, they had an increased risk of recurrent stroke. Nevertheless, about a quarter of the patients regained functional independence, and the risk of other complications, most notably sICH, was not increased.

STUDY FUNDING

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DISCLOSURES

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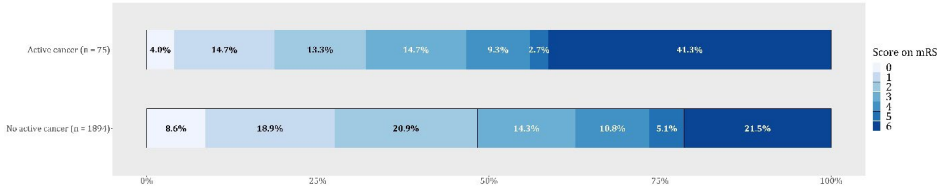
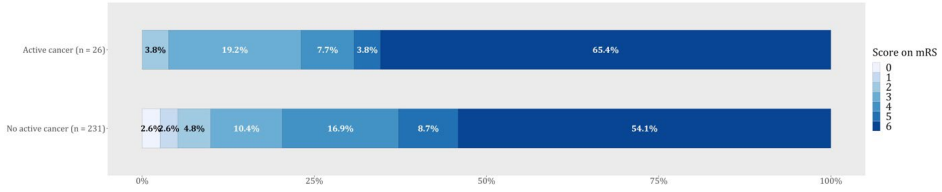
SUPPLEMENTAL MATERIAL

Figure I. mRS scores at 90 days.

A. Subgroup analysis, including only patients with pre-stroke mRS 0 and 1. There was a shift towards worse outcome for patients with active cancer (acOR 1.88, 95% CI 1.19-2.98).



B. Descriptive subgroup analysis*, including only patients with pre-stroke mRS 3-5.
*Due to small group sizes, statistical power for an adjusted shift analysis was lacking.



Chapter 6

General discussion

The aim of this thesis was to explore clinical dilemmas that a neurologist can encounter in the emergency department (ED), in order to provide guidance for clinicians how do deal with these situations. Despite extensive progress in neuroimaging, neurology remains at foremost a clinical specialty. The aging population and advancing technology will only increase the need for neurologists in the ED.[1] Tests, treatment, hospital admission and refraining from these things can both harm and benefit patients. Coupled with the ever-mounting pressure to make timely and cost-effective decisions, the need for answers to commonly occurring clinical dilemmas in acute neurological disorders becomes clear. This thesis describes the results of studies we performed on some of these dilemmas.

MILD TRAUMATIC BRAIN INJURY

In the first part of this work, we focused on mild traumatic brain injury (mTBI). The overall incidence of mTBI is increasing, especially in the elderly, and represents one of the most common reasons for neurological consultation in the ED.[2] Elderly patients are susceptible to admission-related complications, such as urinary tract infections, pneumonia and delirium,[3-6] underlining the need of weighing the harms and benefits of admission extra carefully in these patients.

In Chapter 2, we found that true delayed intracranial hemorrhage (ICH; occurring after an initially normal CT in the absence of recurrent head trauma)) in patients with mTBI on anticoagulation therapy is very rare. In most cases, 'delayed' ICH was actually an initially missed ICH and we, therefore, advocate these patients should not be routinely admitted after their scan is scrupulously investigated. Over the last couple years, direct oral anticoagulants (DOAC) have been prescribed more often than vitamin K antagonists (VKA) as anticoagulation therapy.[7] Currently, available DOACs include dabigatran, a selective anti-factor IIa molecule and three direct factor Xa inhibitors: apixaban, rivaroxaban and edoxaban. DOACs carry a lower risk of (traumatic) ICH than VKAs[8] and have potent antidotes that rapidly and almost completely reverse the action of the DOACs: idarucizumab for dabigatran and andexanet alfa for the factor Xa inhibitors.[9] The possible devastating outcome of traumatic ICH in anticoagulated patients coupled with the possibility to counteract the anticoagulation effect highlights the importance to identify every traumatic ICH on the first computed tomography (CT) and not on the second scan made due to neurological deterioration. Here, there could be a role for artificial intelligence, specifically (deep) machine learning. Deep learning software could flag scans with possible ICH, prioritizing them in de the radiologist's workflow and acting as a second opinion in case of equivocal findings. This could minimize the risk of

a radiologist missing abnormalities in the large number of scans for mTBI. Over the last couple of years, numerous algorithms have been developed aimed at identifying ICH in the ED, with reported diagnostic accuracy of 93.0-95.6%.[10-12] However, it is important to recognize some limitations. Most of these studies were performed at a single hospital and have not been validated in different settings. False positive flags may arise in case of artifacts, post-operative or -ischemic changes and tumors.[13] However, the greatest limitation is the low sensitivity of 71.8% in case of smaller volume ICH (sensitivity 71.8%).[12] Therefore, caution is warranted when depending solely on the algorithm, but is should be noted that the (unaided) radiologist would likely face the same diagnostic challenges. Artificial intelligence will not take over the radiologist's job, at least not in the near future. It can, however, take over radiologist's tasks, aid them in streamlining their workflow and act as a second pair of eyes.

In addition to the elderly, the pediatric population represents another group prone to mTBI, with annual incidence rates in the ED of the southwest region of the Netherlands of 271/100.000.[14] Clinical decision rules lead to a reduction of 21% of cranial CTs, which is, of course, only a modest number.[15] However, a multicenter study conducted in 2018 showed that adherence to clinical guidelines in pediatric patients with mTBI was very poor (49.7%).[16] Mostly, cranial CT underuse (40.1%) and hospital admission overuse (35.0%) was seen, which the authors interpreted as clinicians preferring to err on the side of caution. Even though no cases of clinically important traumatic brain injury were missed in an American study where children were admitted before deciding on performing CT,[17] admission may still be a burden to patients, parents and the hospital. The large proportion of children with head injury that is admitted, however, provides a unique opportunity to evaluate the yield of observation. If the hypothesis that children that do not meet criteria for cranial CT under the current guidelines can be safely discharged home could be substantiated with data, it could result in greatly reducing the number of children that are admitted. This in turn would lead to reduction of costs, bed occupancy and possible negative association children may develop with health care. However, as traumatic intracranial abnormalities in pediatric patients are rare, the dataset would have to be large and very robust before implementation into clinical practice could be considered. When children are concerned, everyone prefers to err on the side of caution.

ACUTE ISCHEMIC STROKE

The second part of this thesis shifts focus from mTBI to stroke. Acute focal neurological deficits represent another common reason to warrant neurological consultation in the ED. Time is of the essence when these deficits are caused by acute ischemic stroke (AIS), as reperfusion therapy aimed at restoring blood flow is extremely time sensitive. Several factors can complicate a timely and correct diagnosis. Both neurological and non-neurological diseases can present as stroke mimics (SM), accounting for up to 43% of patients presented for a possible stroke.[18] When these patients are identified in time, unnecessary treatment and admission can be avoided. A common SM of the posterior circulation is acute alcohol intoxication. Many hospitals that offer intravenous thrombolysis (IVT) and endovascular treatment (EVT) conduct CT perfusion imaging (CTP) as part of their routine stroke workup. Standardized CTP protocols often exclude the infratentorial parts of the brain, which can lead to incorrect diagnosis in patients with posterior circulation stroke. However, when whole-brain CTP protocols are applied, sensitivity reaches 74% in these patients.[19] This still leaves a significant proportion of patients with AIS with a negative CTP. In Chapter 3, we found that 9.4% of patients with posterior circulation stroke symptoms had elevated blood alcohol concentration (BAC) and in half of these patients the final diagnosis was acute alcohol intoxication. Patients with a SM due to alcohol intoxication had higher BAC and more often denied the amount of alcohol they had consumed compared to patients with stroke and concurrent alcohol intoxication.

Although concerns exist regarding increased IVT-related risks in patients with acute and/or chronic alcohol abuse,[20] they were not confirmed by higher frequencies of ICH in the 708 patients treated with IVT in our cohort and that of Gattringer et al.[21] The results of a BAC should, therefore, not be waited on when making the decision to administer IVT. A decision that could be influenced by elevated blood ethanol levels is the decision to start platelet aggregation inhibitors as secondary prophylaxis. Aside from it being unnecessary treatment in patients with a SM due to alcohol intoxication, it could even be harmful as alcohol significantly enhances the effects of the medication.[22] When alcohol intoxication is suspected as alternative diagnosis in patients presented with a possible posterior circulation stroke, blood alcohol measurement should be considered to differentiate between stroke and SM.

Even when there is no doubt about the diagnosis of AIS, there are still numerous factors to consider to maximize chances of good functional outcome as measured on the modified Rankin scale (mRS). Most patients with AIS have elevated blood pressure (BP) values during the first days after stroke, which decline without intervention.[23] Several studies

assessing optimal BP values in AIS report on a U-shaped relationship between initial BP and poor prognosis.[23-25] While extremely elevated BP may lead to hemorrhaging[26] or edema,[27] it was unclear how low BP is associated with poor outcome. It may be a sign of preexisting or coinciding cardiovascular comorbidity limiting BP increase[23] or a pathophysiological mechanism in which hypoperfusion leads to rapid ischemic core expansion.[28] We found that gastrointestinal bleeding, sepsis and heart failure occurred significantly more often in patients with low SBP (Chapter 4). Low SBP in these patients could well be a consequence of one of these three disorders, as they limit the ability to increase BP. Patients with low SBP also presented with higher National Institutes of Stroke Scale (NIHSS) and had worse outcome. This could indicate that in these patients initial SBP was already insufficient to maintain perfusion of the ischemic penumbra, causing more severe stroke. Although retrospectively it is impossible to say with certainty whether these complications are causally related or only coinciding in patients with AIS, the presence of low SBP should prompt clinicians to look for these conditions. The history and physical examination should be focused on signs of gastrointestinal bleeding (e.g. stomach pains, hematemesis or melena, use of NSAIDs), heart failure (e.g. fatigue, orthopnea, peripheral or pulmonary edema, cardiac conditions) and sepsis (e.g. fever, tachycardia, possible focus of infection, immunocompromisation). Laboratory tests should include full blood count, erythrocyte sedimentation rate, C-reactive protein and N-terminal pro-B-type natriuretic peptide. An electrocardiogram should be conducted to evaluate possible underlying conditions for heart failure, such as atrial fibrillation and left ventricular hypertrophy. This should help clinicians diagnose or rule out these three treatable conditions in patients with AIS and low SBP. When low SBP is causing hypotensive symptoms, fluid therapy can be considered. However, this should not be routine treatment in all patients with AIS and lower SBP. There is no research to support its beneficial effect, but elevating SBP does carry the risk of causing ICH.

Between correctly diagnosing patients with AIS and remaining vigilant for short- and long-term complications, the most important factor to improve functional outcome is probably reperfusion therapy. Both IVT and EVT have contraindications and time restrictions, but multiple research efforts are aimed at increasing the number of patients meeting eligibility criteria. One group of patients that is at increased risk of AIS, but which is often excluded from trials, is that of patients with cancer. Comorbid cancer is negatively associated with stroke severity, progression, recurrence and functional outcome.[29] IVT is often contraindicated in these patients due to recent surgery or coagulopathy,[30,31] but the role of EVT remained to be elucidated. In Chapter 5, we found that 22.6% of patients with cancer and AIS treated with EVT regained functional independence, compared to 42.0% of patients without cancer. It is important to note that poor outcome in the active cancer group was highly dependent on the mortality rate of over 50%. The high mortality

rate is hardly surprising, as our cohort consists of patients with more advanced stages of cancer, with almost ¾ with metastatic disease and ¼ in a palliative setting (with a mortality rate of over 80%). Although we lack data on cause of death, it is conceivable that most of these patients died of cancer-related causes, since previous studies of patients with cancer and AIS not targeted at EVT showed similar mortality rates.[29,31] If we focus on only patients that survive at 90 days (mRS 0-5) the distribution of patients with good functional outcome (mRS 0-2) is much more comparable between patients with active cancer and patients without cancer: 26/55 (47.3%) vs. 976/1704 (57.3%). This might paint a more representative picture of the effect of EVT in these patients.

Whether the proportion of functional independence at 90 days, or even the proportion of functional independence just before a patient's passing if this happens within 90 days, is considered sufficient to warrant the invasive and costly EVT procedure probably varies not only among physicians and patients, but also between cultures and countries. In 2014, results of the Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery II (DESTINY II) study were presented.[33] The authors reported that in patients > 60 years with malignant middle cerebral artery infarction an early decompressive hemicraniectomy significantly improved mortality (43% vs 76%), but left the vast majority of survivors with moderately severe or severe disability (51% vs 19%). These results prompted the American Heart Association/American Stroke Association to state that decompressive hemicraniectomy may be considered in patients > 60 years with brain swelling.[34] For the Dutch Association of Neurology it was reason to advise extreme restraint with this procedure.[35]

The generally more reserved attitude of the Dutch is also seen in other aspects of healthcare. The Turkish government regularly sends ambulance planes to bring home patients from the Netherlands who "did not receive the necessary and specific care they required".[33] Mostly, these are Turkish Dutch patients in whom the intensive care treatment would be discontinued, such as Dilara Sahin, a 24-year-old with acute leukemia who survived for another 10 months until her passing at age 25 in an Istanbul hospital.[34] This reflects that different cultures have different views of what constitutes good care, a dignified existence and what is or is not in the best interest of patients.

Inextricably linked to this discussion is the cost aspect. The Dutch Ministery of Health, Welfare and Sport (VWS) published their *Integraal Zorgakkoord* (IZA) in September of 2022; a covenant in which the healthcare sector and the Cabinet state agreements about how our healthcare can remain future-proof.[35] The IZA states that our healthcare is faced with tremendous challenges. In short, accessible, good and affordable healthcare cannot be guaranteed if we continue on the same path. If nothing changes, healthcare costs

will triple between now and 2060. In 2019, 6.5 billion euro was spent on cancer care, which is 6.7% of our total health care expenditure.[36] The treatment of cancer patients near the end of life (EOL) is becoming increasingly aggressive over time.[37] The steering committee for appropriate EOL care of the Royal Dutch Medical Association (KNMG, a federation of medical practitioners' professional associations) published a report titled 'Just because we can, doesn't mean we should'.[38] An estimated 34% of patients with cancer may have been overtreated in the month before their death, defined as 2 or more hospital admissions, hospitalized for longer than 14 days, 2 or more presentations to the emergency department, admission to intensive care, chemotherapy or in-hospital mortality.[38,39] At group level it is important to avoid possible overtreatment as much as possible. However, for an individual patient, this care may have been appropriate.

In order to better frame whether we should view EVT as appropriate treatment, overtreatment or too expensive in patients with AIS and cancer, especially in the palliative phase, it is ultimately important to consider quality of life (QOL). QOL is not static and the patient's perception of QOL may also evolve over time.[40] Interventions should improve QOL even if they do not improve survival, consequently improving quality adjusted life years saved (QALYS).[41] QALYS are focused on healthcare economics and frequently used as a way to express cost-effectiveness to and by policy makers. However, they assume a linear value for the length of life, while patients often place more value on time near the EOL than at the beginning of their illness.[41] This greatly limits their usability in EOL treatments. In addition, there is no single QOL questionnaire that captures all aspects that patients find most important at the EOL: physical and psychological comfort, dying in a favorite place, maintaining hope and pleasure, having good family relationships, feeling fulfilled in having achieved life goals and maintaining independence as long as possible.[42] When we consider these goals, EVT may play a pivotal role for patients with cancer and AIS in achieving them and, therefore, ultimately be invaluable.

In conclusion, this thesis addresses common clinical dilemmas faced by neurologists in the ED, emphasizing the need for guidance in navigating these complex situations within tight time constraints. Despite technological advancements, neurology remains predominantly a clinical specialty, and the growing elderly population and advancing

technology underscore the increasing demand for neurologists in the ED. This thesis provides valuable insights and recommendations in this field.

1. Delayed ICH in patients on anticoagulation therapy is so rare that these patients should not be routinely admitted after mTBI when their CT is normal. However, careful examination of the CT is crucial, as most delayed ICH turned out to be initially missed ICH.
2. In patients presenting outside of working hours with posterior circulation stroke symptoms, extremely elevated BAC is suggestive of alcohol intoxication as a SM rather than as a concurrent diagnosis to stroke. While BAC levels should be weighed before initiating platelet aggregation inhibitors, they should not be waited on for the decision to administer IVT.
3. Low SBP in AIS is uncommon. Instead of considering it as a standalone entity, clinicians should use it as a prompt to look for associated treatable conditions, such as gastrointestinal bleeding, heart failure, and sepsis.
4. A quarter of the patients with AIS and comorbid cancer treated with EVT regain functional independence, without an increase in complication rate. To decide whether this proportion is to be considered enough, QOL should ultimately weigh heaviest.

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Appendices

SUMMARY

Chapter 1: General introduction and thesis outline

Clinical assessment remains the cornerstone of neurology, despite advances in the field of neuroradiology. While historically neurology was a mainly outpatient profession, much has happened in the field of acute neurology in recent years. This has added a new dimension to the profession, one which requires clinicians to make decisions in the emergency department (ED) under tremendous time pressure without losing sight of costs. However, there are numerous clinical dilemmas that can be encountered, impeding these decisions. To lend a helping hand to clinicians, this thesis describes the results of studies we performed on some of these clinical dilemmas in acute neurological disorders.

MILD TRAUMATIC BRAIN INJURY

Chapter 2: Evaluation of the yield of 24-h close observation in patients with mild traumatic brain injury on anticoagulation therapy: a retrospective multicenter study and meta-analysis.

The overall incidence of mild traumatic brain (mTBI) injury is increasing, especially in the elderly, and represents one of the most common reasons for neurological consultation in the ED.[1] We examined the yield of neurological observation in patients with mTBI on anticoagulation therapy. These patients are at increased risk of traumatic intracranial hemorrhage (ICH).[2-3] There are also numerous reports of delayed ICH in patients on anticoagulation with an initial unremarkable cranial computed tomography (CT).[4-6] The risk of this feared complication remained unclear, resulting in different management guidelines, varying from admitting and rescanning all of these patients to providing no recommendation at all stating a lack of evidence.[7,8] In our retrospective observational multicenter study, we examined the frequency of delayed ICH in patients with mTBI on anticoagulants (therapeutic dose heparin (LMWH), direct oral anticoagulant (DOAC), or vitamin K antagonist (VKA) and an international normalized ratio (INR) ≥ 1.7) with an initial cranial CT scan without intracranial traumatic findings. Additionally, we performed a meta-analysis of similar studies. To determine the theoretical yield of clinical observation in these patients, the primary outcome was the development of symptomatic delayed ICH within 24 hours. We included 905 patients, with the majority on VKA therapy (97%, median INR 2.9). None of these patients developed delayed ICH within 24 hours. There were, however, four patients that deteriorated neurologically within 24 hours due to ICH

(0.4%, 95% confidence interval (CI) 0.1–1.2). When their initial scans were reevaluated, ICH was found in all of them. Out of the five patients that deteriorated outside of the 24 hour observation window, another two were determined to have a delayed diagnosis of traumatic ICH rather than a delayed ICH. All in all, only three patients that developed symptoms on day 18, 36 and 52, respectively, had true delayed ICH. In the meta-analysis comprised of 9 studies with data from 2885 patients, the estimated pooled proportion of symptomatic delayed ICH or delayed diagnosis of ICH within 24 hours was 0.2% (95% CI 0.0–0.5). We concluded that symptomatic delayed (diagnosis of) ICH within 24 hours in patients with mTBI on anticoagulation therapy is very rare after a reportedly normal cranial CT. When the initial scan is scrupulously evaluated, routine hospitalization seems unwarranted.

ACUTE ISCHEMIC STROKE

Chapter 3: Alcohol Intoxication as a Stroke Mimic and the Incidence of Acute Alcohol Intoxication in Stroke.

Stroke mimics (SMs) represent up to 43% of presentations to the ED with focal neurological deficits.[9] A common SM of the posterior circulation is acute alcohol intoxication. We described the frequency and clinical characteristics of patients with acute alcohol intoxication as a SM and as a concurrent diagnosis to stroke, both ischemic and hemorrhagic, in a prospective observational single-center study. We included 974 patients presented within 6 hours of symptom onset for possible reperfusion therapy. A total of 60 patients (6.2%) were intoxicated with a mean blood alcohol concentration (BAC) of 1.3‰: 38 (3.9%) patients with stroke and 22 (2.3%) patients with a SM, of which 12 (1.2%) patients had their SM attributed to acute alcohol intoxication. These numbers changed when only the 235 patients that presented with posterior circulation stroke symptoms were considered. Twenty-two (9.4%) had elevated BAC: 8 (3.4%) patients with stroke and 14 (6.0%) with a SM, 11 (4.7%) caused by acute alcohol intoxication.

Patients with elevated BAC presented mostly outside of office hours (81.7%). Compared to the 38 patients with stroke and concurrent alcohol intoxication, the 12 patients with a SM due to alcohol intoxication had a higher mean BAC (2.2‰ versus 1.1‰ ($p = 0.001$)) and more often experienced vertebrobasilary symptoms (91.7% versus 21.1%, $p < 0.001$). They were also more likely to deny or downplay their alcohol intake: 50.0% versus 28.9% ($p = 0.017$). Patients with acute ischemic stroke (AIS) and concurrent alcohol intoxication were less likely to receive reperfusion therapy compared to patients with AIS without elevated

BAC (26.3% versus 52.2%, p = 0.018). No complications occurred in the 11 patients with elevated BAC that received intravenous thrombolysis (IVT) or endovascular treatment (EVT).

We concluded that clinicians should consider measuring blood ethanol levels in patients with a possible stroke of the posterior circulation presenting after working hours, but should not withhold them from reperfusion therapy.

Chapter 4: Association Between Low Blood Pressure and Clinical Outcomes in Patients With Acute Ischemic Stroke.

Patients with AIS most often have elevated blood pressure at presentation and low blood pressure is uncommon.[10] We explored the association between spontaneous low blood pressure and outcome after AIS in a post hoc analysis of the Preventive Antibiotics in Stroke Study (PASS) database.[11] PASS was a nationwide, multicenter, randomized, open-label trial with masked endpoint assessment. Patients with acute stroke (ischemic or hemorrhagic) were randomly assigned within 24 hours after symptom onset to either receive intravenous ceftriaxone or standard stroke care. The trial protocol did not include restrictions on BP values, or recommendations on when to administer antihypertensive treatment in participating patients. We included all patients with AIS and found that systolic BP (SBP) showed the strongest association with functional outcome in a U-shape with worse outcome for SBP lower and higher than 164 mm Hg. The cohort consisting of 2124 patients with AIS was then stratified in three SBP groups: 212 patients in the low SBP group (SBP < 10th percentile (130 mm Hg)), 1440 in the normal SBP group (SBP ≥ 130-185 mm Hg), and 472 in the high SBP group (SBP ≥ 185 mm Hg). After adjustment, there was a trend towards worse functional outcome at 90 days in patients with low SBP (adjusted common odds ratio, 1.24; 95% CI, 0.95–1.61). These patients died more often in the hospital (8.0% versus 4.2%; adjusted odds ratio (aOR), 1.58; 95% CI, 1.13–2.21) and they more often suffered complications within 7 days after stroke onset (16.0% versus 6.5%; aOR, 2.56; 95% CI, 1.60–4.10). Specifically, patients with low SBP had a higher risk of heart failure (2.4% versus 0.1%; aOR, 17.85; 95% CI, 3.36–94.86), major extracranial bleeding (all gastrointestinal hemorrhages: 1.9% versus 0.1%; aOR, 26.04; 95% CI, 2.83–239.30), and sepsis (3.3% versus 0.5%; aOR, 5.53; 95% CI, 1.84–16.67). There was no difference in symptomatic intracranial hemorrhage between the groups. We concluded that patients with AIS and low SBP were at increased risk of in-hospital mortality and major complications, but that this did not translate into significant worse outcomes at 90 days. Whether low SBP is a cause or consequence of these complications is unknown, but the presence of low SBP should prompt clinicians to look for these conditions.

Chapter 5: Clinical Outcome After Endovascular Treatment in Patients With Active Cancer and Ischemic Stroke: A MR CLEAN Registry Substudy.

Comorbid cancer in patients with AIS is associated with worse outcomes.[12] EVT is often the only possible treatment modality, as IVT is frequently contraindicated due to recent surgery or coagulopathy.[13] We assessed the clinical, imaging and safety outcomes of patients with AIS and active cancer who underwent EVT in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry.[14] This was a prospective, observational cohort study of consecutive patients with ischemic stroke undergoing EVT in the Netherlands. We included 2583 patients with anterior circulation stroke: 124 patients (4.8%) with active cancer (defined as cancer diagnosis within 12 months before stroke, metastatic disease, or cancer treatment in the last 30 days) and 2459 patients (95.2%) without (a history of) cancer. The treatment setting was palliative in 25.3% of the patients. A total of 84.8% of patients had received some form of cancer treatment in the 30 days leading up to their AIS. Patients with active cancer were less often treated with IVT (56.6% vs 75.8%, $p < 0.001$). Compared to patients without cancer, their functional outcome was worse at 90 days (acOR for a shift on the modified Rankin scale (mRS) score toward worse outcome 2.2, 95% CI 1.5–3.2), with higher mortality (52.2% vs 26.5%, aOR 3.2, 95% CI 2.1–4.9). This persisted when only patients with pre-stroke mRS of 0-1 were included: acOR 1.9, 95% CI 1.2–3.0. Recurrent stroke within 90 days was ≈3 times more common in patients with active cancer (4.0% vs 1.3%, aOR 3.1, 95% CI 1.2–8.1), but the risk of other complications was comparable. We concluded that, despite similar technical success, patients with active cancer had significantly worse outcomes after EVT for AIS, even when their prestroke functioning was favorable (mRS score 0–1). Moreover, they had an increased risk of recurrent
stroke. Nevertheless, about a quarter of the patients regained functional independence, and the risk of other complications, most notably sICH, was not increased.

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DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

Hoofdstuk 1: Introductie en inhoud van de thesis

De klinische beoordeling blijft de hoeksteen van de neurologie, ondanks vooruitgang op het gebied van neuroradiologie. Hoewel neurologie van oudsher vooral een poliklinisch beroep was, is er de afgelopen jaren veel gebeurd op het gebied van de acute neurologie. Dit heeft een nieuwe dimensie aan het beroep toegevoegd, die clinici dwingt beslissingen te nemen op de spoedeisende hulp (SEH) onder enorme tijdsdruk zonder het kostenaspect uit het oog te verliezen. Er zijn echter tal van klinische dilemma's die deze beslissingen kunnen bemoeilijken. Om clinici een handje te helpen, beschrijft dit proefschrift de resultaten van onderzoeken die we hebben uitgevoerd naar enkele van deze klinische dilemma's bij acute neurologische aandoeningen.

LICHT TRAUMATISCH HERSENLETSEL

Hoofdstuk 2: Evaluatie van 24-uurs klinische observatie bij patiënten met licht traumatisch schedel-/hersenletsel onder antistolling: een retrospectieve multicenter studie en meta-analyse.

De incidentie van licht traumatisch schedel-/hersenletsel (LTSH) neemt toe, vooral bij ouderen, en vormt een van de meest voorkomende redenen voor een neurologisch consult op de SEH. We onderzochten de opbrengst van neurologische observatie bij patiënten met LTSH tijdens therapie met antistolling. Deze patiënten lopen een verhoogd risico op een traumatische intracraniële bloeding (ICB). Verlate ICBs zijn ook vaak beschreven bij patiënten die antistolling krijgen en aanvankelijk een niet afwijkende computertomografie (CT) van het hoofd hebben. Het risico op deze gevreesde complicatie was onduidelijk, wat resulteerde in verschillende richtlijnen, variërend van routinematig opnemen en na 24 uur herscannen van al deze patiënten tot geen aanbeveling geven vanwege een gebrek aan bewijs. In onze retrospectieve observationele multicenter studie onderzochten we de frequentie van verlate ICBs bij patiënten met LTSH onder antistolling (therapeutische dosis heparine (LMWH), directe orale anticoagulantia (DOAC) of vitamine K-antagonisten (VKA) en een international normalized ratio (INR) ≥ 1.7) bij wie de initiële CT-scan van het hoofd geen intracraniële traumatische afwijkingen liet zien. Daarnaast hebben we een meta-analyse uitgevoerd van vergelijkbare onderzoeken. Om de theoretische opbrengst van klinische observatie bij deze patiënten te bepalen, was de primaire uitkomst de ontwikkeling van een symptomatische verlate ICB binnen 24 uur. We includeerden 905 patiënten, waarvan de meerderheid VKAs kreeg (97%, mediane INR 2.9). Geen van deze patiënten ontwikkelde een verlate ICB binnen 24 uur.

Er waren echter vier patiënten die neurologisch verslechterden binnen 24 uur ten gevolge van een ICB (0.4%, 95% betrouwbaarheidsinterval (BI) 0.1–1.2). Toen de eerste scans opnieuw werden geëvalueerd, bleken ze allemaal in retrospect toch al een ICB te hebben. Van de vijf patiënten die verslechterden buiten de observatieperiode van 24 uur, waren er nog twee die een verlate diagnose van een traumatische ICB hadden in plaats van een verlate ICB. Al met al hadden slechts drie patiënten die symptomen ontwikkelden op respectievelijk dag 18, 36 en 52 een echte verlate ICB. In de meta-analyse van 9 onderzoeken met gegevens van 2885 patiënten, was de geschatte samengevoegde proportie van symptomatische verlate ICBs of verlate diagnose van ICBs binnen 24 uur 0.2% (95% BI 0.0-0.5). We concludeerden dat symptomatische verlate (diagnose van) ICB binnen 24 uur bij patiënten met LTSH onder antistolling zeer zeldzaam is na een als niet afwijkend verslagen CT van het hoofd. Wanneer de eerste scan secuur wordt geëvalueerd, lijkt een routinematige ziekenhuisopname niet geïndiceerd.

ACUTE ISCHEMISCHE BEROERTE

Hoofdstuk 3: Alcohol intoxicatie als imitator van een beroerte en de incidentie van acute alcoholintoxicatie bij een beroerte.

Zogeheten *stroke mimics* (SMs) vertegenwoordigen tot wel 43% van de presentaties op de SEH met focale neurologische afwijkingen. Een veelvoorkomende SM van de achterste circulatie is acute alcoholintoxicatie. We beschreven de frequentie en klinische kenmerken van patiënten met acute alcoholintoxicatie als een SM en als een tegelijk optredende diagnose bij een beroerte (zowel herseninfarcten als -bloedingen) in een prospectieve observationele single-center studie. We includeerden 974 patiënten die zich binnen 6 uur na het begin van de symptomen meldden voor mogelijke reperfusietherapie. In totaal waren 60 patiënten (6.2%) onder invloed van alcohol met een gemiddeld promillage van 1.3‰: 38 (3.9%) patiënten met een beroerte en 22 (2.3%) patiënten met een SM, waarvan 12 (1.2%) patiënten hun SM kregen toegeschreven aan acute alcoholintoxicatie. Deze cijfers veranderden toen alleen de 235 patiënten met symptomen van een beroerte in de achterste circulatie werden bekeken. Tweeëntwintig (9.4%) hadden een verhoogd promillage: 8 (3.4%) patiënten met een beroerte en 14 (6.0%) met een SM, 11 (4.7%) veroorzaakt door acute alcoholintoxicatie.

Patiënten met een verhoogd promillage presenteerden zich meestal buiten kantooruren (81.7%). Vergeleken met de 38 patiënten met een beroerte en gelijktijdige alcoholintoxicatie, hadden de 12 patiënten met een SM als gevolg van alcoholintoxicatie een hoger gemiddelde promillage (2.2‰ versus 1.1‰ ($p = 0.001$)) en

vaker vertebrobasilaire symptomen (91.7% versus 21.1 %, p < 0,001). Ze waren ook meer geneigd om hun alcoholgebruik te ontkennen of te bagatelliseren: 50.0% versus 28.9% (p = 0.017). Patiënten met een herseninfarct en gelijktijdige alcoholintoxicatie hadden minder kans te worden behandeld met reperfusietherapie in vergelijking met patiënten met een herseninfarct zonder verhoogd promillage (26.3% versus 52.2%, p = 0.018). Er deden zich geen complicaties voor bij de 11 patiënten met een verhoogd promillage die intraveneuze trombolyse (IVT) of intra-arteriële trombectomie (IAT) kregen.

We concludeerden dat clinici kunnen overwegen om het alcoholpromillage in bloed te meten bij patiënten met een mogelijke beroerte van de achterste circulatie die zich na werktijd presenteren, maar dat zij deze patiënten geen reperfusietherapie moeten onthouden op basis van een verhoogd promillage.

Hoofdstuk 4: Verband tussen lage bloeddruk en klinische uitkomst bij patiënten met een herseninfarct.

Patiënten met een herseninfarct hebben meestal een verhoogde bloeddruk (BD) bij presentatie en lage BD komt niet vaak voor. We onderzochten het verband tussen een spontane lage BD en de klinische uitkomsten na een herseninfarct in een post-hocanalyse van de Preventive Antibiotics in Stroke Study (PASS)-database. PASS was een landelijke, multicenter, gerandomiseerde, open-label studie met gemaskeerde eindpuntbeoordeling. Patiënten met een acute beroerte (herseninfarcten en -bloedingen) werden binnen 24 uur na het begin van de symptomen gerandomiseerd voor intraveneus ceftriaxon of standaardzorg bij een beroerte. Het onderzoeksprotocol bevatte geen beperkingen voor BD-waarden, of aanbevelingen over wanneer antihypertensiva moeten worden toegediend aan deelnemende patiënten. We includeerden alle patiënten met een herseninfarct en ontdekten dat systolische BD (SBD) de sterkste associatie vertoonde met de functionele uitkomst in een U-vorm met slechter resultaat voor SBD lager en hoger dan 164 mm Hg. Het cohort bestaande uit 2124 patiënten met een herseninfarct werd vervolgens gestratificeerd in drie SBD-groepen: 212 patiënten in de lage SBD-groep (SBD < 10e percentiel (130 mm Hg)), 1440 in de normale SBD-groep (SBD ≥ 130-185 mm Hg) en 472 in de hoge SBD-groep (SBP ≥ 185 mm Hg). Gecorrigeerd was er een trend naar een slechtere functionele uitkomst na 90 dagen bij patiënten met lage SBD (gecorrigeerde common odds ratio, 1.24; 95% BI, 0.95-1.61). Deze patiënten overleden vaker in het ziekenhuis (8.0% versus 4.2%; gecorrigeerde odds ratio (cOR), 1.58; 95% BI, 1.13–2.21) en er deden zich vaker complicaties voor binnen 7 dagen na het begin van het herseninfarct (16.0% versOverzichtus 6.5 %; cOR, 2.56; 95% BI, 1.60-4.10). Specifiek hadden patiënten met lage SBD een hoger risico op hartfalen (2.4% versus 0.1%; cOR, 17.85; 95% BI, 3.36-94.86), ernstige extracraniële bloedingen (allemaal gastro-intestinale

bloedingen: 1.9% versus 0.1%; cOR 26.04; 95% BI 2.83–239.30) en sepsis (3.3% versus 0.5%; cOR 5.53; 95% BI 1.84–16.67). Er was geen verschil in symptomatische ICB tussen de groepen. We concludeerden dat patiënten met een herseninfarct en lage SBD een verhoogd risico hadden op overlijden in het ziekenhuis en ernstige complicaties, maar dat dit zich na 90 dagen niet vertaalde in significant slechtere uitkomsten. Of een lage SBD oorzaak of gevolg is van deze complicaties is onbekend, maar de aanwezigheid van een lage SBD zou clinici ertoe moeten aanzetten om naar deze aandoeningen te zoeken.

Hoofdstuk 5: Klinische uitkomst na intra-arteriële trombectomie bij patiënten met actieve kanker en een herseninfarct: een MR CLEAN Registry substudie.

Comorbide kanker bij patiënten met een herseninfarct gaat gepaard met slechtere uitkomsten. IAT is vaak de enige behandeling die mogelijk is, aangezien IVT vaak gecontra-indiceerd is vanwege een recente operatie of stollingsstoornis. We beoordeelden de klinische, radiologische- en veiligheidsresultaten van patiënten met een herseninfarct en actieve kanker die IAT ondergingen in de Multicenter Randomised Clinical Trial of Endovasculair Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry. Dit was een prospectieve, observationele cohortstudie van opeenvolgende patiënten met een herseninfarct die IAT ondergingen in Nederland. We includeerden 2583 patiënten met een herseninfarct in de voorste circulatie: 124 patiënten (4.8%) met actieve kanker (gedefinieerd als kankerdiagnose binnen 12 maanden vóór het herseninfarct, gemetastaseerde ziekte of kankerbehandeling in de afgelopen 30 dagen) en 2459 patiënten (95.2%) zonder (een voorgeschiedenis van) kanker. De setting was palliatief bij 25.3% van de patiënten. In totaal had 84.8% van de patiënten een vorm van kankerbehandeling ondergaan in de 30 dagen voorafgaand aan hun herseninfarct. Patiënten met actieve kanker werden minder vaak behandeld met IVT (56.6% versus 75.8%, $p < 0.001$). Vergeleken met patiënten zonder kanker was hun functionele uitkomst slechter na 90 dagen (common cOR voor een verschuiving op de modified Rankin scale (mRS) score naar slechtere uitkomst 2.2, 95% BI 1.5-3.2), de mortaliteit hoger (52.2% versus 26.5%, cOR 3.2, 95% BI 2.1–4.9). Dit bleef overeind toen alleen patiënten met een mRS van 0-1 vóór de beroerte werden opgenomen: common cOR 1.9, 95% BI 1.2–3.0. Een recidief herseninfarct binnen 90 dagen kwam ≈3 keer vaker voor bij patiënten met actieve kanker (4.0% versus 1.3%, cOR 3.1, 95% BI 1.2–8.1), maar het risico op andere complicaties was vergelijkbaar. We concludeerden dat, ondanks vergelijkbaar technisch resultaat, patiënten met actieve kanker significant slechtere uitkomsten hadden na IAT voor een herseninfarct, zelfs wanneer hun functioneren vóór de beroerte goed was (mRS-score 0-1). Bovendien hadden ze een verhoogd risico op een recidief hartinfarct. Niettemin herwon ongeveer een kwart van de patiënten hun functionele onafhankelijkheid en het risico op andere complicaties, met name symptomatische ICB, was niet verhoogd.

LIST OF ABBREVIATIONS

AIS	acute ischemic stroke
ACOR	adjusted common odds ratio
AOR	adjusted odds ratio
BAC	blood alcohol concentration
BP	blood pressure
CI	confidence interval
CT	computed tomography
CTA	CT angiography
CTP	CT perfusion
DOAC	direct oral anticoagulant
ED	emergency department
ENCHANTED	ENCHANTED enhanced control of hypertension and thrombolysis
EOL	end of life
ETICI	expanded treatment in cerebral infarction
EVT	endovascular treatment
GCS	Glasgow coma scale
ICH	intracranial hemorrhage
INR	international normalized ratio
IQR	interquartile range
IVT	intravenous thrombolysis
LIS	dutch injury surveillance system
LMWH	low molecular weight heparin
MR CLEAN	MR CLEAN multicenter randomized clinical trial of endovascular treatment of acute ischemic stroke in the Netherlands
MRI	magnetic resonance imaging
MRS	modified Rankin scale
MTBI	mild traumatic brain injury
NIHSS	national institutes of health stroke scale
PASS	preventive antibiotics in stroke study
QALY	quality adjusted life years
QOL	quality of life
RT-PA	recombinant plasminogen activator
SBP	systolic blood pressure
SM	stroke mimic
TBI	traumatic brain injury
VKA	vitamin K antagonist

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LIST OF PUBLICATIONS

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Verschoof MA, Groot AE, Vermeij JD, Westendorp WF, van den Berg SA, Nederkoorn PJ, van de Beek D, Coutinho JM. Association Between Low Blood Pressure and Clinical Outcomes in Patients With Acute Ischemic Stroke. Stroke. 2020 Jan;51(1):338-341.

Verschoof MA, Groot AE, de Bruijn SFTM, Roozenbeek B, van der Worp HB, Dippel DWJ, Emmer BJ, Roosendaal SD, Majoie CBLM, Roos YBWEM, Coutinho JM; MR CLEAN Registry Investigators. Clinical Outcome After Endovascular Treatment in Patients With Active Cancer and Ischemic Stroke: A MR CLEAN Registry Substudy. Neurology. 2022 Mar 8;98(10):e993-e1001.

Verschoof MA, Groot AE, de Bruijn SFTM, Roozenbeek B, van der Worp HB, Dippel DWJ, Emmer BJ, Roosendaal SD, Majoie CBLM, Roos YBWM, Coutinho JM. Author Response: Clinical Outcome After Endovascular Treatment in Patients With Active Cancer and Ischemic Stroke: A MR CLEAN Registry Substudy. Neurology. 2022 Jul 26;99(4):175.

Verschoof MA, van Meenen LCC, Andriessen MVE, Brinkman DMC, Kamphuis S, Kuijpers TW, Leavis HL, Legger GE, Mulders-Manders CM, de Pagter APJ, Rutgers A, van Well GTJ, Coutinho JM, Hak AE, van Montfrans JM, Klouwer FCC. Neurological phenotype of adenosine deaminase 2 deficient patients: a cohort study. Eur J Neurol. 2023 Aug 16. Epub ahead of print.

PHD PORTFOLIO

Name PhD student: Merelijne Verschoof PhD period: 2017-2023 Names of PhD supervisor(s) & co-supervisor(s): prof. dr. Y.B.W.E.M. Roos, dr. J.M. Coutinho and dr. S.F.T.M. de Bruijn		
1. PhD training		
	Year	**ECTS**
General courses		
Basic Course Legislation and Organisation for Clinical Research (eBROK)	2022	1.0
Practical Biostatistics	2022	1.1
Seminars, workshops and master classes		
Weekly seminars and journal club, Department of Neurology, The Hague	2015-2022	8.0
Nascholing Nederlandse Neurovasculaire Werkgroup	2017-2020	1.0
Presentations		
Poster presentation, Wetenschapsdagen Nederlandse Vereniging Neurologie (NVN)	2016	0.5
Oral presentation, Wetenschapsdagen NVN	2017	0.5
Poster presentation, Wetenschapsdag HagaZiekenhuis	2017	0.5
Oral presentation, 3rd European Academy of Neurology Congress, Amsterdam, the Netherlands	2019	0.5
Oral presentations (2 studies), Wetenschapsdagen NVN	2019	1.0
Poster presentations (3 studies), 5th European Stroke Organisation Conference, Milan, Italy	2019	1.5
Poster presentations (2 studies), Wetenschapsdag HagaZiekenhuis	2019	1.0
Oral presentation, 6th NLHI/DCVA Translational Cardiovascular Research Meeting, Utrecht, the Netherlands	2022	0.5
Oral presentation, voorjaarsvergadering Nederlandse vereniging Kinderneurologie (NVKN), Haarlem, the Netherlands	2023	0.5

(Inter)national conferences		
Wetenschapsdagen NVN	2016-2022	3.5
3rd European Academy of Neurology Congress , Amsterdam, the Netherlands	2017	0.75
4th European Stroke Organisation Conference, Gothenburg, Sweden	2018	0.75
11th World Stroke Congress, Montreal, Canada	2018	1.0
5th European Stroke Organisation Conference, Milan, Italy	2019	0.75
Organization Cursorium Kinderneurologie, Nijmegen, the Netherlands	2022	1.5
1st International Pediatric Stroke Organization Conference, Vienna, Austria	2022	1.0
Organization Cursorium Kinderneurologie, Utrecht, the Netherlands	2023	1.5
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2. Teaching

	Year	ECTS
Lecturing		
Haga Academy (Acute Neurologie Startklas)	2018-2020	1.5
Tutoring, Mentoring		
Critical Appraised Topic student groups, LUMC, Leiden	2017-2019	0.5