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ACUTE STROKE CARE: STRATEGIES FOR IMPROVING DIAGNOSTICS

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Be kind, for everyone you meet is fighting a hard battle.

"...success in medicine has dimensions that cannot be found on a playing field. For one, lives are on the line. Our decisions and omissions are therefore moral in nature. We also face daunting expectations. In medicine, our task is to cope with illness and to enable every human being to lead a life as long and free of frailty as science will allow. The steps are often uncertain. The knowledge to be mastered is both vast and incomplete. Yet we are expected to act with swiftness and consistency, even when the task requires marshaling hundreds of people—from laboratory technicians to the nurses on each change of shift to the engineers who keep the oxygen supply system working—for the care of a single person. We are also expected to do our work humanely, with gentleness and concern. It's not only the stakes but also the complexity of performance in medicine that makes it so interesting and, at the same time, so unsettling."

Atul Gawande – Better

To all of us who may someday face acute stroke symptoms
– and to my family.

ABSTRACT

Stroke is one of the leading causes of death and disability, with a high incidence of over 11 million cases annually worldwide. Costs of treatment and rehabilitation, loss of work, and the hardships resulting from stroke are a major burden both at the individual and at the societal level. Importantly, stroke therapies need to be initiated early for them to be effective. Thrombolytic therapy and mechanical thrombectomy are early treatment options of ischemic stroke. In hemorrhagic stroke, optimization of hemodynamic and hemostatic parameters is central, and surgery is considered in a subset of patients.

Efficient treatment of stroke requires early and precise recognition of stroke at all stages of the treatment chain. This includes identification of patients with suspected acute stroke by emergency medical dispatchers and emergency medical services staff, and precise admission diagnostics by the receiving on-call stroke team. Success requires grasping the complexity of stroke symptoms that depend on the brain areas affected, and the plethora of medical conditions that can mimic stroke.

The Helsinki Ultra-acute Stroke Biomarker Study includes a cohort of 1015 patients transported to hospital due to suspected acute stroke, as candidates for revascularization therapies. Based on this cohort, this thesis work has explored new avenues to improve early stroke diagnostics in all stages of the treatment chain.

In a detailed investigation into the identification of stroke by emergency medical dispatchers, we analyzed emergency phone calls with missed stroke identification. We also combined data on dispatch and EMS and hospital records to identify causes for missing stroke during emergency calls. Most importantly, we found that a patient's fall at onset and patient confusion were strongly associated with missed identification. Regarding the Face Arm Speech Test (FAST), the most likely symptom to be misidentified was acute speech disturbance.

Using prehospital blood sampling of stroke patients, and ultrasensitive measurement, we investigated the early dynamics of the plasma biomarkers glial fibrillary acidic protein (GFAP) and total tau. Utilizing serial sampling, we demonstrate for the first time that monitoring the early release rate of GFAP can improve the diagnostic performance of this biomarker for early differentiation between ischemic and hemorrhagic stroke. In our analysis of early GFAP levels, we were able to differentiate with high accuracy two-thirds of all patients with acute cerebral ischemia from those with hemorrhagic stroke,

supporting further investigation of this biomarker as a promising point-of-care tool for prehospital stroke diagnostics.

We performed a detailed review of the admission diagnostics of our cohort of 1015 patients to explore causes and predictors of admission misdiagnosis. We then investigated the consequences of misdiagnosis on outcomes. We demonstrate in this large cohort that the highly optimized and rapid admission evaluation in our hospital district (door-to-needle times below 20 minutes) did not compromise the accuracy and safety of admission evaluation. In addition, we discovered targets for improving future diagnostics.

Finally, our detailed neuropathological investigation of a case of cerebral amyloid angiopathy (CAA) -related hemorrhage after stroke thrombolysis provided unique tissue-level evidence for this common vasculopathy as a notable risk factor for intracranial hemorrhagic complications in the setting of stroke. These findings support research to improve the diagnostics of CAA, and the prediction of hemorrhagic complications associated with stroke thrombolysis.

In conclusion, these proposed targets and strategies will aid in the future improvement and development of this highly important field of diagnostics. Our proof-of-concept discoveries on early GFAP kinetics help guide further study into this diagnostic approach just as highly sensitive point-of-care GFAP measurement instruments are becoming available. Finally, our results support the safety of worldwide efforts to optimize emergency department door-to-needle times when care is taken to ensure sufficient expertise is in place, highlighting the role of the on-call vascular neurologist as a central diagnostic asset.

TIIVISTELMÄ

Aivohalvaus on yksi yleisimpiä kuolinsyitä ja työkyvyttömyyden aiheuttajia, ja sen maailmanlaajuinen vuosittainen ilmaantuvuus on yli 11 miljoonaa tapausta. Hoito- ja kuntoutuskustannukset, työkyvyn menetys ja aivohalvauksen aiheuttamat arkielämän vaikeudet ovat suuri taakka sekä yksilön että yhteiskunnan tasoilla. Vaikka hoitovaihtoehtoja on useita, kuten liuotushoito ja mekaaninen trombektomia iskeemisen aivohalvauksen hoitoon, sekä hemodynamiikan ja hemostaasin optimointi ja leikkaushoito aivoverenvuotojen hoitoon, nämä hoidot on aloitettava nopeasti, jotta ne olisivat tehokkaita.

Aivohalvauksen hoitojen vaatima nopeus edellyttää aivohalvauksen varhaista ja tarkkaa tunnistamista hoitoketjun kaikilla tasoilla. Tähän sisältyy aivohalvauksen tunnistaminen hätäkeskuksen ja ensihoidon toimesta, nopea triage ja kuljetus oikeaan sairaalaan, ja onnistunut diagnostiikka päivystyspoliklinikan vastaanottavalta aivohalvaustiimiltä. Haasteina ovat monimutkaisuus aivohalvauksen oireissa, jotka riippuvat sairastuneista aivoalueista, sekä lukuisat muut sairaudet, jotka voivat jäljitellä aivohalvauksen oireita.

Helsinki Ultra-acute Stroke Biomarker Study -tutkimus käsittää 1015 potilaan kohortin, jotka kuljetettiin sairaalaan epäillyn akuutin aivohalvauksen vuoksi arvioitavaksi ja diagnosoitavaksi rekanalisaatiohoitojen varhaista aloittamista varten. Tässä väitöskirjatyössä etsittiin uusia keinoja kehittää aivohalvauksen varhaisdiagnostiikkaa hoitoketjun kaikissa eri vaiheissa.

Yksityiskohtaisessa tutkimuksessa aivohalvauksen tunnistamisesta hätäkeskuspäivystäjien toimesta analysoimme hätäpuheluita, joissa aivohalvauksen tunnistaminen epäonnistui. Lisäksi yhdistimme hätäpuheluiden, ensihoitokertomusten ja sairaskertomusten tietoja löytääksemme syitä aivohalvauksen tunnistamisen epäonnistumiseen hätäpuhelujen aikana. Havaitsimme, että potilaan kaatuminen ja potilaan sekavuus olivat keskeisiä tekijöitä, jotka liittyivät epäonnistuneeseen tunnistamiseen. Face Arm Speech Test (FAST) -seulontaoireista puhehäiriö oli todennäköisimmin väärin tunnistettu.

Akuuttivaiheen verinäytteitä ja äärimmäisen herkkää määritysmenetelmää hyödyntäen tutkimme kahden verestä mitattavan merkkiaineen, tähtisolujen säikeisen happaman proteiinin (GFAP) ja taun varhaista dynamiikkaa aivohalvauspotilailla. Osoitamme ensimmäistä kertaa, että GFAP:n varhaisen vapautumisnopeuden seurantaa sarjanäytteistä voidaan hyödyntää parantamaan tämän merkkiaineen diagnostista suorituskykyä iskeemisen ja hemorragisen aivohalvauksen varhaisessa erottamisessa. Varhaisten GFAP-

tasojen analyysissämme pystyimme erottamaan suurella varmuudella kaksi kolmasosaa kaikista iskeemiseen aivohalvaukseen sairastuneista niistä potilaista, joilla oli aivoverenvuoto. Tulokset viittaavat siihen, että GFAP merkkiaine voisi olla jatkossa kehitettävissä ambulansseissa hyödynnettäväksi pikaverikokeeksi, joka auttaisi aivohalvauksen eri muotojen varhaisessa erottelussa.

Teimme yksityiskohtaisen katsauksen kaikkien kohorttimme potilaiden (n = 1015) päivystysdiagnostiikkaan selvittääksemme diagnostisten vaikeuksien syitä ja ennustajia sekä tutkimme virheellisen tulovaiheen diagnoosin seurauksia potilaiden ennusteeseen. Osoitamme ensimmäistä kertaa suuressa aineistossa, että sairaanhoitopiirissämme käytetty aivohalvauksen rekanalisaatiokandidaattien erittäin nopea vastaanottoarviointi (liuotushoidon mediaaniviive alle 20 minuuttia) ei vaaranna diagnostiikan tarkkuutta ja turvallisuutta. Lisäksi kuvailemme diagnostiikan kehittämiskohteita tulevaisuudessa.

Väitöskirjan viimeisessä osatyössä laadimme yksityiskohtaisen neuropatologisen tapausselostuksen aivojen amyloidiangiopatiaan liittyvästä verenvuodosta aivohalvauksen liuotushoidon jälkeen saadaksemme ainutlaatuista kudostason näyttöä tämän yleisen verisuonisairauden aiheuttamasta komplikaatioriskistä aivohalvauksen rekanalisaatiohoidoissa. Havaintomme tukevat tutkimusta aivojen amyloidiangiopatian diagnostiikan parantamiseksi ja verenvuotokomplikaatioiden ennustamisen kehittämiseksi.

Yhteenvetona voidaan todeta, että esitetyt tutkimukset havainnollistavat aivohalvauksen varhaisen diagnosoinnin monitahoisia haasteita. Väitöskirjatyössä esitetyt kehityskohteet ja menetelmät auttavat tämän erittäin tärkeän diagnostisen alan tulevassa kehitystyössä. Mikä tärkeintä, nämä tulokset sisältävät uusia ja ainutlaatuisia konseptihavaintoja varhaisen GFAP-kinetiikan käytöstä aivohalvauksen diagnostiikassa ja erittäin nopean päivystysarvion turvallisuudesta käytettäessä sairaanhoitopiirimme nopeaa liuotushoitoprotokollaa.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals:

I **Mattila OS**, Puolakka T, Ritvonen J, Pihlasviita S, Harve H, Alanen A, Sibolt G, Curtze S, Strbian D, Pystynen M, Tatlisumak T, Kuisma M, Lindsberg PJ. Targets for improving dispatcher identification of acute stroke. Int J Stroke. 2019 Jun;14(4):409-416.

II **Mattila OS**, Ashton NJ, Blennow K, Zetterberg H, Harve-Rytsälä H, Pihlasviita S, Ritvonen J, Sibolt G, Nukarinen T, Curtze S, Strbian D, Pystynen M, Tatlisumak T, Kuisma M, Lindsberg PJ. Ultra-early differential diagnosis of acute cerebral ischemia and hemorrhagic stroke by measuring the prehospital release rate of GFAP. Clinical Chemistry. 2021 Oct;67(10):1361-1372.

III Pihlasviita S, **Mattila OS**, Ritvonen J, Sibolt G, Curtze S, Strbian D, Harve H, Pystynen M, Kuisma M, Tatlisumak T, Lindsberg PJ. Diagnosing cerebral ischemia with door-to-thrombolysis times below 20 minutes. Neurology. 2018 Aug 7;91(6):e498-e508.

IV **Mattila OS**, Sairanen T, Laakso E, Paetau A, Tanskanen M, Lindsberg PJ. Cerebral amyloid angiopathy related hemorrhage after stroke thrombolysis: case report and literature review. Neuropathology. 2015 Feb;35(1):70-4.

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ABBREVIATIONS

ACI	Acute cerebral ischemia
CAA	Cerebral amyloid angiopathy
CI	Confidence interval
CMB	Cerebral microbleed
CSF	Cerebrospinal fluid
CT	Computer tomography
CTA	Computer tomography angiography
CTP	Computer tomography perfusion
DALY	Disability-adjusted life year
ED	Emergency department
EMD	Emergency medical dispatcher
EMS	Emergency medical services
EMT	Emergency medical technician
EVT	Endovascular thrombectomy
FAST	Face Arm Speech (Time) test
GCS	Glasgow coma scale
GFAP	Glial fibrillary acidic protein
HS	Hemorrhagic stroke
HUH	Helsinki University Hospital
HUS	Helsinki and Uusimaa Hospital District
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
INR	International normalized ratio
IQR	Interquartile range
IVT	Intravenous thrombolysis
LVO	Large-vessel occlusion
MRI	Magnetic resonance imaging
MSU	Mobile stroke unit
mRS	Modified Rankin Scale
NCCT	Non-contrast computer tomography
NIHSS	National Institutes of Health Stroke Scale
POC	Point-of-care
rtPA	Recombinant tissue plasminogen activator
SAH	Subarachnoid hemorrhage
SC	Stroke code
SM	Stroke mimic
TBI	Traumatic brain injury

TCD	Transcranial Doppler
TIA	Transient ischemic attack
VIPS	Volumetric impedance phase-shift spectroscopy
YLL	Years of life lost

1 INTRODUCTION

Acute stroke, a medical emergency requiring rapid initiation of treatment, is for emergency care, one of its most challenging diagnostic areas. Due to the wide spectrum of different symptoms and presentations, and because symptom onset is usually not accompanied by pain, stroke symptoms are difficult for laypeople to identify, and often do not trigger the necessary urgency in seeking immediate help.

The diagnostic difficulties are challenging also for emergency medical dispatchers and emergency medical services (EMS) personnel. Stroke-like symptoms can result from a plethora of other acute neurological and non-neurological conditions only differentiated by clinical expertise and complicated diagnostic equipment. Dispatchers and EMS in most parts of the world have very limited means to make triage decisions for these patients, and initiation of specific therapies before hospital arrival is rarely possible. Patients with acute stroke-like symptoms and sufficiently short delays from symptom onset are therefore transported as stroke code patients to the closest stroke center for diagnostics and treatment.

The challenges are greatest at the end of the line, the receiving emergency department, where the on-call physician must rapidly synthesize all available information. This includes medical and EMS records, information from the patient, next of kin, and EMS personnel, and findings from clinical examination, point-of-care blood tests, hemodynamics, and multimodal neuroimaging. Further, all of this must be done immediately, skillfully identifying conditions mimicking stroke.

Although stroke medicine steadily progresses, challenging professionals to make timely changes and improvements in their stroke code pathway, acute diagnostic and therapeutic decisions have become more complicated, with new therapies and diagnostic capabilities, requiring decisions for which evidence-based guidelines are limited. In the Helsinki Ultra-acute Stroke Biomarker Study and in this thesis, the goal has been to examine the diagnostic performance of our stroke code care pathway to identify strategies for improving diagnostic accuracy and speed of treatment at all levels, from the emergency call to the emergency department.

2 REVIEW OF THE LITERATURE

2.1 THE SOCIETAL BURDEN OF STROKE

For epidemiological purposes, stroke is traditionally defined based on World Health Organization (WHO) descriptions, which define stroke through clinical findings and symptoms as rapidly developed signs of focal or global disturbance of cerebral function lasting more than 24 hours (unless interrupted by death), with no apparent origin other than vascular (Aho & Fogelholm 1974).

For the purposes of clinical work and research, where more exacting diagnostic methods are readily available, the definition of stroke has undergone refinement towards a tissue-based definition. According to the definition in an expert consensus document of the American Heart and Stroke Associations, central nervous system (CNS) infarction is brain, spinal cord, or retinal cell death attributable to ischemia, based on 1) pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2) clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded. In addition to CNS infarction, stroke specifically also includes non-traumatic intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), and cerebral venous thrombosis (Sacco et al. 2013). The benefit of this tissue-based definition is the inclusion of asymptomatic CNS ischemia and hemorrhage not included in the traditional epidemiological definition.

Globally, stroke is the third leading cause of lost disability-adjusted life years (DALYs), an epidemiological measure of disease burden, when considering all age groups (GBD 2019 Diseases and Injuries Collaborators 2020). Further, stroke is the third leading cause, worldwide, of years of life lost (YLLs) (GBD 2017 Causes of Death Collaborators 2018). Based on the Global Burden of Disease Study, the crude total number of new stroke cases worldwide (incidence) increased between 1990 and 2017 by 76%, to a total estimate in 2017 of 11.9 million annual cases. The corresponding age-standardized global rate of new strokes in 2017 was estimated to be 150.5 cases per 100 000 (Avan et al. 2019). The total crude global prevalence of stroke was estimated in 2017 to be 104.2 million (Avan et al. 2019).

Importantly, the incidence of stroke is highly dependent on age and traditional vascular risk factors such as hypertension, smoking, poor diet,

impaired glucose tolerance, obesity, and hypercholesterolemia (Lawes et al. 2004; Buttar et al. 2005; Prospective Studies Collaboration et al. 2007) (O'Donnell et al. 2010). On a global scale, 1.3% of stroke incidence is in people aged < 40 years, 10.9% in 40- to 64-year-olds, and 87.8% in those ≥65 years (Avan et al. 2019). It is particularly alarming that the incidence of stroke has increased in recent decades particularly in younger generations (<55 years) (Béjot et al. 2014; Tibæk et al. 2016; L. Li et al. 2022).

Stroke leaves survivors with varying degrees of long-lasting neurological deficits, including motor and sensory impairment, pain, disturbances in speech, apraxia, and cognitive issues (Kotila et al. 1999; Morley et al. 2005; G. Chen et al. 2005; Mukherjee et al. 2006; Snaphaan et al. 2009; Kyrozis et al. 2009; Broomfield et al. 2014; Jokinen et al. 2015). These deficits often disrupt daily life, leading to loss of work, difficulties in carrying out daily activities, and sometimes requiring daily assistance and care. Finally, stroke has a myriad of emotional, mental, and social effects on survivors, further disrupting life. Due to this complexity, stroke is a devastating disease, on both societal and individual levels.

2.2 ACUTE STROKE AND STROKE MIMICS: PRESENTATION AND ACUTE TREATMENT

2.2.1 ACUTE CEREBRAL ISCHEMIA: ISCHEMIC STROKE AND TIA

In its normal state, cerebral energy metabolism is highly dependent on the oxidative metabolism of glucose, its main energy source (Vannucci et al. 1997). When a cerebral artery is suddenly occluded, a gradient of insufficient blood flow forms, with a central tissue area of very deep ischemia, surrounded by a larger area with less severe blood flow deficiencies. The severity of ischemia and oxygen deficiency ranges from benign oligemia with minor effects on cellular metabolism, to more severe ischemia in the so-called penumbral area, which leads to various disruptions in cellular physiology including shutdown of protein synthesis, disruption in the electrical activity of the brain tissue, peri-infarct spreading depression, increases in lactate production, glucose depletion, and finally severe membrane depolarization as cellular ion pumps fail (Heiss 1992; Hossmann 1993b; Hossmann 1993a; Hossmann 1994; DeGracia et al. 2008). The deepest zone of ischemia is in the infarct core where ischemia quickly leads to necrosis and permanent damage to brain tissue (Hossmann 1994; Bandera et al. 2006).

Whereas neurons are the most sensitive cell type facing ischemia, the other components forming the basic structural and functional element of cerebral tissue – the neurovascular unit – including astrocytes, endothelial cells, pericytes, resident inflammatory cells, and oligodendrocytes, are also severely affected, leading to a cascade of disruptive events (del Zoppo 2009; Stanimirovic & Friedman 2012; Dalkara & Alarcon-Martinez 2015). This includes loss of blood flow regulation, accumulation of waste products, microvascular failure with microvascular plugging, cellular and vascular tissue edema, an uncontrolled inflammatory response, and uncontrolled proteolysis (del Zoppo 2009; Iadecola & Anrather 2011). At later stages, recanalization of the occluded artery can lead to reperfusion injury, with severe oxidative injury and further inflammatory activation and infiltration of inflammatory cells (del Zoppo 2009; Bai & Lyden 2015). Inflammatory injury and later apoptotic cell death continue in the days after ischemia, sometimes together with more severe complications such as tissue hemorrhage and severe edema (Beghi et al. 1989; Bai & Lyden 2015).

Symptoms of acute cerebral ischemia (ACI) begin suddenly, and depend largely on which central nervous system (CNS) areas are undergoing ischemia. Symptoms usually reach their maximum intensity in a few minutes or hours. Presentations of ACI are typically classified according to the vascular territory affected (Table 1), with four out of every five occlusions occurring in the anterior carotid circulation, and one-fifth in the posterior vertebrobasilar circulation (Bogousslavsky 1994; Nouh et al. 2014; Yassi et al. 2015; C.-H. Park et al. 2016).

The five main branches arising from the internal cerebral artery include the middle cerebral artery, the anterior cerebral artery, the anterior choroidal artery, the posterior communicating artery, and the ophthalmic artery (Tatu et al. 1998). The posterior circulation consists of the two vertebral arteries that join to form the basilar artery. Smaller paramedian and circumferential branches and four cerebellar arteries arise from the basilar artery, which finally divides into two posterior cerebral arteries (Tatu et al. 1996). Cerebral ischemia in any of these specific vascular territories leads to a corresponding clinical syndrome (Table 1) (Grivé et al. 2005). Notably, a multitude of congenital anatomical variants of the cerebral vasculature exist (Dimmick & Faulder 2009; Varga et al. 2019). For example, a relatively common variant is decreased or absent patency of the posterior communicating artery, which may also influence the clinical manifestation and prognosis of posterior circulation strokes (Ahn et al. 2018; J. S. Park et al. 2022). Although many of these variants are uncommon, what is important is to remember their existence in clinical practice.

In addition to occlusion of major vascular arterial branches, two other lesion types are worth noting. Lacunar ischemic lesions are small subcortical infarcts with a diameter under 1.5 cm, which involve occlusion of deep perforant

arteries (FISHER 1965; Cannistraro et al. 2019). Watershed infarcts involve the junctional areas between the distal regions of two separate arteries, and are typically caused by systemic hemodynamic failure, either alone or in combination with tight stenosis of a larger proximal artery (Momjian-Mayor & Baron 2005).

Table 1. Common stroke syndromes

Anterior circulation		
Site of arterial occlusion	Common acute symptoms	Other notes
MCA (M1)	Contralateral hemiparesis, hemihypoesthesia, hemianopsia, ipsilateral conjugated eye and head deviation (towards lesion). Left MCA: aphasia, ideomotor apraxia. Right MCA: contralateral multimodal hemineglect, anosognosia, anosodiaphoria, asomatognosia, confusion.	When untreated leads to massive brain edema and herniation, with very high mortality
MCA (anterior M2)	Contralateral isolated brachiofacial paresis, partial brachiofacial hypoesthesia, ipsilateral conjugated eye and head deviation (towards lesion). Left MCA: Broca's aphasia, ideomotor apraxia. Right MCA: contralateral multimodal hemineglect, anosognosia, anosodiaphoria, confusion. No visual defects.	
MCA (posterior M2)	Contralateral homonymous hemianopsia, mild brachiofacial paresis, cognitive difficulties. Left MCA: Wernicke's aphasia or conduction aphasia. Right MCA: hemineglect, dyspraxia, spatial disorientation, confusion, behavioral changes.	
ACA	Paresis and hypoesthesia of the distal lower limb, motor hemineglect, motor aphasia, behavioral changes, sphincter dysfunction, mutism, anterograde amnesia, callosal disconnection syndrome.	
AChA	Motor or sensorimotor hemiparesis, sensory deficit alone, ataxic hemiparesis. More rarely: triad of severe hemiparesis, hemihypoesthesia, and upper quadrantanopia.	
ICA	Severe presentation with combination of symptoms related to anterior circulation arteries	Slowly developing atherosclerotic stenosis and subsequent occlusion is usually less severe and can even be asymptomatic
OA	Visual loss in a single eye. Ocular ischemic syndrome, amaurosis fugax.	

Posterior circulation		
VA	Déjerine syndrome, Wallenberg syndrome, Babinski-Nageotte syndrome.	
PICA	Vertigo, nausea, vomiting, nystagmus, ipsilateral ataxia, gait ataxia.	
AICA	Vertigo, nausea, vomiting, nystagmus, ipsilateral deafness with tinnitus, ipsilateral peripheral type facial palsy, facial hypoesthesia, Horner's syndrome, ipsilateral ataxia, dysarthria, contralateral thermoalgesic sensory deficit.	
SCA	Ipsilateral limb and gait ataxia, dysarthria, nystagmus, Horner's syndrome	
BA	Quadriplegia, bilateral facial palsy, horizontal gaze palsy, locked-in syndrome, coma. A multitude of specific brainstem syndromes have been described.	Often the most severe form of stroke with high mortality, although presentations vary depending on collateral circulation
PCA	Contralateral thermoalgesic sensory deficit, contralateral hemianopsia, contralateral facial nerve, vagus nerve and hypoglossal nerve paresis, ipsilateral oculomotor nerve deficit	In 2-10% of patients the PCA is fed mainly from the anterior circulation via a large PCoA
Thalamic	Thalamic pain syndrome, neuropsychiatric symptoms	

MCA: middle cerebral artery, ACA: anterior cerebral artery, AChA: anterior choroidal artery, ICA: internal carotid artery, OA: ophthalmic artery, VA: vertebral artery, PICA: posterior inferior cerebellar artery, AICA: anterior inferior cerebellar artery, SCA: superior cerebellar artery, BA: basilar artery, PCA: posterior cerebral artery, PCoA: posterior communicating artery.

Early treatment of acute ischemic stroke focuses on ensuring hemodynamic stability of the patient, recanalizing the occluded cerebral artery as swiftly as possible, and preventing complications (Powers et al. 2019). As prehospital differentiation of ACI and hemorrhagic stroke (HS) is currently in most cases impossible, early prehospital care focuses on ensuring an adequate airway, breathing, and oxygenation, and circulatory stability, including control of very low or high blood pressure, and initiation of basic fluid resuscitation with a crystalloid solution. Other symptoms such as severe nausea and vomiting, pain, confusion, or early seizures also require treatment early in the prehospital setting. In general, most ACI patients are hypertensive but otherwise hemodynamically stable, and the need for intubation is rare.

The main approaches to recanalization include thrombolytic therapy and mechanical thrombectomy, both of which require more detailed in-hospital work-up, including neuroimaging, to ensure correct patient selection (Powers

et al. 2019). Thrombolysis is based on intravenous infusion of a thrombolytic drug such as tissue-plasminogen activator (tPA) or tenecteplase, which bind to the fibrin-rich areas of the culprit cerebrovascular occlusion, and are thus activated to induce rapid fibrinolysis and dissolution of the clot through local production of plasmin from endogenous plasminogen (Medcalf 2017). Whereas thrombolysis shows high recanalization rates in milder strokes, occlusion of larger vessels and tandem occlusions of cervical arteries are often resistant to thrombolysis alone (Lees et al. 2010; Riedel et al. 2011). Mechanical thrombectomy is highly effective and valuable in these larger occlusions, and involves an intervention performed using intra-arterial catheters and x-ray illumination, usually by an interventional radiologist, to either aspirate or mechanically retrieve the occluding blood clot (M. Goyal et al. 2016; Powers et al. 2019). Finally, prevention of early complications of ACI such as aspiration pneumonia, deep-vein thrombosis, or recurrent stroke, requires monitoring and specialist care. This occurs ideally in a dedicated stroke unit, to optimize all physiological parameters including hematological factors, to actively treat early symptoms, and to provide the seamless multidisciplinary care that eases the way toward active rehabilitation (Davenport et al. 1996; Stroke Unit Trialists' Collaboration 1997; Powers et al. 2019).

Transient ischemic attack (TIA) is a milder form of ACI, in which symptoms do not persist, but end spontaneously through endogenous recanalization of the culprit occlusion (J. Wang et al. 2020; Mendelson & Prabhakaran 2021). Frequently, short-lived TIA symptoms, which follow the vascular territories as described above, precede more severe ACI (J. Yang et al. 2010). In the setting of symptomatic stroke code patients being transported to a hospital, ACI patients' symptoms sometimes disappear during transport or quickly after hospital arrival, leading to a final classification of TIA. Nonetheless, TIA patients also require detailed examination and early etiological studies, ideally at an experienced stroke center, as these patients are at risk of more severe strokes, often prevented with correct interventions (Amarenco 2020; Mendelson & Prabhakaran 2021).

2.2.2 HEMORRHAGIC STROKE: INTRACEREBRAL AND SUBARACHNOID HEMORRHAGE

Intracerebral hemorrhage (ICH), a severe and deadly form of stroke, is characterized by sudden spontaneous bleeding into brain tissue (Sacco et al. 1984; Qureshi et al. 2001). Its common causes include chronic degeneration of deep cerebral small vessels due to hypertension and other vascular risk factors (lipohyalinosis) (Juvela et al. 1995), and cerebral amyloid angiopathy

(CAA), a form of cerebrovascular degeneration characterized by lobar and meningeal accumulation of beta-amyloid protein around vessels (Viswanathan & Greenberg 2011). ICH can also result from other underlying conditions, including vascular malformations, cerebral venous thrombosis, hematological disorders, Moyamoya disease, reversible cerebral vasoconstrictive syndrome, infective endocarditis, neoplasms, anticoagulant therapy, substance abuse, and vasculitis (Meretoja, Strbian, Putaala, et al. 2012; Koivunen et al. 2015; Martí-Fábregas et al. 2018).

When intracerebral bleeding begins, usually from a small artery, blood is rapidly and aggressively pushed into the cerebral tissue, resulting in immediate mechanical disruption, with the expanding hematoma compressing surrounding tissue and dissecting surrounding neural structures (Qureshi et al. 2001; Boltze et al. 2019). This is thought to lead to further rupture of new vessels surrounding the expanding hematoma, leading to sudden new sites of bleeding, and thus to a cascade of tissue disruption and enlargement of the hematoma within the first hours after ICH (Brott et al. 1997). As blood enters the intercellular space, the coagulation cascade is immediately activated due to tissue factor, and mixing of plasma and CSF activates the complement system (Lindsberg et al. 1996; Lee et al. 1996; Xi et al. 1998; Holste et al. 2021). Thrombin, the major end product of the coagulation cascade, is also a highly proinflammatory molecule, inducing inflammatory effects in the surrounding tissue through dedicated PAR-receptors (Hua et al. 2007; Xue et al. 2009). Further mechanisms also contributing to cerebral injury include hemolysis of red blood cells and release of heme-associated iron, uncontrolled inflammatory cell infiltration, immediate blood brain barrier disruption and vascular edema, cellular necrosis and apoptosis, intraventricular hemorrhage, and disruption of CSF flow (Lee et al. 1996; Xi et al. 1998; Tuhrim et al. 1999; Power et al. 2003; Hua et al. 2007; Xue et al. 2009; Dixon et al. 2012; Qian Li et al. 2018; Boltze et al. 2019; W.-S. Yang et al. 2020; Holste et al. 2021).

Neurological symptoms of ICH are similar to those resulting from ACI, corresponding to the brain areas affected by the enlarging hematoma in the same manner as the vascular territories described above for ACI. In cases of severe ICH, symptoms can progress rapidly as the hematoma is enlarging, with progressive deterioration of consciousness (Lord et al. 2015). Rupture of the hemorrhage into the cerebral ventricles can lead to posturing and sudden coma (Lord et al. 2015). Most importantly, ICH and ACI cannot be safely distinguished by clinical symptoms alone (Weir et al. 1994). However, some symptoms do differ in their frequency between these two central diagnosis groups, and presentation with these symptoms, including coma, neck stiffness, seizures, diastolic BP >110 mmHg, vomiting, and headache, do, in undiagnosed patients, raise the likelihood of hemorrhagic stroke (Runchey & McGee 2010).

Conversely, a cervical bruit on auscultation and a prior TIA reduces the likelihood of a hemorrhagic stroke diagnosis (Runchey & McGee 2010).

Treatment options for ICH are still limited, focusing mainly on optimizing hemodynamic parameters to reduce the enlargement of the acute hematoma, stabilize the patient, and prevent complications (Hemphill et al. 2015). Early reversal of any anticoagulant medication is important. Vitamin-K antagonists are primarily reversed with prothrombin complex concentrate (PCC) and vitamin-K (Huttner et al. 2006; Kuramatsu et al. 2015; Steiner et al. 2016). Non-vitamin-K antagonist oral anticoagulants (NOAC) are generally best reversed with dedicated antidotes (Siegal et al. 2015; Purrucker et al. 2016; Pollack et al. 2017). Although the prior use of acetosalicylic acid and other antiplatelet medications may be associated with more fatal outcomes (Saloheimo et al. 2006; Thompson et al. 2010), administration of platelets to patients previously on antiplatelet medication is, however, deleterious (Baharoglu et al. 2016). In ICH patients taking no anticoagulant medications, trials exploring administration of coagulation factors and fibrinolysis inhibitors have found no efficacy (Yuan et al. 2010; Hemphill et al. 2015; Sprigg et al. 2018; Meretoja et al. 2020).

For now, surgical treatment of ICH is still controversial, and is mainly reserved for selected cases with cortical, easily accessible, hematomas, or with posterior fossa bleeds that, if left untreated, show a high risk for rapid herniation and death (Mendelow et al. 2013; Hemphill et al. 2015; Mendelow 2015; Hanley et al. 2017; Staykov et al. 2017; Hanley et al. 2019). Blood-pressure reduction seems to be safe and may improve functional recovery, at least to a systolic level of 140 mmHg (C. S. Anderson et al. 2013). Although the ATACH-2 trial investigating aggressive systolic BP reduction further below 140 mmHg was negative (Qureshi et al. 2016), an important later post-hoc analysis suggested that the subgroup with early treatment within 2 hours of onset showed benefit (Qi Li et al. 2020).

Proposed future treatment options include elegant endoscopic microsurgical approaches to aspirate the developing hematoma and ensure that bleeding has ceased (Kellner et al. 2020; Troiani et al. 2021; M. Ali et al. 2021). Methods to diagnose ICH earlier, in the prehospital setting, may prove crucial, as a significant proportion of hematoma enlargement, an important therapeutic target, is thought to occur very early, withing the first hours after symptom onset (Brott et al. 1997; Demchuk et al. 2012).

Subarachnoid hemorrhage (SAH), the third most common form of stroke, is a result of sudden bleeding into the subarachnoid space, the area surrounding brain tissue that is normally filled with circulating CSF (Sacco et al. 1984). The most common SAH etiology is rupture of an intracranial aneurysm: a chronic bulbous enlargement of a cerebral vessel that grows slowly. Aneurysm formation depends on both genetic and acquired risk factors, most importantly smoking

and high blood pressure (Feigin et al. 2005; Vlak et al. 2011). Additionally, a small portion of non-traumatic SAH cases result from spontaneous bleeding from a cortical vessel (Cuvinciuc et al. 2010).

Just as in ICH, the blood that is released into the CSF space in SAH initiates immediate activation of hemostatic and inflammatory pathways. In addition to this, because large cerebral arteries and veins extend across the surface of the brain adjacent to the CSF space, SAH can cause disruption in these vessels' regulation and lead to unregulated vasoconstriction of arteries, which can further lead to what is called secondary, delayed cerebral ischemia (Dankbaar et al. 2009; Rostami et al. 2018). Finally, disruption of CSF flow can lead to communicative hydrocephalus, which causes increased intracranial pressure and can lead to herniation.

The typical symptoms and patient history of SAH patients differ from those of ACI and ICH patients to a degree that allows EMS in most hospital districts to recognize these patients in the prehospital setting, and transport them directly to a dedicated neurosurgical unit. Key symptoms of SAH include thunderclap headache immediately reaching peak intensity, vomiting, neck stiffness and loss of consciousness (Suwatcharangkoon et al. 2016; Mac Grory et al. 2018). Difficulty in prehospital differential diagnosis arises especially in cases where SAH is so severe as to also cause intraparenchymal bleeding; in these cases, symptoms can resemble those of ICH. It is therefore usual for a small proportion of SAH patients and of patients with combined SAH and ICH to be among the stroke code patient population preselected by EMS.

Acute treatment of SAH includes optimization of hemodynamic parameters to prevent increase in the subarachnoid bleeding. After initial stabilization, the ruptured aneurysm is usually treated with either intravascular coiling or with microsurgical clipping of the artery, both highly challenging procedures performed in experienced neurosurgical units (Etminan & Macdonald 2017). SAH patients often require intensive care and watchful follow-up to prevent further complications (Roquer et al. 2020; Virta et al. 2021).

2.2.3 STROKE MIMICS AND CHAMELEONS

Whereas the main forms of stroke, ACI and HS, may often be difficult to distinguish, a further challenge to diagnostic efforts arises from other disease states with symptoms similar to those of stroke. These disease states, neurological or non-neurological, are collectively called "stroke mimics" (SM). For the common SM diagnoses see Table 2. Two reviews have recently described rates of the most common SM types (McClelland et al. 2019; Pohl et al. 2021).

Another source of misdiagnosis is the "stroke chameleon"; a stroke with symptoms resembling those of other diseases, being thus the opposite of a stroke mimic. This type of stroke includes bilateral thalamic infarcts (Lok et al. 2013), limb-shaking TIA (Alonso et al. 2015; Bartolini et al. 2018), capsular warning syndrome (He et al. 2019), and bilateral occipital strokes (Holt & S. F. Anderson 2000).

Table 2.

Stroke mimics		
Neurological causes		
Diagnosis	**Key diagnostic findings**	**References**
Intracranial epidural hemorrhage	Preceding head trauma, traumatic findings on physical exam, CT/MRI findings	(Charcos et al. 2021)
Intracranial subdural hemorrhage	Preceding head trauma (in most cases), traumatic findings on physical exam, may also be chronic with transient neurological deficits, CT/MRI findings	(Blaauw, Meelis, et al. 2022) (Blaauw, Hertog, et al. 2022)
Traumatic brain injury	Preceding head trauma, traumatic findings on physical exam, CT/MRI findings	(A. R. Mayer et al. 2017) (Howley et al. 2021)
CNS neoplasm	Slow onset, symptoms of elevated ICP, CT/MRI findings	
Encephalitis, abscess	Signs of infection, elevated inflammatory parameters (CRP), antibody determination (in autoimmune encephalitis), CT/MRI findings, findings on lumbar puncture, EEG findings	(Bagga & Simons 2011)
Meningitis	Signs of infection, elevated inflammatory parameters (CRP), neck stiffness, CT/MRI findings, findings on lumbar puncture	(Mathern & Calestino 2020)
Epileptic seizure and postictal state (Todd's paralysis)	History of epilepsy, typical symptom progression, EEG-findings, spontaneous resolution of symptoms, CT-perfusion findings	(Manganotti et al. 2019)
Migraine	History of migraine symptoms, typical symptom progression, hypoperfusion in CTP	(Granato et al. 2020)
Multiple sclerosis	History of MS, subacute onset, CT/MRI findings, CSF findings	(Khedr et al. 2013)
Spinal epidural hematoma	Occipital, neck, and/or back pain, and hemiparesis occurring simultaneously or within 1 h after onset of pain; spinal CT/MRI findings	(Inatomi et al. 2020) (Akimoto et al. 2014)

Posterior reversible encephalopathy syndrome (PRES)	MRI findings, underlying high BP, typical presentation (headache, visual symptoms, seizures, altered mental state)	(Malomo & Ntlholang 2016)
Transient global amnesia	Typical anterograde amnesia without other neurological symptoms, spontaneous resolution of symptoms	(Werner & Woehrle 2021)
Peripheral neuropathies (Bell's palsy)	Symptoms limited to area of peripheral nerve, ENMG, (typical facial paresis of Bell's palsy also involving the upper branches of the facial nerve)	(Mackay et al. 2016)
Other causes		
Vestibulocochlear diseases (benign paroxysmal positional vertigo, vestibuloneuronitis)	Typical findings in tests of balance and inner ear, HINTS test	(Kohn 2014) (Newman-Toker et al. 2008)
Hypoglycemia	Low blood glucose, history of diabetes, insulin use	(Ohshita et al. 2015)
Electrolyte disturbances	Laboratory results, history of electrolyte disturbances; focal neurological findings rare	(Wareing et al. 2015)
Hepatic encephalopathy	History of liver disease/ insufficiency/failure, ultrasound findings in liver, levels of ammonia in blood	(Younes et al. 2019)
Systemic infection	Elevated inflammatory parameters in blood, findings in blood cultures, fever, other symptoms of infection	(Zuurbier et al. 2021)
Functional neurologic disorder, conversion disorder	History of conversion/functional symptoms, psychiatric history, findings in specific tests for these symptoms.	(Popkirov et al. 2020; Jones et al. 2020)
Malingering	Similar findings as in functional/ conversion symptoms, evident external benefit from hospital admission/tests	(Sequeira et al. 2018)
Delirium	Recent history of significant alcohol use, history of other causes of delirium, altered mental state	(Jesse et al. 2017)
Limb trauma	X-ray/CT-findings of fractures and other trauma, skin findings, recent history of falls or other trauma, limb pain	(Daly & Langhammer 2022)
Limb ischemia	Cold limb with weak capillary reaction, ischemic limb pain, imaging findings in CT-angiography of limb	(Verma et al. 2020)
Ocular diseases	Findings limited to eye/eyes, ophthalmoscopy findings, ultrasound/MRI imaging findings	(Khaleeli et al. 2018)

Alcohol intoxication	Breathalyzer measurement, blood alcohol measurement, history of alcohol abuse, intoxicated behavior and findings on exam, odor on breath, alcohol use observed by EMS	(Hassing et al. 2019)
Substance abuse	History of substance abuse, needle marks on skin, findings on drug tests, altered mental state, findings of intoxication (of note: some substances can cause stroke)	(Finch & Vilke 2020)

2.2.4 DISTRIBUTION OF DIAGNOSES WITHIN STROKE CODE PATIENTS

EMDs and EMS personnel assign a high-priority stroke code to all patients suspected of an acute stroke without evident contraindications for stroke treatment. This code leads to a prespecified rapid transport protocol, specific to each hospital district, triaging the patient to an appropriate stroke center. The challenge of diagnosing acute SC patients is largely dependent on their initial selection, and on the resulting distribution of their main diagnoses: ACI, HS, and SM.

By far the most common stroke sub-type is ischemic stroke. In a study from the United States, 87% of all strokes were ischemic, 10% were intracerebral hemorrhage, and 3% subarachnoid hemorrhage (Mozaffarian et al. 2015). These proportion differ slightly for the Finnish population, in which these figures are 79%, 14%, and 7% (Meretoja et al. 2011). Notably, the distribution of the stroke code patient population differs somewhat from these distributions, because of the inevitable inclusion of stroke mimics. In addition, the distribution of diagnoses among the SC patients of each hospital district depends on demographic factors and the selection criteria of both EMD and EMS for identifying SC patients.

Table 3. Distribution of main diagnosis classes in a small illustrative set of earlier study cohorts of SC patients. Any SAH patients found are included in the HS group.

Study	*n*	ACI %	HS%	SM%
(Requena et al. 2018)	2778	69.3	13	17.7
(Quenardelle et al. 2016)	1361	57	5	38
(Suzuki et al. 2018)	1482	44.7	31.8	23.5
(RIGHT-2 Investigators 2019)	1149	61	13	26
(Gioia et al. 2016)	960	51.5	5.3	43.2

2.3 DIAGNOSTIC CHECKPOINTS IN ACUTE STROKE CARE

2.3.1 RECOGNITION OF STROKE SYMPTOMS BY LAYPEOPLE

The sudden onset of new stroke symptoms is a shocking and unsuspected event for every stroke victim. As timely evaluation and transportation to hospital is key, it is highly important that stroke victims and those accompanying them be alerted to the immediate danger implied by their symptoms, and the need to call the emergency number. Unfortunately, stroke symptoms can be mild, can resemble other less dangerous diseases, and often include no pain. In addition, stroke symptoms themselves, ones such as neglect and confusion, may prevent the victim from recognizing their symptoms for themselves.

In a survey of 10,228 individuals from nine European countries, researchers estimated that only 51% would call an ambulance when someone suffers a stroke (Mata et al. 2014). In a US survey in 2014, of 35,862 queried, 68.3% of respondents identified all five stroke symptoms listed (Patel et al. 2019). In comparison, a recent US survey of 9,844 young adults aged <45 years found that only 28.9% of respondents were not aware of all five stroke symptoms listed (Mszar et al. 2020). In addition, the study found less stroke awareness in ethnic minorities and in people with a lower educational level (Mszar et al. 2020), which is in line with some older findings (Greenlund et al. 2003; Fussman et al. 2009). All in all, these large and most recent studies illustrate the lack of stroke knowledge in the general public. It is still unclear how this level of knowledge could be improved.

A body of literature exists on campaigns to improve recognition of stroke symptoms in widely differing populations (Silver et al. 2003; Hodgson et al. 2007; Williams & Noble 2008; Reeves et al. 2008; Kleindorfer et al. 2008; Miyamatsu et al. 2012; Dombrowski et al. 2013; Mellon et al. 2014; Flynn et al. 2014). Although guidelines recommend educational stroke programs (Powers et al. 2019), as of now, no standardized or widely accepted approaches are available for achieving improved stroke recognition. The strategies of these campaigns have most often included acronyms describing stroke symptoms (such as FAST), and have utilized mass-media outlets (Advani et al. 2016; Tan et al. 2021). Unfortunately, achieving long-standing retention of this type of generic medical information may be difficult; in a recent Norwegian study, a mass-media intervention led to an increased number of stroke-related admissions for approximately 6 months before this increase tapered off (Advani et al. 2016).

2.3.2 THE EMERGENCY CALL

After stroke victims themselves or the individuals surrounding them recognize any symptoms as dangerous, the usual reaction is to call the local emergency number. Emergency medical dispatchers answering these calls must recognize those cases meriting a stroke code dispatch from among tens of thousands of other calls, and it is also common for other emergency calls related to police, fire, or other emergencies to go through the same call centers, further complicating matters.

Approaches to call processing differ between hospital districts, including strictly algorithmic approaches with carefully designed prespecified question-and-answer options (such as the Medical Priority Dispatch System). In comparison, other systems provide more freedom for dispatchers to carry out the call with only general notes regarding their approach to different presentations. Generally, telephone-based stroke recognition relies on executing typical stroke recognition scales, like the Face, Arm, Speech Test (FAST).

Sufficient awareness to call the emergency number, and the accuracy of stroke identification by emergency medical dispatchers (EMD) are central checkpoints in the stroke treatment chain; they determine whether the patient will be swiftly transported by EMS. In a US study of 204,591 stroke patients, EMS transport was independently associated with earlier hospital arrival, and faster ED evaluation and treatment, including shorter door-to-needle times, and a larger proportion of patients eligible for thrombolytic treatment (Ekundayo et al. 2013).

In a 2015 US study of 398,798 stroke patients, only 59% arrived at a hospital by EMS (Mochari-Greenberger et al. 2015). Use of EMS was lower for many ethnic minorities, with Hispanic men being least likely to use EMS (52%) (Mochari-Greenberger et al. 2015). In that study, a paresis, an altered level of consciousness, or aphasia were associated with EMS utilization.

EMD stroke identification is an area still insufficiently studied, with a limited evidence base to guide practice. Most importantly, guidelines recommend the use of a prehospital stroke identification tool, one like FAST or CPSS, to improve stroke recognition, although such tools' positive predictive values and sensitivity are limited when used over the phone (De Luca et al. 2013; Dami et al. 2017; Powers et al. 2019).

2.3.3 PREHOSPITAL STROKE DIAGNOSTICS BY EMS

2.3.3.1 Initial evaluation

Upon arrival on scene, EMS protocols focus on evaluating and ensuring basic vital functions, most typically according to a ABCDE evaluation (airway, breathing, circulation, disability, exposure), with some differences between the specific tests and evaluations involved (Drenck et al. 2019; T. Li et al. 2021). This type of initial evaluation is then quickly followed by–or it coincides with–collection of a more detailed medical history. This is often largely guided by the initial dispatch code of the EMS run and initiated with open-ended questions.

The initial evaluation is a critical phase of the diagnostic process in cases in which a suspicion of an acute stroke has not arisen during the emergency call and dispatch phase, requiring EMS to be sufficiently exact and alert in their initial evaluation to raise this possibility, and to test for stroke symptoms. Importantly, prehospital delays have been found to be longer in stroke cases in which the dispatch code was not stroke-related (Abbas et al. 2021). EMS stroke recognition might be improved by including more routine testing of stroke symptoms in situations where stroke may be a possibility, for example based on certain presentations or demographic factors. However, research in this area is still scarce, and is made difficult by the large differences in EMS procedures between hospital districts, with detailed EMS instructions and training often being confidential.

2.3.3.2 Prehospital stroke scales

Validated and thoroughly researched clinical scales remain the backbone of prehospital stroke recognition. These diagnostic instruments include prespecified symptoms and factors for determination on scene and are usually the main method by which EMS selects patients for a high-priority stroke code transport to hospital.

The best-known prehospital stroke recognition scales include the Face, Arm, Speech Test (FAST), the Cincinnati Prehospital Stroke Scale (CPSS), and the Los Angeles Prehospital Stroke Screen (LAPSS), which have only minor differences (Kothari et al. 1999; Kidwell et al. 2000; Harbison et al. 2003). The FAST, used widely by Finnish EMS, includes evaluation for facial droop and asymmetry, unilateral arm weakness, and speech difficulty. In practice, Finnish EMS usually also evaluate for unilateral leg weakness, although this is not officially a part of the FAST. In comparison, the CPSS also evaluates

patient age (>45 years), and the LAPSS is significantly more complicated, also evaluating history of seizures, previous disposition (wheelchair-bound or bedridden), blood glucose, time since symptom onset, and handgrip; it does not screen for speech disturbances. Other more widely known stroke recognition instruments include the MASS, Med PACS, OPSS, and ROSIER, the detailed scoring of which falls outside the scope of this review (Bray et al. 2005; Nor et al. 2005; Chenkin et al. 2009; Studnek et al. 2013).

A large set of studies from 2000 to 2014 have evaluated and compared the accuracy of these stroke-recognition instruments, using differing study settings and sample sizes. Estimates of sensitivity and specificity have differed widely, with sensitivities between 74% and 99%, and specificities between 13% and 99% (Kidwell et al. 2000; Bray et al. 2005; Wojner-Alexandrov et al. 2005; Chenkin et al. 2009; Bray et al. 2010; Studnek et al. 2013; S. Chen et al. 2013; Fothergill et al. 2013; Asimos et al. 2014).

An important caveat concerning these standard stroke scales is their modest accuracy in identifying strokes occurring in the posterior cerebral circulation, often associated with symptoms differing from the spectrum captured by the scales (Gulli & Markus 2012).

The advent of mechanical thrombectomy in treatment of LVO stroke, and its significant time-dependent benefits, have introduced new challenges in the prehospital triage of stroke patients. Mechanical thrombectomy requires both advanced CT-angiography imaging and a suitable angiography suite, with dedicated nursing staff, expensive equipment, and trained operators, usually interventional radiologists, to perform the procedure (M. Goyal et al. 2016; Mendelson & Prabhakaran 2021). Due to these requirements, hospital districts usually have only one or few such thrombectomy-capable stroke centers (in Finland, five university hospitals), with other hospitals equipped only to administer thrombolysis. Thus, EMS urgently require new methods to identify LVO patients in order to provide the thrombectomy team with prenotification, and to transport the appropriate patients to a thrombectomy-capable center (Kass-Hout et al. 2021).

One strategy aiding in prehospital LVO detection has been the development of new prehospital symptom scales for EMS screening of stroke code patients. These scores have been based on the NIHSS, by selecting among its sub-tests to generate new scales with optimized accuracy for LVO detection (Lima et al. 2016). A large number of these scores quickly emerged, as their development was straightforward from old registries. Most of these scores have now been prospectively or retrospectively evaluated in a prehospital setting, with largely similar, but modest sensitivity and positive predictive values (Nguyen et al. 2021; Duvekot et al. 2021; Puolakka, Virtanen, Kuisma, et al. 2021). Naturally, none of these simple scores will outperform their antecedent, the NIHSS, which

is limited in LVO detection to begin with, because as high a percentage as 15% of acute LVO patients have low NIHSS scores in their acute phase, likely due to good collateral blood flow (Heldner et al. 2013). In addition, one must note when using these scores that cases of severe HS are an important false-positive group (Pérez de la Ossa et al. 2014).

2.3.3.3 Phone and video consultation

Although it is economically or practically unfeasible to have an experienced vascular neurologist on board each ambulance, most hospital districts, to improve EMS stroke recognition and to aid in triage decisions, have organized the possibility for physician consultation, usually by phone. These stroke-specific consultations are typically routed to the on-call stroke physician or emergency medicine physician.

United States stroke treatment guidelines recommend EMS prenotification for stroke code patients arriving at the emergency department, an action known to reduce in-hospital delays, but these guidelines omit specific recommendations as to the organization of diagnostic and decision support for EMS (Powers et al. 2019). In general, when compared to the often complex EMS systems in the USA, EMS systems are more centralized and streamlined in European countries.

Limited formal studies exist on the diagnostic benefit provided by EMS phone consultations (Alhanati et al. 2014; Mazya et al. 2020; Gude et al. 2022), but these seem to be diagnostically useful, a finding also supported by the ongoing use of phone consultations in many hospital districts. Larger formal studies would be beneficial to allow for the inclusion in guidelines of this important part of EMS diagnosis support.

Further improving EMS consultations with a video feed to support symptom evaluation has been shown to be feasible (Bergrath et al. 2012; Wu et al. 2014; Lippman et al. 2016; Valenzuela Espinoza et al. 2016), but further data on the usefulness of such a feed is still required. One suggestion is that EMS video consultation and the additional information it provides could help the receiving stroke team reduce in-hospital delays (Koster et al. 2018; Kasab et al. 2021).

Interestingly, stroke neurologists consulted by phone may be superior in identifying LVO cases than are prehospital LVO scales alone (Puolakka, Virtanen, Kinnunen, et al. 2021). Notably, the Stockholm EMS has, in their hospital district, recently used physician phone consultation to improve LVO triage, thus supporting its wider use (Mazya et al. 2020).

2.3.3.4 Point-of-care blood biomarkers

Blood-based laboratory tests for diagnosis of acute myocardial infarction have been in clinical use for decades, but no such markers have emerged for the diagnosis of acute stroke patients, despite several decades of active research, and such are still not in clinical use today. This has been thought to be due to the blood-brain barrier (BBB) and its ability to reduce the release of CNS-specific biomarkers. This results in very low systemic circulation concentrations of these targets (Lindsberg et al. 2017).

Because levels of circulating biomarkers are unlikely to provide spatial information on possible CNS lesions, neurologists have generally been skeptical of their usefulness in clinical practice. Highly accurate neuroimaging with CT technology is already widely available across emergency departments around the world, but in rural areas and in prehospital settings, a diagnostic stroke biomarker, if measurable with rapid and easy point-of-care methodology, could prove useful and cost-effective in the early triage of stroke patients. Such a biomarker could also have the potential to guide suitable therapies, including optimization of hemodynamic and hemostatic parameters in acute HS (Foerch et al. 2009; Lindsberg et al. 2017).

Blood, perfusing through most of the tissues in the body, is a complex research target. Efforts to identify circulating diagnostic biomarkers have included measurement of all available molecular targets, including cells, microvesicles, exosomes, proteins, free DNA, peptides, metabolites, neurotransmitters, and lipid particles, to list those of highest importance. Protein biomarkers have generally been the most common research target. The wide-ranging literature on candidate diagnostic stroke biomarkers has been reviewed thoroughly elsewhere, and is outside the scope of this work (Foerch et al. 2009; Saenger & Christenson 2010; Jickling & Sharp 2011; Whiteley et al. 2012; Monbailliu et al. 2017; Dolmans et al. 2019; Dagonnier et al. 2021). Unfortunately, a large part of that literature involves single-timepoint sampling, generally with collection occurring outside the very early time window (<3 hour from symptom onset), and measured with poorly validated and low-sensitivity methodology (Dolmans et al. 2019; Dagonnier et al. 2021).

Two specific protein biomarkers, glial fibrillary acidic protein (GFAP) and tau, are relevant to this thesis work. GFAP, an intermediate-filament protein part of the astrocyte cytoskeleton, has the capability to form polymeric filaments (Z. Yang & K. K. W. Wang 2015). Highly specific to CNS tissues, and abundantly expressed, GFAP is released into the circulation upon BBB disruption as a results of injury to astrocyte end-feet (Herrmann et al. 2000). Relevantly for acute stroke diagnostics, in HS, GFAP is rapidly elevated, but in ACI shows a significantly slower elevation (Dvorak et al. 2009). Further, levels in SM patients have been low (C. A. Mayer et al. 2013). Thus, GFAP seems to have

an important diagnostic potential in stroke code patients for differentiating HS from other diagnoses. Diagnostic studies under recent review concerning GFAP in acute stroke patients showed its significant potential, although these studies took place primarily with samples collected in-hospital, and at one single time-point (Perry et al. 2018).

Tau protein is a structural microtubule-associated protein mainly expressed in neurons and axons; due to this CNS specificity, it serves as a potential stroke biomarker. Studies have found elevated levels of tau in ACI patients' CSF (Strand et al. 1984; Hesse et al. 2001; Hjalmarsson et al. 2014). Tau elevations also appeared in the serum of ACI patients, but that study was limited by assay sensitivity. Thus far, the diagnostic usefulness of tau in very early stroke remains undetermined (Bitsch et al. 2002).

2.3.3.5 Mobile stroke units

A leading innovation to reduce treatment times for stroke patients is the mobile stroke unit (MSU) concept, which aims to bring the capabilities of emergency department stroke diagnostics directly to the patient (Fassbender et al. 2003). Originally developed and piloted at the university of Saarland, Germany (Walter et al. 2010), MSUs are ambulances equipped with a compact CT-scanner and radiation shielding, telecommunication instruments, a point-of-care laboratory, and skilled staff, including a paramedic with radiology training, and a vascular neurologist (Ebinger et al. 2013). Such MSUs respond to stroke dispatches and perform all the needed examinations on-site, including physician evaluation, laboratory tests, and neuroimaging, which can also include CTA images (Alexandrov et al. 2021). Radiologist teleconsultation can take place by telecommunication. These capabilities allow for immediate diagnosis of LVO and HS, and enable prehospital thrombolysis of suitable ACI patients (Fassbender et al. 2017). Furthermore, in HS, anticoagulation can be swiftly reversed (Cooley et al. 2021), and LVO patients can be rapidly triaged with prenotification to a suitable thrombectomy center (Czap et al. 2021).

Though evidence of MSU success in improving outcomes has been unclear, and MSU cost-effectiveness has been questioned, an increasing number of MSUs have been introduced to metropolitan cities, mostly in Western countries (Fassbender et al. 2021). The concept has progressed the farthest in Berlin, Germany, which currently has three operating MSUs (Ebinger et al. 2021). In 2021, two highly important prospective studies demonstrated the benefit of MSU-based stroke thrombolysis for patient outcomes, comparing MSUs with traditional EMS transport to an emergency department (Grotta et al. 2021; Ebinger et al. 2021). More-detailed studies of cost-effectiveness are underway,

because the largest barrier to wider application of this approach is its high operational cost (Walter, Grunwald, et al. 2018). In addition, mobile stroke units are limited by their operational range, and the fact that only a small proportion of all MSU dispatches, around 10%, involve thrombolysis (Grotta et al. 2021).

The costs of MSUs are likely to decrease as ambulance and mobile CT-scanner technologies improve. In addition, it may be possible to perform the duties of the vascular neurologist over telecommunication from the closest stroke center, which would dramatically reduce personnel costs (Wu et al. 2017). Further, instituting a rendezvous model utilizing existing EMS units to transport patients part-way to an approaching MSU may improve the units' reach (Parker et al. 2020). Finally, plans are underway to establish MSU capabilities on helicopters and planes to dramatically increase their operational range (Walter, Zhao, et al. 2018).

2.3.3.6 Portable diagnostic devices

New non-invasive imaging and sensor technology are an important new research area for prehospital stroke diagnostics. While none of these new technologies is ready for clinical use, research into this technology is a rapidly expanding field, with numerous companies involved in their development (Young & MacDougall 2019; Walsh 2019). The diagnostic targets of these devices include exclusion of stroke mimics, differentiation of ischemic from hemorrhagic stroke, and detection of LVO, depending on the technology. As development is led largely by industry, most findings remain unpublished. Developmental goals include point-of-care capability in the ambulance setting that aims at significantly better cost effectiveness than with traditional CT-based MSUs.

Microwave imaging devices utilize microwaves to visualize intracranial pathologies, primarily ICH. The spatial resolution of microwaves is, however, significantly weaker than is that of CT or MRI, and image processing is more complicated. Microwave technologies promise to mean lower costs, with a potential for compact instruments (Persson et al. 2014; Walsh 2019).

Near-infrared spectroscopy (NIR) measures tissue absorption of near-infrared light, and has served for measurement both of tissue oxygenation and of free hemoglobin in tissues (Moreau et al. 2016; Walsh 2019). Most notably, a new hand-held infrascanner can detect intracranial hematomas, with some preliminary reports on its diagnostic accuracy. This device is, however, limited by its tissue penetration being only a couple of centimeters below the brain surface, and it can miss very small hematomas (<3.5mL) (Robertson et al. 2010; Xu et al. 2017).

Transcranial Doppler ultrasound (TCD) is in routine use in neurological and neurosurgical clinics for assessment of blood flow in the major intracranial arteries, but it requires significant training and relatively large instrumentation (D'Andrea et al. 2016). Development is underway to reduce the size of these instruments, and to apply robotics and autonomous signal processing to automate these examinations for prehospital LVO detection, especially in the middle cerebral arteries (Walsh 2019).

Volumetric impedance phase-shift spectroscopy (VIPS) passes electromagnetic waves through the head from a helmet-type instrument to reveal changes in the electrical properties of brain tissue, which could indicate a large ICH or LVO. Promisingly, several studies already concern the validation of VIPS (Kellner et al. 2018). Although its technology is limited to detection of very severe intracranial events, results suggest the instrument can be very fast (30-second measurement), and can be entirely contained in a small helmet (Kellner et al. 2018; Walsh 2019).

	Hospital	Mobile stroke unit	LVO-score	Tele-consultation	Sonography	Biomarkers (GFAP)	Other sensors
1) Ruling out hemorrhage	+	+	-	-	-	+	+
2) LVO identification	+	+	+	+	+	-	+
3) Stroke mimic identification	+	+	-	+	-	-	-
4) Estimating penumbra	+	-	-	-	-	-	-
	€€€€€	€€€	€	€	€	€	€

Figure 1. Comparison of approaches to early stroke diagnostics, regarding diagnostic capabilities and relative costs of several technologies under development.

2.3.4 ADMISSION DIAGNOSTICS

Upon EMS arrival at the emergency department, a strictly choreographed sequence of diagnostic steps becomes activated, with the on-call vascular neurologist in charge of orchestrating the process.

2.3.4.1 Medical history and clinical examination

A central step in admission evaluation is collection of the patient's medical history, to find clues to the possible diagnosis, determine the course of symptoms and their severity during the prehospital phase, and evaluate the suitability of the patient for all of the interventions available (Powers et al. 2019). In hospital districts where it is possible, this work is usually begun in the prehospital setting. In our hospital district, electronic EMS records are already available before at-hospital arrival. In addition, electronic medical records can be reviewed in advance to identify underlying diseases and risk factors, or a history of any of the relevant diagnoses: ACI, HS, or SM (Meretoja, Strbian, Mustanoja, et al. 2012). This pre-arrival information is further supported by information provided during EMS consultation and prenotification calls (Lindsberg et al. 2006).

Upon hospital arrival, EMS provide a handover report (Flynn et al. 2017), and what is then customary is for the vascular neurologist to verify and further specify important parts of the patient history, with approaches and wording varying between physicians. Checklists can be helpful in this phase (Berekashvili et al. 2020). In addition, bystanders and family members with knowledge of the acute events can be contacted by phone. Although important questions of the patient history, especially regarding contraindications for therapy, are specified in detail in the literature (Powers et al. 2019), one finds few formal studies on how history collection should take place in this setting. The key challenge of this phase is to work rapidly while still identifying and collecting all the central points of the patient history – a demanding task.

The mainstay of clinical examination of the acute stroke patient is the NIHSS evaluation, upon which all therapeutic stroke studies are based, and which is central to verify eligibility for these therapies (Josephson et al. 2006; Lyden et al. 2009). The NIHSS is essentially a neurological symptom-severity scale, and is targeted mainly at evaluating anterior circulation stroke. It is often sufficiently thorough to suggest to the physician whether the symptoms are in line with an acute stroke, or whether to consider an SM (Quenardelle et al. 2016). Supplementation of the NIHSS with additional tests to evaluate for posterior stroke or specific SM diagnoses may be necessary, which requires from the evaluating physician significant expertise encompassing the wide spectrum of acute neurological presentations and their symptoms, a key aspect supporting the need for dedicated experts in the evaluation of acute SC patients (Kattah et al. 2009; Merino et al. 2013).

2.3.4.2 Blood work

For now, laboratory testing is not a significant part of the admission evaluation of stroke code patients. US stroke guidelines recommend the measurement of blood glucose in all stroke code patients, which, in our district, is done with POC measurement by EMS (Meretoja, Strbian, Mustanoja, et al. 2012; Powers et al. 2019). As for other testing, these guidelines do not recommend additional testing before therapy, most importantly before thrombolysis, if they cannot be performed quickly (Powers et al. 2019). However, in our center, POC testing of INR is always performed upon hospital arrival (Meretoja, Strbian, Mustanoja, et al. 2012). In addition, blood samples for routine admission laboratory tests are drawn by the on-call laboratory technician immediately upon hospital arrival, although treatment and diagnosis decisions cannot await the results (Meretoja, Strbian, Mustanoja, et al. 2012). In theory, some routine tests, such as electrolytes, may have significance in identifying certain SM diagnoses, but the incidence of these cases is so rare that testing for all patients before treatment decisions is not warranted.

Research is still ongoing to identify blood-based biomarkers for hemorrhagic complications of thrombolysis, but such markers are not close yet to clinical use (Pan et al. 2017; Krishnamoorthy et al. 2021). Biomarkers also may aid in evaluating prognosis and could perhaps also aid in identifying certain SM diagnoses (Foerch et al. 2009; Bustamante et al. 2021; Jickling & Russo 2019).

2.3.4.3 Neuroimaging

Neuroimaging plays a central role in the in-hospital evaluation of stroke code patients. The on-call stroke physician of the receiving emergency department decides the most suitable neuroimaging protocol case-by-case, in line with institutional guidelines. Generally, due to its speed and cost-effectiveness, CT-based imaging is still the preferred first-line imaging modality in most stroke centers.

Diagnosing hemorrhagic stroke

Noncontrast CT imaging is typically the starting point of the imaging protocol of SC patients, with an excellent capability to rule out HS (Kidwell & Wintermark 2008; Powers et al. 2019). Often thrombolysis, if indicated, can and should be initiated after this first imaging, which typically takes under a minute to perform. Assuming use of the correct sequences, MRI is as effective as noncontrast CT in identifying HS (Chalela et al. 2007; Kidwell et al. 2004). However, MRI is not

readily available in most emergency departments, and due to its strong magnetic field, MRI requires more preparations and precautions before the imaging.

Diagnosing acute cerebral ischemia at tissue level

Ischemic brain injury is significantly harder to detect than is hemorrhage, especially on noncontrast CT, where changes resulting from ischemia develop slowly, and are often not present in the hyperacute phase (Parsons et al. 2007). Because of the difficulty of this assessment, it is common for a radiologist or neuroradiologist to participate in the admission evaluation of acute stroke patients. The ASPECTS scoring system can help to assess and quantify the extent of ischemic findings (Barber et al. 2000).

MRI, especially diffusion-weighted imaging, has a far superior capability to detect tissue ischemia than does noncontrast CT (Schellinger et al. 2010). Other methods to evaluate the level and extent of ischemia include CT and MRI perfusion imaging, which demonstrate the level of blood volume and extent of circulation in various brain areas (Bill et al. 2017). Finally, evaluation of collateral vessels can predict the speed at which ischemic damage may progress (Faizy et al. 2022). Software packages aid in swift analysis of these essential vascular imaging parameters (CT and MRI) to determine the ischemic core, salvageable tissue volume (penumbra), and extent of collaterals (Potreck et al. 2022).

In cases with unknown symptom onset, both CT perfusion and a combination of MRI sequences are valid approaches to determining the extent of salvageable brain tissue, and estimating the time from symptom onset (Silvennoinen et al. 2008; Thomalla et al. 2018). In selected cases, if sufficient viable tissue exists, and no hemorrhagic transformation has occurred, these imaging findings can allow one to proceed with recanalization therapies outside the traditional time windows of therapy (Nogueira et al. 2017).

Diagnosing acute vascular occlusion

When the occluded vessel in ischemic stroke is sufficiently large, it can be visualized with CT or MRI angiography (Dundamadappa et al. 2021; Greve et al. 2021), which demonstrates a lack of contrast enhancement in the occluded portion of the cerebral vasculature. This is highly important when deciding on the correct treatment: thrombolysis, mechanical thrombectomy, or both. Traditional angiography is performed during mechanical thrombectomy, and has excellent resolution, but is typically not part of admission imaging.

Diagnosing stroke mimics

Many, but not all stroke mimics show findings on admission imaging. These diagnoses obviously include all stroke mimics with large cerebral lesions, like neoplasms, abscesses, multiple sclerosis, epi- and subdural hemorrhage, and TBI. Seizures and migraines can show changes in perfusion imaging (Prodi et al. 2022).

2.3.4.4 Diagnostic clinical scores

Some diagnostic clinical scores recently developed aid in admission evaluation: in better identifying stroke mimics, in evaluating risk for hemorrhagic complications of thrombolysis, and in evaluating patient prognosis. These scoring systems combine information collected during admission evaluation to provide a rough estimate of the predicted diagnosis or prognosis in order to guide the receiving physician.

Proposed SM scores include the FABS score (N. Goyal et al. 2016), the telestroke mimic score (S. F. Ali et al. 2014), and the Khan score (Khan et al. 2018). Evidence on the performance of these scores and on their usefulness is still scarce, and little validation has occurred (S. F. Ali et al. 2018; Qin et al. 2017; Tu et al. 2020; Carlin et al. 2021).

Scores to evaluate the risk of hemorrhage after intravenous thrombolysis include the SEDAN score (Strbian, Engelter, et al. 2012), HAT score (Lou et al. 2008), GRASPS score (Menon et al. 2012), and THRIVE score, to name some of the most prominent (W. Chen et al. 2015). These scores have been reviewed in detail (Asuzu, Nyström, Amin, et al. 2015). In theory, these scores could serve in triage of at-risk patients directly to mechanical thrombectomy, and perhaps to exclude thrombolysis in cases with mild symptoms and very high complication risk. Data has emerged neither concerning the actual benefit of these scores for patient outcomes, nor showing how they should be applied in practice, although admittedly such a study would be difficult to organize due to the complexities of these decisions. Recently, these scores have also been proposed for predicting hemorrhage associated with endovascular therapy (Fu et al. 2021; Ben Hassen et al. 2020).

Finally, early outcome prediction scores include for example the Dragon score (Strbian, Meretoja, et al. 2012), TURN score (Asuzu, Nyström, Schindler, et al. 2015), iScore (Saposnik et al. 2011), and the ASTRAL score (Ntaios et al. 2012). These scores could allow communication of risks to patients and families, and perhaps help to guide some decisions on in-hospital treatment and follow-up, or aid in triage between hospitals (transferring high-risk patients to tertiary

centers). However, the risk of a self-fulfilling prophecy needs to be kept in mind (i.e. too early withdrawal of treatment in cases with very poor prognosis).

2.3.4.5 Emergency department organization

Careful organization of emergency department resources, simulation training, and stroke code protocols are necessary to ensure sufficient staff performance and long-term development of team performance in every hospital (Sattin et al. 2006; Lindsberg et al. 2006; Meretoja, Strbian, Mustanoja, et al. 2012). This organizational work includes marshaling sufficient resources, most importantly expert staff and diagnostic equipment, organizing training, ensuring speed and accuracy of the stroke code protocol, and close following of stroke research, to keep on track with developments, and to ensure sufficient quality control and in-house research, ideally through systematic registries and automated data collection (Powers et al. 2019). Importantly, though speed of the stroke code work-up is important, its possible detrimental effect on diagnostic accuracy and smart decision-making needs to be minimal.

A challenging part of this organizational work is the need to unite across hospital departments and with EMS to ensure high performance throughout all the steps of the acute treatment chain. This challenge requires communication skills, negotiation skills, and time (Rajendram et al. 2020; Langhorne et al. 2020). Community outreach is also an important factor improving stroke knowledge in the local population (Tan et al. 2021).

Although the literature on stroke-treatment-pathway management is huge, a few projects in this area are worth noting here. Development of the Helsinki model of stroke thrombolysis began in the latter part of the 1990s, soon after the European placebo-controlled ECASS I and II trials, and it built on the experience gained (Hacke et al. 1995). The first performance results of the model, started in routine management in 1998, appeared in 2003 (Lindsberg et al. 2003). The results compared well with those of the intention-to-treat (rtPA) groups of the ECASS trials as well as the National Institutes of Health-funded NINDS rtPA stroke trial (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995). The model and hospital infrastructure have been honed and tuned in multidisciplinary quality assurance cooperation ever since (Lindsberg et al. 2006), and Helsinki University Hospital is still well known for its highly optimized stroke service, which has also been validated to work elsewhere (Lindsberg et al. 2006; Meretoja, Strbian, Mustanoja, et al. 2012; Meretoja et al. 2013). The Get With The Guidelines project in the USA is the largest such organizational project, with a significant publication record (Schwamm et al. 2013; Xian et al. 2021). The European version of this

development work, the ESO EAST program, aims to improve emergency stroke treatment in Eastern Europe.

3 STUDY AIMS

I To investigate factors that impair identification of stroke during emergency calls.

II To investigate the diagnostic usefulness and dynamics of plasma GFAP and total tau as biomarkers for prehospital differentiation of acute cerebral ischemia and hemorrhagic stroke.

III To determine the diagnostic accuracy and potential pitfalls of emergency department evaluation of stroke code patients in a tertiary stroke center with highly optimized door-to-needle times.

IV To provide unique neuropathological evidence of cerebral amyloid angiopathy as a novel risk factor for symptomatic intracranial hemorrhage after stroke thrombolysis.

4 SUBJECTS AND METHODS

4.1 THE HELSINKI ULTRA-ACUTE STROKE BIOMARKER STUDY

This thesis was built upon the Helsinki Ultra-acute Stroke Biomarker Study, a prospective observational project aimed at improvement of the diagnostics of acute stroke through biomarker discovery and validation, and at detailed investigation into the diagnostics of the stroke treatment chain of our hospital district. The project's principal investigator is Professor Perttu Lindsberg, my supervisor, and I have acted as the organizing researcher.

The study protocol of the Helsinki Ultra-acute Stroke Biomarker Study was approved by our local institutional review board (397/13/03/01/2012) and registered as NCT02145663 (clinicaltrials.gov). Written informed consent came from each patient or the next of kin.

Planning, registration, and organization of the study began in 2012. Study recruitment began on May 20, 2013, and continued until November 19, 2015.

4.2 STUDY SETTING AND DESIGN

Our hospital district of Helsinki and Uusimaa (HUS) has a population base of an estimated 1.6 million inhabitants, spanning the ≈9,000-km^2 metropolitan area of Helsinki, Finland. As part of the universal government-funded health care system of Finland, the regional EMS of our hospital district operate under centralized management. Within the HUS district, acute recanalization therapies for acute stroke: thrombolysis and thrombectomy, have been centralized to the Helsinki University Hospital, which is the only 24/7 neurology service within the district, and receives all SC patients deemed to be candidates for these therapies.

Within our district, recognition of acute stroke by EMS is based on the Face Arm Speech Test (FAST), with leg weakness also tested. If needed, EMS also have the option for phone consultation with the on-call vascular neurologist or EMS physician. Prenotification of the arriving SC patient always comes from EMS before arrival. Currently, HUH receives over 1,400 SC patients annually.

An antecubital intravenous cannula is placed for all SC patients by EMS, with intravenous fluids typically initiated in the ambulance.

Based on prenotification, the on-call vascular neurologist has time to prepare and read the electronic EMS records and previous medical records of the arriving patient. After the SC patient arrives at the emergency department doors, they are transported directly on an ambulance gurney to the CT suite, where the SC team await. To achieve a fast door-to-treatment pace, the EMS report, collection of medical history, collection of point-of-care INR and blood samples, and NIHSS testing must occur in rapid succession. Promptly following this comes neuroimaging, primarily CT-based. A treatment decision is then the responsibility of the on-call vascular neurologist. In selected cases, if LVO verification has occurred in a primary hospital, the patient may go directly from the ambulance to the angiosuite for thrombectomy.

During our study's recruitment period, a total of 2,392 SC patients arrived at HUH. Our study inclusion criteria included: 1) primary SC transport to HUH, 2) age ≥18 years, 3) successful collection and processing of prehospital blood samples. Patients arriving from other EDs or hospital wards we excluded from the study.

Because not all EMS units performed blood sampling, our study cohort represents a convenience sample of SC patients. Of the total 1,079 patients who fulfilled the inclusion criteria, no written informed consent was available for 61, and EMS or hospital records were missing for 3, leaving the final Helsinki Ultra-acute Stroke Biomarker Study cohort of 1,015 patients.

In Study I, we investigated the accuracy and pitfalls of stroke recognition during calls to the national emergency number, 112. All of these calls are routed to governmental, regionally located Emergency Response Centers (ERC), where trained emergency dispatchers utilize FAST-based questions to identify stroke. For details of ERC call-processing, consult Study I. For this sub-study, we included only those 820 patients from our study cohort who had electronic EMS records available, because dispatch codes and caller details were not included in handwritten EMS notes.

Study II was a proof-of-concept study to explore the dynamics and diagnostic power of two plasma biomarkers, GFAP and total tau, in the acute phase of stroke. To explore the evolution of change in these biomarkers, our study focused on those patients with a final diagnosis of ACI or HS, with plasma samples from all relevant timepoints (prehospital, admission, following morning), and with an admission NIHSS of ≥3. Of these, we excluded a further 3 patients due to missing last-known-well times, leaving for analysis a final cohort of 272 patients.

In Study III, we investigated the accuracy of admission stroke diagnostics in the full Helsinki Ultra-acute Stroke Biomarker Study cohort comprising 1,015 patients.

In Study IV, we describe a fatal multifocal intracranial hemorrhage after stroke thrombolysis in a patient treated at our hospital, together with detailed neuropathological findings. We explore the etiology of hemorrhage and review the associated literature.

4.3 BLOOD SAMPLING, SAMPLE PROCESSING, AND BIOMARKER MEASUREMENT

All EMS personnel of our hospital district were trained to collect prehospital blood samples using a cannula-adapter technique utilizing the antecubital large-bore cannula routinely inserted in all SC patients in the prehospital setting in our district (Mattila et al. 2017). We collected samples immediately after cannula placement before infusion of fluids, utilizing a Vacutainer® Luer-Lok™ adaptor from BD, and Venosafe® vacuum tubes from Terumo. Admission samples and follow-up samples were collected by hospital laboratory staff by venipuncture into vacuum tubes. All samples were immediately centrifuged in the hospital laboratory at 2,000 g for 10 minutes at 20 °C, and then aliquoted into cryotubes for long-term storage at -80 °C.

For Study II, measurement of GFAP and total tau were performed at the University of Gothenburg by means of commercially available GFAP Discovery and Tau 2.0 kits on the Simoa® HD-1 Analyzer in accordance with kit inserts (Quanterix). Simoa is a highly sensitive measurement technique with reported lower limits of quantification of 0.061 pg/mL for total tau, and 0.686 pg/mL for GFAP. For further details of biomarker measurement, see Study II.

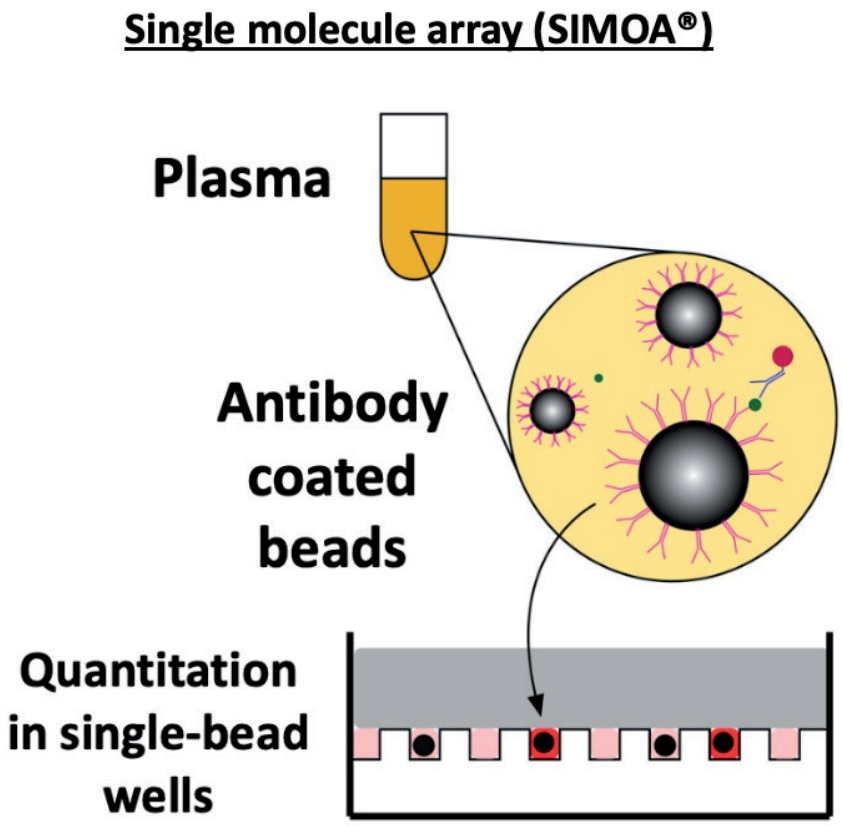

Figure 2. Single-molecule array (SIMOA) methodology is based on binding the target analyte on antibody-coated microscopic beads. After their later collection, these beads are distributed into single-bead wells, which are sealed, forming isolated reaction chambers in which a fluorescent signal reaction indicates the presence of analyte. This approach allows for a digital readout of the final signal, thus providing highly accurate results despite very low analyte concentrations.

4.4 DATA COLLECTION AND EMERGENCY CALL ANALYSIS

Input into the study database came by means of retrospective chart review of electronic health records after conclusion of all follow-up investigations. A data collection form ensured consistency of chart review. For emergency call analysis in Study I, the 46 selected EMS calls underwent analysis by two researchers experienced in stroke research (O.S.M, T.P.), with classifications decided by consensus, with use of a data-collection form to ensure consistency.

4.5 STATISTICAL METHODS

Continuous variables are summarized as medians and interquartile range, and categorical variables as absolute counts and percentages. Continuous variables we tested for normality and equality of variances where appropriate. In all studies, two-sided p-values ≤0.05 were considered significant, and SPSS software (IBM) was used.

For Study I, we performed univariate comparisons with student's t-test or the Mann-Whitney *U*-test for continuous variables, and the Pearson X^2-test or Fishers' exact test for discrete variables where appropriate. A binary backward stepwise logistic regression model served for multivariate analysis, including all confounders with p<0.10 in univariate analysis. Retention of covariates in the model we decided with the likelihood-ratio statistic using a limit of p≤0.05, and no collinearity emerged between variables.

For Study II, we performed univariate analyses with the Mann-Whitney *U*-test for continuous variables. The nonparametric Spearman rank test measured correlation. Area under the receiver operating characteristic curve (AUC-ROC) analysis served to explore diagnostic performance of these biomarkers. Diagnostic measures came from cross-tabulations, and cut-off values were based on AUC-ROC analysis and plotting.

For Study III, we performed univariate comparisons with the Mann-Whitney *U*-test for continuous variables, and the Pearson X^2-test or Fishers' exact test for discrete variables where appropriate. For multivariate analysis, a binary backward stepwise logistic regression model was used, including all variables with significant p-values in univariate analysis. Again, retention of covariates in the model we decided with the likelihood-ratio statistic, using a limit of p≤0.05.

For Study IV no advanced statistical methods were necessary.

For methodological details not covered in this section refer to the studies at the end of this thesis.

5 RESULTS

5.1 TARGETS FOR IMPROVING STROKE DETECTION DURING EMERGENCY PHONE CALLS (I)

The study cohort included 820 patients transported as SC patients to our hospital with a high-priority stroke-transport code. Of these, 625 had acute stroke, for which the sensitivity of dispatcher identification was 72.0% (95% CI, 68.5-75.5), with the remaining 175 acute stroke patients (28.0%) receiving a transport code other than a high-priority stroke dispatch code. Of these misdiagnosed patients, the incorrect dispatch code had a lower priority for 54.9%, which was reflected in the length of time experienced by each from dispatch to ambulance arrival (median 7 min [IQR, 6–9] vs. 10 min [7–14] for incorrect dispatch codes, $p < 0.001$). Delays to ambulance arrival were longest in the less-urgent dispatches: C-priority (46.9%, 12 min [9-15]) and D-priority (8.0%, 21 min [11-28]).

Multivariate analysis to identify factors associated with an incorrect dispatch code revealed the following: independent predictors of dispatcher-missed acute stroke were bystander as the caller, patient confusion, fall at onset, and older age. In particular, confusion or a fall at onset or both occurred in 49.1% of cases with dispatcher-missed acute stroke, and were associated in univariate analysis with higher NIHSS scores upon hospital arrival.

We performed a detailed analysis of emergency phone calls with missed stroke identification and with descriptive dispatch codes indicating a fall or unknown acute illness, as a potential target for improvement. We found that a significant proportion (47.8%) of these calls were affected by distracting factors, which are listed in detail in that Study. Generally, most calls had a calm caller and dispatcher, with good to moderate ability to relay information. We found that 71.7% of the phone calls showed targets for improvement, which included either failure to recognize a FAST symptom that arose during the call, or failure to thoroughly evaluate the patient's symptoms (when compared to EMS records). The most common symptom missed or misdiagnosed was speech disturbance, accounting for 85.7% of the cases with missed FAST symptoms.

5.2 PREHOSPITAL USE OF PLASMA GFAP TO RULE OUT HEMORRHAGIC STROKE (II)

In Study III, we first explored the early dynamics of both plasma GFAP and total tau in ACI and HS. At group level, HS patients had significantly higher plasma GFAP concentrations than did ACI patients, a difference seen at all sampling timepoints ($p<0.001$). In comparison, no intergroup difference appeared in plasma total tau concentrations.

Based on our findings, we proceeded to explore the diagnostic value of early plasma GFAP levels in more detail. Thanks to our sequential blood sampling, we were able to determine the early release rate of GFAP for each patient, expressed in pg/mL/min. Importantly, we found this novel parameter to be significantly elevated in HS compared to levels in ACI patients (2.4 [0.6–14.1] versus 0.3 [-0.3 to 0.9] pg/mL/minute, $P < 0.001$, n=263).

AUC estimates for the differentiation of ACI and HS in patients with <3-hour prehospital samples were 0.781 (95% CI 0.712-0.850) for initial prehospital GFAP, 0.850 (95% CI 0.795–0.905) for secondary acute samples, and 0.740 (95% CI 0.651–0.829) for prehospital GFAP release rate. Although the AUCs of initial prehospital GFAP and GFAP release rate were similar, further analysis revealed these parameters to have independent value for differential diagnosis, and that combining these parameters further improved diagnostic accuracy.

Based on the concept of combining initial prehospital GFAP and GFAP release rate, we formed a diagnostic rule using both parameters. In the subgroup of patients with <3-hour prehospital sampling, patients with HS typically had a high initial prehospital GFAP concentration >410 pg/mL, or had a more moderate prehospital GFAP concentration of 90-140 pg/mL together with active release of GFAP, showing a GFAP release rate >0.6 pg/mL/min. These cutoff values detected HS with high sensitivity (96.6%), and provided a very high negative predictive value of 98.4% for ruling out HS in two-thirds of patients with ACI (specificity 68%, PPV 50%).

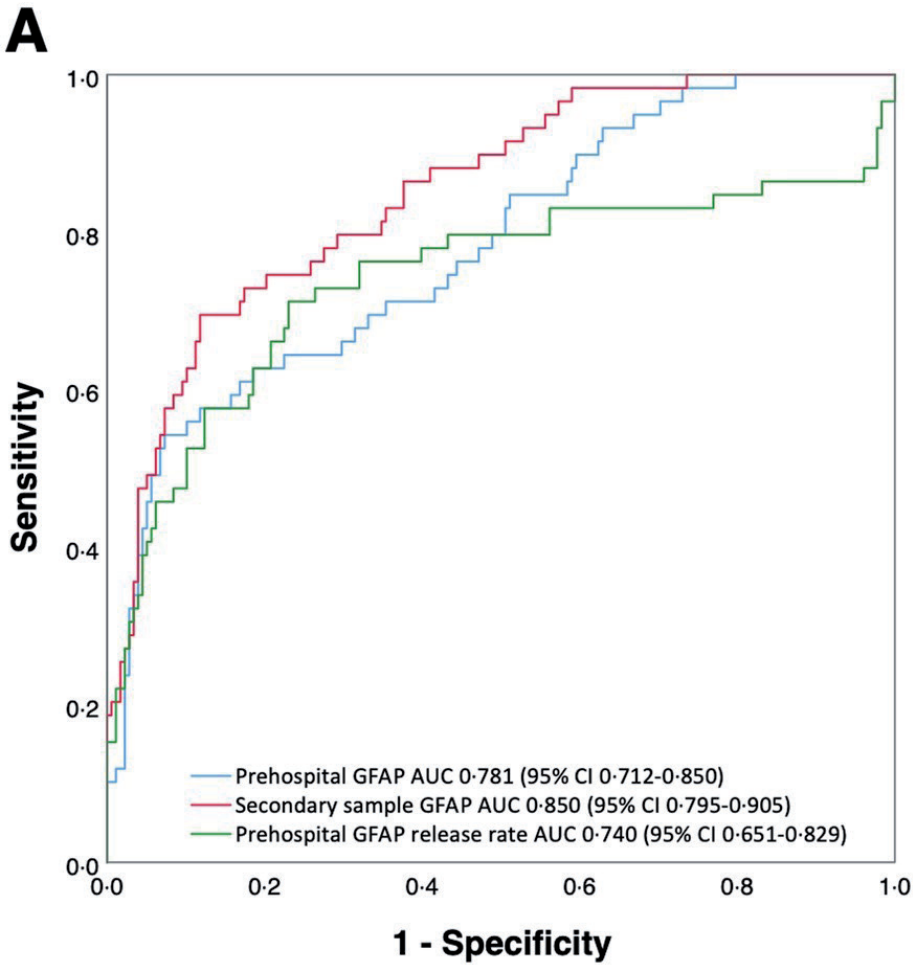

Figure 3. Receiver operating characteristic curves showing the diagnostic accuracy of GFAP in differentiating ACI from HS. Reproduced in accordance with the Creative Commons license from Mattila et al. Ultra-Early Differential Diagnosis of Acute Cerebral Ischemia and Hemorrhagic Stroke by Measuring the Prehospital Release Rate of GFAP. Clinical Chemistry. 2021 Oct;67(10):1361-1372.

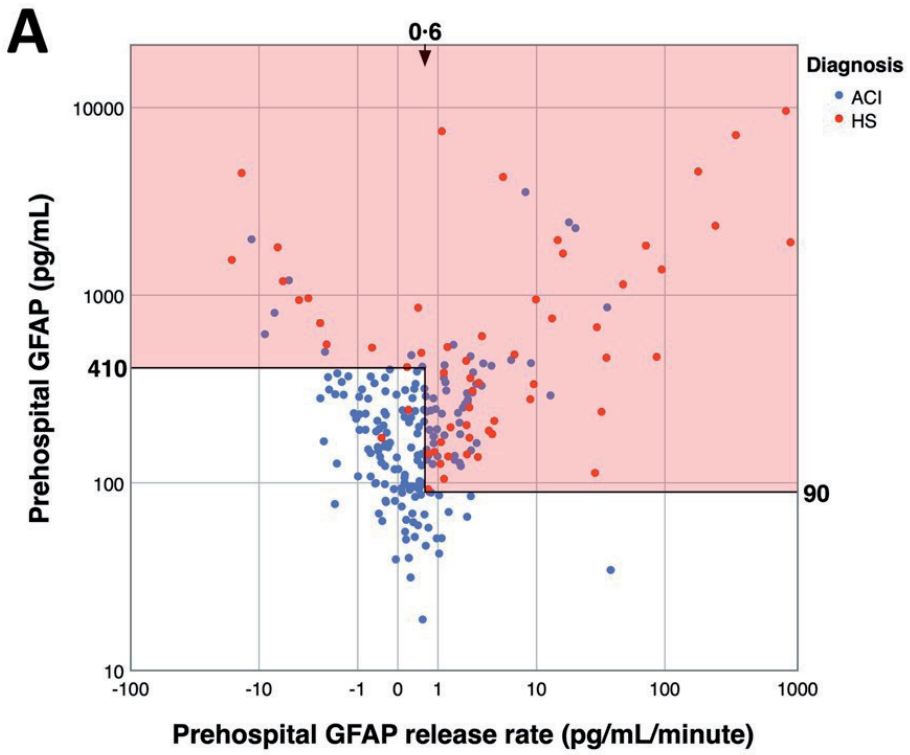

Figure 4. Plots demonstrating differentiation of ACI and HS by utilizing both initial prehospital GFAP concentrations (y axis, pg/mL) and prehospital GFAP release rate (x axis, pg/mL/min), with test-positivity in the area highlighted in red. (A), Patients had prehospital samples collected within 3 hours (ACI n=178, HS n=59). Reproduced in accordance with the Creative Commons license from Mattila et al. Ultra-Early Differential Diagnosis of Acute Cerebral Ischemia and Hemorrhagic Stroke by Measuring the Prehospital Release Rate of GFAP. Clinical Chemistry. 2021 Oct;67(10):1361-1372.

5.3 PITFALLS IN THE ADMISSION EVALUATION OF STROKE CODE PATIENTS (III)

Our cohort included a total of 1015 SC patients, of whom 663 (65.3%) had ACI, 118 (11.6%) HS, and 234 (23.1%) SM. The median DNT for all 331 thrombolysis patients was markedly brief: 19 (16-28) minutes. In the whole cohort, admission-imaging was CT-based in 989 cases (97.4%), with 646 (64.2%) having no acute imaging findings.

The initial working diagnosis on admission was correct in 865 patients (85.2%). In the remaining misdiagnosed cases, the admission diagnosis was incorrect in 41 (27.3%), unclear in 85 (56.7%), and unreported in 24 cases (16.0%).

Most misdiagnosed patients had very mild symptoms, in 100 cases with a NIHSS of 0 to 2 (67.6%). Univariate analysis showed misdiagnosis to be associated with a lack of admission imaging findings and with mild symptoms. In multivariate analysis, older age, unknown time of onset, higher NIHSS scores, and acute findings on initial imaging were independently associated with lower odds, and diabetes and previous TIA associated with higher odds for misdiagnosis.

In the misdiagnosed patient group, the final diagnosis was ACI in 59 (39.3%), ICH in 1 (0.7%), and SM in 90 cases (60.0%). Misdiagnosis affected medical management in 70 misdiagnosed cases (46.7%). Effects, detailed in the Study, included delay to imaging, delay to correct treatment, missed thrombolysis of ACI, accidental thrombolysis of SM, unnecessary patient transfers, inadequate monitoring, longer ED stay, and unnecessary treatments.

In a detailed investigation into the possible effect of misdiagnosis on outcomes, we identified only 8 cases (0.8%) in which misdiagnosis may have worsened outcomes. However, only 2 cases were found where misdiagnosis may have contributed to an unfavorable outcome (3-month mRS >2). We identified no cases in which misdiagnosis would have led to mortality.

5.4 CAA AS A RISK FACTOR FOR POST-THROMBOLYTIC HEMORRHAGE (IV)

In Study IV, we describe a stroke code patient with mild symptoms of 3 NIHSS points on hospital arrival, and with no evident acute findings on admission CT. This patient was promptly treated with stroke thrombolysis, but quickly developed a severe bleeding complication with multifocal lobar and subarachnoid intracranial bleeding, and died 6 days after admission.

Upon neuropathological evaluation, this patient showed underlying extensive CAA in the cortical regions, including sites of hemorrhage, demonstrating the main etiology of the hemorrhagic complications.

Our review of neuropathological evidence in the literature that has shown CAA as a risk factor for post-thrombolytic hemorrhage produced only one case report describing this phenomenon in stroke thrombolysis. Several other instances have been described in cases with concurrent anticoagulation and thrombolysis of myocardial infarction.

6 DISCUSSION

6.1.1 IMPROVING DISPATCHER STROKE IDENTIFICATION (I)

Despite its importance as the first step in the stroke-treatment chain, stroke identification by emergency dispatchers is a field providing limited scientific studies and scant evidence supporting its commonly used practices. Applying stroke recognition scales like the FAST over the phone is the typical approach, and while ample evidence of these scores exists for face-to-face evaluation in the ambulance setting, their exact performance in various situations by phone without visual support is significantly less studied. One systematic review of dispatcher screening tools found positive predictive values (PPV) of 42% to 68%, and sensitivities of 41% to 83%, which represents low accuracy (Oostema et al. 2016). The findings of our study improve upon this literature with a large sample size and multivariate analysis.

During the period of our study, our emergency dispatchers operated with a model in which dispatchers have specific guidelines for the recognition of each dispatch group, such as high-priority stroke, but are left with full autonomy to decide the structure of the call and to choose any preferred wording to ask the patient for symptoms. This contrasts with the automated dispatch systems used in many districts around the world, where a dispatcher strictly follows a computer-based algorithm, reading out the questions provided by the program. These differences need to be considered when applying the results of our study.

Before ours, two studies had identified, in univariate analysis, a fall at onset as a risk factor resulting in missed stroke identification (Chenaitia et al. 2013; Berglund et al. 2015). Our study further shows that this central risk factor remains statistically significant in multivariate analysis, demonstrating its importance as a keyword in stroke dispatch work.

One of the main findings in our analysis of call recordings of missed stroke identification was that screening for FAST symptoms was missed, or was performed only incompletely. Stricter rules for screening for stroke symptoms are therefore essential for all calls that include risk factors such as a fall, confusion, or altered mental status. This type of screening protocol has already been suggested (Krebes et al. 2012), and is supported by our findings. However, this will require significant additional dispatcher work, because such complaints are common reasons for emergency calls.

6.1.2 POINT-OF-CARE BIOMARKERS TO SUPPORT PREHOSPITAL STROKE THERAPY (II)

Neuroimaging with CT or MRI upon hospital admission, together with skilled clinical evaluation, are the cornerstones of acute stroke diagnostics. Whereas stroke biomarkers have been researched for decades, this field has provided no biomarkers that are currently clinically useful. This, together with the ever-improving capabilities of rapid neuroimaging, have left stroke neurologists skeptical and unimpressed with the biomarker research field.

Because blood-based biomarkers cannot provide localizing information for cerebral injury, they are unlikely to provide additional diagnostic benefit for the current imaging-based diagnostics of ACI and HS on hospital admission. The story may be different in the prehospital setting, where EMS is currently unable to differentiate among stroke subtypes or to initiate therapies, and the number of ambulances is high. Specialized MSU ambulances equipped with CT-based imaging have been introduced in several metropolitan areas around the world, and have been shown to be both fast and effective in prehospital stroke diagnostics, and to improve outcomes (Grotta et al. 2021; Ebinger et al. 2021). This supports their wider application in the near future. However, their cost-effectiveness is still unclear in less inhabited areas. Most countries, like Finland, thus have not allocated the necessary funding to introduce such units. Other methods for more cost-effective diagnostics will still be needed to improve prehospital stroke diagnostics in most parts of the world.

Before our study, GFAP had been shown to have diagnostic value for the differentiation of ACI and HS in single-timepoint studies performed upon hospital admission (Foerch et al. 2009; Foerch et al. 2012; Luger et al. 2017; Perry et al. 2018). As to its usefulness in the prehospital setting, only one small GFAP study had investigated this, and due to its low-sensitivity GFAP assay, provided discouraging evidence of usefulness (Rozanski et al. 2017).

We demonstrate here, to our knowledge for the first time, that when a sufficiently sensitive assay is in place, serial GFAP measurement can be successful for early and accurate stroke diagnostics, just as serial measurement of cardiac troponins has been successful in the diagnosis of acute myocardial infarction. Our findings emerge alongside other promising findings combining diagnostic biomarkers such as RBP4 and nt-proBNP to provide a multimarker approach for improved biomarker diagnostics of stroke (Bustamante et al. 2021).

6.1.3 THE STROKE NEUROLOGIST AS A CENTRAL DIAGNOSTIC ASSET (III)

Our large study on the accuracy of admission stroke diagnostics relates to several ongoing research questions in the field. First and foremost, our hospital district has a highly optimized treatment chain, with admission evaluation streamlined based on the Helsinki model of stroke thrombolysis, with door-to-needle times (DNT) of below 20 minutes. While these types of rapid protocols to optimize DNTs have been developed and adopted worldwide, they have come with questions as to the safety and diagnostic accuracy of this approach. Our results show that diagnostic accuracy and safety are not compromised, but this requires highly trained physicians and in-hospital organization, including internal treatment guidelines to ensure consistency between cases.

Another significant question related to stroke thrombolysis is which specialties should participate in administering thrombolysis, and to what extent it necessitates the expertise of neurologists. This includes systems like ours, in which neurology oversees the whole process, systems in which neurology supports emergency medicine physicians over telecommunication, and systems in which other specialties like emergency medicine have fully taken control of initial stroke treatment. Our findings highlight the extreme complexity of SM diagnoses, and the difficulty of admission diagnostics even when they are performed by neurologists with the widest possible knowledge of the differential diagnostics of acute neurology. Importantly, decisions rely mainly on clinical judgement, because most patients lack any imaging findings. Thus, our results support a central role for the on-call vascular neurologist as the expert with the best knowledge to succeed in this difficult task.

Thirdly, while CT-based imaging has been the long-term and most widely adopted approach for admission stroke diagnostics, the increasing availability of MRI has raised the question of when this significantly more accurate, but slower and more expensive imaging modality should be used. Our results suggest that MRI imaging may prove most useful in cases with risk factors for misdiagnosis, including mild symptoms and young age. Clinical scores evaluating misdiagnosis risk may perhaps also aid in this selection.

6.1.4 IMPROVING THE SAFETY OF STROKE THROMBOLYSIS (IV)

At the time of publication of our Study IV, only one case report existed with neuropathological evidence of CAA-related hemorrhage after stroke thrombolysis, which our findings further supported (Felling et al. 2014). Since then, research into the usefulness of MRI-identified cortical cerebral microbleeds (CMB) in evaluating risk for post-thrombolytic hemorrhage progresses. Several studies indicate that a significant burden of >10 CMBs on

MRI seems to correlate with increased risk for post-thrombolytic hemorrhage (Tsivgoulis et al. 2016; Zand et al. 2017; Charidimou et al. 2017). These studies have, however, generally not considered the location of the CMBs. Whereas deep CMBs are associated with classic hypertension-related vascular degeneration, CMBs in cortical brain areas are associated with CAA. Further investigation should evaluate the specific post-thrombolytic hemorrhage risk that is related to CAA-type CMBs.

CAA is highly prevalent, with an estimated prevalence of about 30% in 70- to 79-year-olds, and 40% to 60% in those 80 to 97 years old, all based upon autopsy studies (McCarron & Nicoll 2004). The main challenge relates to the rapid diagnosis of CAA, because most stroke services still rely on CT-based imaging, which cannot be used to identify CAA; and no known blood biomarkers of CAA currently exist. Noting any presence of CAA-type cortical findings (CMBs, hemosiderosis) visible on old MRI scans would be a wise first step, although it may be impractical, and many patients have not already undergone MRI scans.

Interestingly, patients with advanced CAA have shown transient focal neurological episodes (Charidimou et al. 2012), episodes often associated with small hemorrhage in a cortical sulcus, and obviously requiring no thrombolysis as their treatment. As CAA diagnostics and resolution of neuroimaging improve, it is likely that more of these episodes will be identifiable in SC patients, and will thus improve thrombolysis safety.

6.2 STUDY LIMITATIONS

First and foremost, the Helsinki Ultra-acute Stroke Biomarker Study cohort has a few limitations. It represents a convenience sample rather than a consecutive series of SC patients. Although we provided sample-collection training for all EMS personnel in our district, and made efforts to equip all EMS units with sampling bags, events of missed sampling were fairly common. This issue was affected significantly by the considerable number of EMS staff (>800 personnel in the district), our reliance on the voluntary participation of this EMS staff, and the fact that high-priority SC patients are only a minor portion of all transported cases, making it difficult to remember the details of the sampling. Other causes for missed sampling we have discussed in detail earlier (Mattila et al. 2017). Despite having convenience sampling, our study is protected against sampling bias by the fact that EMS personnel were not aware of the final diagnosis of the patients, the main parameter that we studied. Further, we challenge other research groups to achieve a higher percentage of recruitment at a scale of this size.

A second limitation includes the setting of our study: in a Nordic country with a universal health care system, a hospital district with triage of SC patients into a single tertiary hospital with on-call vascular neurologists, and EMS and emergency-call dispatchers working under a highly centralized structure and management. These factors may limit the applicability of our findings to other hospital districts and countries. However, for the purpose of these studies, these factors also provide consistency, with every SC patient being processed according to the same protocols throughout the treatment chain, from the emergency call until hospital arrival.

A limitation of our study of dispatcher stroke identification (I) is the fact that we analyzed a sample of stroke patients who had ultimately been transported as high-priority SC patients. This approach misses the small but significant proportion of stroke patients that are missed by dispatchers and transported by EMS to inappropriate hospitals or are not transported at all. Identifying this group of patients would require a different study design, one aiming to investigate dispatcher accuracy in a cohort of patients with stroke as a final discharge or as a post-mortem diagnosis, with cases identified based on national or district-wide records across different hospitals.

In our proof-of-concept study on early GFAP diagnostics (II), our cohort included mainly ACI and HS patients, with only a very small subset of nine SM patients. Thus, further study into the performance of GFAP in full cohorts of SC patients including all SM patients will still be necessary. Similarly, our patient selection criteria included clear stroke symptoms (admission NIHSS ≥ 3), a selection rule that cannot be applied by EMS. This calls for a more practical patients selection method in future studies. No validated universal calibrator for GFAP currently exists, which means that absolute GFAP values in our study cannot be compared to values in studies using different measurement techniques. Additionally, at the time of our study, we were aware of no other cohorts that would have been available for the replication and validation of our findings.

Our study on admission diagnostics (III) was limited by the fact that final diagnoses were determined based on all examinations available at follow-up, these did not include admission and follow-up MRI for all patients. However, such an MRI-based study setting, although theoretically ideal, would not be practically and financially possible in a study of this size in our country.

Finally, the obvious limitation of our case study (IV) is that it represents only one patient, and not a study cohort. Nevertheless, we provide highly valuable and unique neuropathological evidence of a rare complication, one for which data proves difficult to obtain, as rates of autopsy are low in modern medicine.

6.3 IMPLICATIONS FOR PRACTICE AND FUTURE RESEARCH

The findings of this thesis include numerous direct implications for clinical practice and highlight new avenues for further research.

Our analysis of emergency calls (Study I) revealed several specific situations, especially ones involving patients with a fall at onset, patients with confusion, or ones with a speech disturbance, as high-risk situations for missing a stroke diagnosis. Thus, the diligent screening for stroke in these calls is a direct target for improvement both in dispatch centers with autonomous dispatchers, and for systems using prespecified dispatch question algorithms. Our findings suggest that, in stroke identification, further tools to investigate the causes of confusion and of speech disturbances during emergency calls and improved evaluation of FAST symptoms may prove valuable.

One of the most promising approaches—in selected emergency calls—could be video-based calls, and utilization of more-detailed aphasia and dysarthria testing, like that included in the NIHSS score. Modern sensor technology could also be utilized, like smart watches with pulse oximetry, ECG, and motion-sensor capabilities, and mobile applications that could compare findings of the FAST to earlier images and videos of the patient's face, or recordings of the patient's voice, or older motion-sensor data during limb testing.

Our investigation into the early dynamics of plasma GFAP (Study II) reveals, for the first time, that measurement of early GFAP release rate provides superior diagnostic performance when compared to that of single-timepoint measurement. And when measurement sensitivity was sufficient, GFAP alone had the capability to identify two-thirds of ACI patients in the prehospital time-phase with high accuracy. Although biomarkers are still far from prehospital use, our results indicate that further development, testing, and validation of new point-of-care GFAP measurement instruments is crucial. Luckily, one such measurement cartridge has just been released for the iSTAT point-of-care system (Abbott), and presents a perfect starting point for further research. In-laboratory and prehospital testing of these biomarker devices will proceed hand in hand with investigation into other promising biomarker candidates; most biomarker researchers are in agreement that the complex differential diagnosis of SC patients will eventually demand support from a biomarker panel. Combining biomarkers with diagnostic scores and rapid diagnostic sensors is an even stronger option.

Rapidly identifying patients with an actively expanding cerebral hemorrhage would be highly beneficial for future investigation of therapies to limit hemorrhage expansion, such as prehospital administration of hemostatic factors. From a pathophysiological standpoint, a high GFAP release rate indicates continuously increasing biomarker release, and thus might correlate

with the speed of hematoma growth. This theory could be tested in MSUs, which would allow for two early serial noncontrast CT images (prehospital and admission), revealing any correlation of the speed of hematoma growth with GFAP release rate.

Our evaluation of the diagnostic accuracy of our ED stroke treatment pathway (Study III) demonstrates that highly optimized DNTs are safe, and they do not compromise diagnostic accuracy when sufficient expertise can be assumed. This further supports and argues for the implementation of optimized DNTs in hospitals worldwide, and further validates the Helsinki model of thrombolysis.

Our study clearly specifies risk factors for misdiagnosis, which should be incorporated into physician training. Such risk-factors, especially mild symptoms and an absence of CT-based imaging findings, are a clear target for further research. Possible new diagnostic methods may include additional MRIs, biomarkers, training on cognitive biases, improved diagnosis identification, and inter-physician communication when cases feature unsure working diagnoses; we need also clinical scores to specifically identify stroke mimics.

Our report on the neuropathological findings of CAA-related intracranial hemorrhage after stroke thrombolysis adds to the actively expanding literature on preexisting vasculopathy as a risk factor for thrombolytic complications. CAA is often difficult to diagnose, with cortical CMBs in MRI being a typical surrogate marker. We thus encourage further research on how to better identify CAA in SC patients, and how to evaluate the extent of associated risk for thrombolysis.

As a final general notion, diagnostic medical operations like dispatch work, EMS evaluation, and admission evaluation largely operate in a vacuum of feedback, where it is rare to receive later information on the success of the diagnostic work, making it difficult for these services to undergo improvement. A great need is for infrastructure that automatically computes the final success of these efforts by comparing assigned dispatch codes, transport codes, and admission diagnoses to final discharge diagnoses. These types of systems would offer a continuous capability to notice, catalogue, and improve upon mistakes in the diagnostics of these services.

7 CONCLUSIONS

In conclusion, the Helsinki Ultra-acute Stroke Biomarker study and this thesis provide investigation into the current diagnostic performance of the stroke treatment chain within our hospital district. Our findings highlight several important points for operational improvement, but also provide new proof-of-concept findings.

Our analysis into emergency calls of stroke patients (I) revealed patient confusion, fall at onset, and speech disturbances as important factors for potential misdiagnosis. Emergency-call processing is a highly challenging task that is still performed with old technology: audio-only phone calls. The practices of dispatcher stroke recognition are backed by an unfortunately weak literature and evidence base, with few systematic or trial-based comparative studies. As personal health technology and smart phones develop, we have high hopes that this important starting point of the stroke treatment chain will continue to improve and to attract more research interest. Together with its centralized emergency call processing and its strong health technology sector, Finland would be a valuable location for this type of research.

We provide proof-of-concept evidence (Study II) to show that GFAP should be used in early stroke detection just as troponins are used in the diagnosis of acute myocardial infarction: by following the early rate of change. This new approach provided initial evidence to suggest that GFAP may prove a highly valuable instrument for future prehospital stroke diagnostics, assuming sufficiently rapid measurement and later validation. Although stroke biomarker research has long been a discouraging area of research, our findings may spark new interest and promise in this field.

Our hospital district has achieved some of the fastest door-to-needle times for stroke thrombolysis, and the Helsinki model of stroke treatment organization is well known. However, short DNTs have come with criticism, questioning whether rapid admission evaluation sacrifices diagnostic accuracy.

The findings of our study on admission diagnostics (Study III) demonstrate that when sufficient in-house training and expertise are in place, short DNTs do not compromise diagnostic accuracy, which for us was high. There still exists room for improvement, particularly in the diagnostics of specific SM types, and for patients with very mild symptoms. MRI as additional imaging in selected patients directly after the admission evaluation is a promising future approach, but will need further investigation to demonstrate cost-effectiveness. On a larger scale, our findings highlight the extreme complexity of differential diagnostics of SC patients, and the wide knowledge of emergency neurology

required. This supports, for this patient group, the continued importance of the highly trained vascular neurologist as the main admission evaluator.

Our case study on CAA-related hemorrhage (Study IV) provides valuable neuropathological evidence of the importance and implications of this common vasculopathy for the safety of stroke thrombolysis, and contributes to this so-active area of research into prediction and prevention of hemorrhagic complications of thrombolysis. Any earlier MRI findings available for SC patients could be better utilized to illuminate the bleeding risk associated with CAA findings and other forms of small-vessel vascular degeneration. However, new approaches for classifying imaging findings and stratifying risk are still essential.

In summary, this thesis contributes to the highly active field of acute stroke diagnostics. Through the deployment of MSUs, this important research area has already demonstrated that early stroke therapy—already in the prehospital setting–is possible and highly beneficial. The ongoing development of dispatcher accuracy, prehospital imaging, sensors, biomarkers, telecommunication, and clinical scores promises to further improve prehospital stroke diagnostics worldwide. Ultimately, accurate prehospital diagnosis of stroke will allow for new therapeutic interventions to target the earliest phases of ischemic and hemorrhagic brain injury that have so far been out of reach.

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REFERENCES

Abbas, A.Y., Odom, E.C. & Nwaise, I., 2021. Association between dispatch complaint and critical prehospital time intervals in suspected stroke 911 activations in the National Emergency Medical Services Information System, 2012-2016. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 31(3), p.106228.

Advani, R., Næss, H. & Kurz, M., 2016. Mass Media Intervention in Western Norway Aimed at Improving Public Recognition of Stroke, Emergency Response, and Acute Treatment. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 25(6), pp.1467–1472.

Ahn, S.-H. et al., 2018. Patterns and Outcomes of the Top of the Basilar Artery Syndrome: The Role of the Posterior Communicating Artery. Cerebrovascular Diseases, 46(3-4), pp.108–117.

Aho, K. & Fogelholm, R., 1974. Incidence and early prognosis of stroke in Espoo-Kauniainen area, Finland, in 1972. Stroke; a journal of cerebral circulation, 5(5), pp.258–261.

Akimoto, T. et al., 2014. Spontaneous spinal epidural hematoma as a potentially important stroke mimic. Journal of central nervous system disease, 6, pp.15–20.

Alexandrov, A.W. et al., 2021. High-resolution CT with arch/neck/head CT angiography on a mobile stroke unit. Journal of neurointerventional surgery.

Alhanati, L. et al., 2014. Stroke: prospective evaluation of a prehospital management process based on rescuers under medical direction. The American journal of emergency medicine, 32(5), pp.438–442.

Ali, M. et al., 2021. Early Minimally Invasive Endoscopic Intracerebral Hemorrhage Evacuation. World neurosurgery, 148, p.115.

Ali, S.F. et al., 2014. The TeleStroke mimic (TM)-score: a prediction rule for identifying stroke mimics evaluated in a Telestroke Network. Journal of the American Heart Association, 3(3), pp.e000838–e000838.

Ali, S.F. et al., 2018. Validating the TeleStroke Mimic Score: A Prediction Rule for Identifying Stroke Mimics Evaluated Over Telestroke Networks. Stroke; a journal of cerebral circulation, 49(3), pp.688–692.

Alonso, J.V. et al., 2015. Limb-Shaking TIA Presenting as Hemichorea-Hemiballismus: TIA Chameleons Diagnostic Challenge in the Emergency Department. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 24(11), pp.e327–31.

Amarenco, P., 2020. Transient Ischemic Attack. The New England journal of medicine, 382(20), pp.1933–1941.

Anderson, C.S. et al., 2013. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. The New England journal of medicine, 368(25), pp.2355–2365.

Asimos, A.W. et al., 2014. Out-of-Hospital Stroke Screen Accuracy in a State With an Emergency Medical Services Protocol for Routing Patients to Acute Stroke Centers. Annals of emergency medicine, 64(5), pp.509–515.

Asuzu, D., Nyström, K., Amin, H., et al., 2015. Comparison of 8 scores for predicting symptomatic intracerebral hemorrhage after IV thrombolysis. Neurocritical care, 22(2), pp.229–233.

Asuzu, D., Nyström, K., Schindler, J., et al., 2015. TURN Score Predicts 90-day Outcome in Acute Ischemic Stroke Patients After IV Thrombolysis. Neurocritical care, 23(2), pp.172–178.

Avan, A. et al., 2019. Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden: an ecological analysis from the Global Burden of Disease Study 2017. BMC medicine, 17(1), pp.191–30.

Bagga, V. & Simons, M.-A., 2011. Cerebral abscesses--a stroke mimic. Age and ageing, 40(5), p.645.

Baharoglu, M.I. et al., 2016. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet, 387(10038), pp.2605–2613.

Bai, J. & Lyden, P.D., 2015. Revisiting cerebral postischemic reperfusion injury: new insights in understanding reperfusion failure, hemorrhage, and edema. International journal of stroke, 10(2), pp.143–152.

Bandera, E. et al., 2006. Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review. Stroke; a journal of cerebral circulation, 37(5), pp.1334–1339.

Barber, P.A. et al., 2000. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. The Lancet, 355(9216), pp.1670–1674.

Bartolini, E., Napolitano, A. & Mazzoni, M., 2018. Limb Shaking Transient Ischemic Attacks with Normal Neurovascular Ultrasound may Herald Cardioembolic Stroke: A Case Report. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 27(10), pp.e228–e229.

Beghi, E. et al., 1989. Hemorrhagic infarction: risk factors, clinical and tomographic features, and outcome. A case-control study. Acta neurologica Scandinavica, 80(3), pp.226–231.

Ben Hassen, W. et al., 2020. MT-DRAGON score for outcome prediction in acute ischemic stroke treated by mechanical thrombectomy within 8 hours. Journal of neurointerventional surgery, 12(3), pp.246–251.

Berekashvili, K. et al., 2020. Emergency Medicine Physicians Accurately Select Acute Stroke Patients for Tissue-Type Plasminogen Activator Treatment Using a Checklist. Stroke; a journal of cerebral circulation, 51(2), pp.663–665.

Berglund, A. et al., 2015. Identification of stroke during the emergency call: a descriptive study of callers' presentation of stroke. BMJ open, 5(4), p.e007661.

Bergrath, S. et al., 2012. Feasibility of prehospital teleconsultation in acute stroke--a pilot study in clinical routine. PLoS ONE, 7(5), p.e36796.

Béjot, Y. et al., 2014. Trends in the incidence of ischaemic stroke in young adults between 1985 and 2011: the Dijon Stroke Registry. Journal of neurology, neurosurgery, and psychiatry, 85(5), pp.509–513.

Bill, O. et al., 2017. Added value of multimodal computed tomography imaging: analysis of 1994 acute ischaemic strokes. European journal of neurology : the official journal of the European Federation of Neurological Societies, 24(1), pp.167–174.

Bitsch, A. et al., 2002. Serum tau protein level as a marker of axonal damage in acute ischemic stroke. European neurology, 47(1), pp.45–51.

Blaauw, J., Hertog, den, H.M., et al., 2022. Transient neurological deficit in patients with chronic subdural hematoma: a retrospective cohort analysis. Journal of neurology, pp.1–9.

Blaauw, J., Meelis, G.A., et al., 2022. Presenting symptoms and functional outcome of chronic subdural hematoma patients. Acta neurologica Scandinavica, 145(1), pp.38–46.

Bogousslavsky, J., 1994. Frontal stroke syndromes. European neurology, 34(6), pp.306–315.

Boltze, J. et al., 2019. Lesional and perilesional tissue characterization by automated image processing in a novel gyrencephalic animal model of peracute intracerebral hemorrhage. Journal of Cerebral Blood Flow & Metabolism, 39(12), pp.2521–2535.

Bray, J.E. et al., 2010. Paramedic diagnosis of stroke: examining long-term use of the Melbourne Ambulance Stroke Screen (MASS) in the field. Stroke; a journal of cerebral circulation, 41(7), pp.1363–1366.

Bray, J.E. et al., 2005. Paramedic identification of stroke: community validation of the melbourne ambulance stroke screen. Cerebrovascular Diseases, 20(1), pp.28–33.

Broomfield, N.M. et al., 2014. Depression and anxiety symptoms post-stroke/TIA: prevalence and associations in cross-sectional data from a regional stroke registry. BMC Neurology, 14(1), pp.198–9.

Brott, T. et al., 1997. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke; a journal of cerebral circulation, 28(1), pp.1–5.

Bustamante, A. et al., 2021. Blood Biomarkers to Differentiate Ischemic and Hemorrhagic Strokes. Neurology, 96(15), pp.e1928–e1939.

Buttar, H.S., Li, T. & Ravi, N., 2005. Prevention of cardiovascular diseases: Role of exercise, dietary interventions, obesity and smoking cessation. Experimental and clinical cardiology, 10(4), pp.229–249.

Cannistraro, R.J. et al., 2019. CNS small vessel disease: A clinical review. Neurology, 92(24), pp.1146–1156.

Carlin, R., Zhang, N. & Demaerschalk, B.M., 2021. Validation of the Telestroke Mimic Score in Mayo Clinic Population. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 30(10), p.106021.

Chalela, J.A. et al., 2007. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet, 369(9558), pp.293–298.

Charcos, I.B. et al., 2021. Location of Traumatic Cranial Epidural Hematoma Correlates with the Source of Hemorrhage: A 12-Year Surgical Review. World neurosurgery, 152, pp.e138–e143.

Charidimou, A. et al., 2017. Microbleeds, Cerebral Hemorrhage, and Functional Outcome After Stroke Thrombolysis. Stroke; a journal of cerebral circulation, 48(8), pp.2084–2090.

Charidimou, A. et al., 2012. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis., 43(9), pp.2324–2330.

Chen, G. et al., 2005. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. Gait & posture, 22(1), pp.51–56.

Chen, S. et al., 2013. Validation of the Los Angeles pre-hospital stroke screen (LAPSS) in a Chinese urban emergency medical service population. PLoS ONE, 8(8), p.e70742.

Chen, W. et al., 2015. Totaled health risks in vascular events score predicts clinical outcome and symptomatic intracranial hemorrhage in chinese patients after thrombolysis. Stroke; a journal of cerebral circulation, 46(3), pp.864–866.

Chenaitia, H. et al., 2013. Emergency medical service in the stroke chain of survival. European journal of emergency medicine : official journal of the European Society for Emergency Medicine, 20(1), pp.39–44.

Chenkin, J. et al., 2009. Predictive value of the Ontario prehospital stroke screening tool for the identification of patients with acute stroke. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors, 13(2), pp.153–159.

Cooley, S.R. et al., 2021. Mobile Stroke Units Facilitate Prehospital Management of Intracerebral Hemorrhage. Stroke; a journal of cerebral circulation, 52(10), pp.3163–3166.

Cuvinciuc, V. et al., 2010. Isolated acute nontraumatic cortical subarachnoid hemorrhage. AJNR American journal of neuroradiology, 31(8), pp.1355–1362.

Czap, A.L. et al., 2021. Machine Learning Automated Detection of Large Vessel Occlusion From Mobile Stroke Unit Computed Tomography Angiography. Stroke; a journal of cerebral circulation, p.STROKEAHA121036091.

D'Andrea, A. et al., 2016. Transcranial Doppler Ultrasound: Physical Principles and Principal Applications in Neurocritical Care Unit. Journal of cardiovascular echography, 26(2), pp.28–41.

Dagonnier, M. et al., 2021. Acute Stroke Biomarkers: Are We There Yet? Frontiers in neurology, 12, p.619721.

Dalkara, T. & Alarcon-Martinez, L., 2015. Cerebral microvascular pericytes and neurogliovascular signaling in health and disease. Brain research, 1623, pp.3–17.

Daly, M. & Langhammer, C., 2022. Radial Nerve Injury in Humeral Shaft Fracture. The Orthopedic clinics of North America, 53(2), pp.145–154.

Dami, F. et al., 2017. Proposition and operational characteristics of a new dispatch scale to specifically identify acute strokes. European journal of emergency medicine : official journal of the European Society for Emergency Medicine, 24(3), pp.202–207.

Dankbaar, J.W. et al., 2009. Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neuroradiology, 51(12), pp.813–819.

Davenport, R.J. et al., 1996. Complications after acute stroke. Stroke; a journal of cerebral circulation, 27(3), pp.415–420.

De Luca, A. et al., 2013. The use of Cincinnati Prehospital Stroke Scale during telephone dispatch interview increases the accuracy in identifying stroke and transient ischemic attack symptoms. BMC health services research, 13(1), p.513.

DeGracia, D.J. et al., 2008. Translation arrest and ribonomics in post-ischemic brain: layers and layers of players. Journal of neurochemistry, 106(6), pp.2288–2301.

del Zoppo, G.J., 2009. Inflammation and the neurovascular unit in the setting of focal cerebral ischemia. Neuroscience, 158(3), pp.972–982.

Demchuk, A.M. et al., 2012. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. Lancet neurology, 11(4), pp.307–314.

Dimmick, S.J. & Faulder, K.C., 2009. Normal variants of the cerebral circulation at multidetector CT angiography. Radiographics : a review publication of the Radiological Society of North America, Inc, 29(4), pp.1027–1043.

Dixon, S.J. et al., 2012. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell, 149(5), pp.1060–1072.

Dolmans, L.S. et al., 2019. Candidate Biomarkers for the Diagnosis of Transient Ischemic Attack: A Systematic Review. Cerebrovascular Diseases, 47(5-6), pp.207–216.

Dombrowski, S.U. et al., 2013. The impact of the UK 'Act FAST' stroke awareness campaign: content analysis of patients, witness and primary care clinicians' perceptions. BMC public health, 13(1), pp.915–8.

Drenck, N. et al., 2019. Pre-hospital management of acute stroke patients eligible for thrombolysis - an evaluation of ambulance on-scene time. Scandinavian journal of trauma, resuscitation and emergency medicine, 27(1), pp.3–8.

Dundamadappa, S. et al., 2021. Multiphase CT Angiography: A Useful Technique in Acute Stroke Imaging-Collaterals and Beyond. AJNR American journal of neuroradiology, 42(2), pp.221–227.

Duvekot, M.H.C. et al., 2021. Comparison of eight prehospital stroke scales to detect intracranial large-vessel occlusion in suspected stroke (PRESTO): a prospective observational study. Lancet neurology, 20(3), pp.213–221.

Dvorak, F. et al., 2009. Characterisation of the diagnostic window of serum glial fibrillary acidic protein for the differentiation of intracerebral haemorrhage and ischaemic stroke. Cerebrovascular Diseases, 27(1), pp.37–41.

Ebinger, M. et al., 2021. Association Between Dispatch of Mobile Stroke Units and Functional Outcomes Among Patients With Acute Ischemic Stroke in Berlin. JAMA : the journal of the American Medical Association, 325(5), pp.454–466.

Ebinger, M. et al., 2013. Prehospital thrombolysis: a manual from Berlin. Journal of visualized experiments : JoVE, (81), pp.e50534–e50534.

Ekundayo, O.J. et al., 2013. Patterns of emergency medical services use and its association with timely stroke treatment: findings from Get With the Guidelines-Stroke. Circulation. Cardiovascular quality and outcomes, 6(3), pp.262–269.

Etminan, N. & Macdonald, R.L., 2017. Management of aneurysmal subarachnoid hemorrhage. Handbook of clinical neurology, 140, pp.195–228.

Faizy, T.D. et al., 2022. The Cerebral Collateral Cascade: Comprehensive Blood Flow in Ischemic Stroke. Neurology, 98(23), pp.e2296–e2306.

Fassbender, K. et al., 2003. "Mobile stroke unit" for hyperacute stroke treatment. Stroke; a journal of cerebral circulation, 34(6), p.e44.

Fassbender, K. et al., 2021. Impact of mobile stroke units. Journal of neurology, neurosurgery, and psychiatry, 92(8), pp.815–822.

Fassbender, K. et al., 2017. Mobile stroke units for prehospital thrombolysis, triage, and beyond: benefits and challenges. Lancet neurology, 16(3), pp.227–237.

Feigin, V.L. et al., 2005. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke; a journal of cerebral circulation, 36(12), pp.2773–2780.

Felling, R.J. et al., 2014. Cerebral Amyloid Angiopathy: A Hidden Risk for IV Thrombolysis? J Neurol Transl Neurosci, 2(1).

Finch, N.A. & Vilke, G.M., 2020. Unknown Tetrahydrocannabinol Edible Ingestion Resulting in Acute Stroke Presentation. The Journal of emergency medicine, 58(2), pp.296–298.

FISHER, C.M., 1965. LACUNES: SMALL, DEEP CEREBRAL INFARCTS. Neurology, 15(8), pp.774–784.

Flynn, D. et al., 2017. A review of enhanced paramedic roles during and after hospital handover of stroke, myocardial infarction and trauma patients. BMC emergency medicine, 17(1), pp.5–13.

Flynn, D. et al., 2014. A time series evaluation of the FAST National Stroke Awareness Campaign in England. PLoS ONE, 9(8), p.e104289.

Foerch, C. et al., 2012. Diagnostic accuracy of plasma glial fibrillary acidic protein for differentiating intracerebral hemorrhage and cerebral ischemia in patients with symptoms of acute stroke. Clinical chemistry, 58(1), pp.237–245.

Foerch, C. et al., 2009. Invited article: searching for oracles? Blood biomarkers in acute stroke. Neurology, 73(5), pp.393–399.

Fothergill, R.T. et al., 2013. Does use of the recognition of stroke in the emergency room stroke assessment tool enhance stroke recognition by ambulance clinicians? Stroke; a journal of cerebral circulation, 44(11), pp.3007–3012.

Fu, C.-H. et al., 2021. Comparison of risk scores in predicting symptomatic intracerebral hemorrhage after endovascular thrombectomy. Journal of the Formosan Medical Association = Taiwan yi zhi.

Fussman, C. et al., 2009. Racial disparities in knowledge of stroke and heart attack risk factors and warning signs among Michigan adults. Ethnicity & disease, 19(2), pp.128–134.

GBD 2017 Causes of Death Collaborators, 2018. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet, 392(10159), pp.1736–1788.

GBD 2019 Diseases and Injuries Collaborators, 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet, 396(10258), pp.1204–1222.

Gioia, L.C. et al., 2016. Prehospital systolic blood pressure is higher in acute stroke compared with stroke mimics. Neurology, 86(23), pp.2146–2153.

Goyal, M. et al., 2016. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet, 387(10029), pp.1723–1731.

Goyal, N. et al., 2016. FABS: An Intuitive Tool for Screening of Stroke Mimics in the Emergency Department. Stroke; a journal of cerebral circulation, 47(9), pp.2216–2220.

Granato, A. et al., 2020. A novel computed tomography perfusion-based quantitative tool for evaluation of perfusional abnormalities in migrainous aura stroke mimic. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 41(11), pp.3321–3328.

Greenlund, K.J. et al., 2003. Low public recognition of major stroke symptoms. American journal of preventive medicine, 25(4), pp.315–319.

Greve, T. et al., 2021. Novel Ultrafast Spiral Head MR Angiography Compared to Standard MR and CT Angiography. Journal of neuroimaging : official journal of the American Society of Neuroimaging, 31(1), pp.45–56.

Grivé, E., Rovira, A. & Alvarez-Sabín, J., 2005. Distribution territories and causative mechanisms of ischemic stroke. European radiology, 15(3), pp.416–426.

Grotta, J.C. et al., 2021. Prospective, Multicenter, Controlled Trial of Mobile Stroke Units. The New England journal of medicine, 385(11), pp.971–981.

Gude, M.F. et al., 2022. The Prehospital Stroke Score and telephone conference: A prospective validation. Acta neurologica Scandinavica.

Gulli, G. & Markus, H.S., 2012. The use of FAST and ABCD2 scores in posterior circulation, compared with anterior circulation, stroke and transient ischemic attack. Journal of neurology, neurosurgery, and psychiatry, 83(2), pp.228–229.

Hacke, W. et al., 1995. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA : the journal of the American Medical Association, 274(13), pp.1017–1025.

Hanley, D.F. et al., 2019. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. Lancet, 393(10175), pp.1021–1032.

Hanley, D.F. et al., 2017. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. Lancet, 389(10069), pp.603–611.

Harbison, J. et al., 2003. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the face arm speech test. Stroke; a journal of cerebral circulation, 34(1), pp.71–76.

Hassing, L.T., Verschoof, M.A. & Koppen, H., 2019. Alcohol Intoxication as a Stroke Mimic and the Incidence of Acute Alcohol Intoxication in Stroke. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 28(12), p.104424.

He, L. et al., 2019. Capsular warning syndrome: clinical analysis and treatment. BMC Neurology, 19(1), pp.285–7.

Heiss, W.D., 1992. Experimental evidence of ischemic thresholds and functional recovery. Stroke; a journal of cerebral circulation, 23(11), pp.1668–1672.

Heldner, M.R. et al., 2013. National Institutes of Health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. Stroke; a journal of cerebral circulation, 44(4), pp.1153–1157.

Hemphill, J.C. et al., 2015. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke; a journal of cerebral circulation, 46(7), pp.2032–2060.

Herrmann, M. et al., 2000. Release of glial tissue-specific proteins after acute stroke: A comparative analysis of serum concentrations of protein S-100B and glial fibrillary acidic protein., 31(11), pp.2670–2677.

Hesse, C. et al., 2001. Transient increase in total tau but not phospho-tau in human cerebrospinal fluid after acute stroke. Neuroscience letters, 297(3), pp.187–190.

Hjalmarsson, C. et al., 2014. Neuronal and glia-related biomarkers in cerebrospinal fluid of patients with acute ischemic stroke. Journal of central nervous system disease, 6, pp.51–58.

Hodgson, C., Lindsay, P. & Rubini, F., 2007. Can mass media influence emergency department visits for stroke? Stroke; a journal of cerebral circulation, 38(7), pp.2115–2122.

Holste, K. et al., 2021. The role of complement in brain injury following intracerebral hemorrhage: A review. Experimental neurology, 340, p.113654.

Holt, L.J. & Anderson, S.F., 2000. Bilateral occipital lobe stroke with inferior altitudinal defects. Optometry (St. Louis, Mo.), 71(11), pp.690–702.

Hossmann, K.A., 1993a. Disturbances of cerebral protein synthesis and ischemic cell death. Progress in brain research, 96, pp.161–177.

Hossmann, K.A., 1993b. Ischemia-mediated neuronal injury. Resuscitation, 26(3), pp.225–235.

Hossmann, K.A., 1994. Viability thresholds and the penumbra of focal ischemia. Annals of neurology, 36(4), pp.557–565.

Howley, I.W., Bennett, J.D. & Stein, D.M., 2021. Rapid Detection of Significant Traumatic Brain Injury Requiring Emergency Intervention. The American surgeon, 87(9), pp.1504–1510.

Hua, Y. et al., 2007. Brain injury after intracerebral hemorrhage: the role of thrombin and iron. Stroke; a journal of cerebral circulation, 38(2 Suppl), pp.759–762.

Huttner, H.B. et al., 2006. Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: comparison of acute treatment strategies using vitamin K, fresh frozen plasma, and prothrombin complex concentrates. Stroke; a journal of cerebral circulation, 37(6), pp.1465–1470.

Iadecola, C. & Anrather, J., 2011. The immunology of stroke: from mechanisms to translation. Nature Medicine, 17(7), pp.796–808.

Inatomi, Y., Nakajima, M. & Yonehara, T., 2020. Spinal epidural hematoma as a stroke mimic. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 29(9), p.105030.

Jesse, S. et al., 2017. Alcohol withdrawal syndrome: mechanisms, manifestations, and management. Acta neurologica Scandinavica, 135(1), pp.4–16.

Jickling, G.C. & Russo, T.L., 2019. Predicting stroke outcome: Role of a biomarker panel. Neurology, 92(4), pp.157–158.

Jickling, G.C. & Sharp, F.R., 2011. Blood biomarkers of ischemic stroke. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics, 8(3), pp.349–360.

Jokinen, H. et al., 2015. Post-stroke cognitive impairment is common even after successful clinical recovery. European journal of neurology : the official journal of the European Federation of Neurological Societies, 22(9), pp.1288–1294.

Jones, A.T., O'Connell, N.K. & David, A.S., 2020. Epidemiology of functional stroke mimic patients: a systematic review and meta-analysis. European journal of neurology : the official journal of the European Federation of Neurological Societies, 27(1), pp.18–26.

Josephson, S.A., Hills, N.K. & Johnston, S.C., 2006. NIH Stroke Scale reliability in ratings from a large sample of clinicians. Cerebrovascular Diseases, 22(5-6), pp.389–395.

Juvela, S., Hillbom, M. & Palomäki, H., 1995. Risk factors for spontaneous intracerebral hemorrhage. Stroke; a journal of cerebral circulation, 26(9), pp.1558–1564.

Kasab, Al, S. et al., 2021. Telestroke Consultation in the Emergency Medical Services Unit: A Novel Approach to Improve Thrombolysis Times. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 30(5), p.105710.

Kass-Hout, T. et al., 2021. Prehospital Comprehensive Stroke Center vs Primary Stroke Center Triage in Patients With Suspected Large Vessel Occlusion Stroke. JAMA neurology, 78(10), pp.1220–1227.

Kattah, J.C. et al., 2009. HINTS to diagnose stroke in the acute vestibular syndrome: three-step bedside oculomotor examination more sensitive than early MRI diffusion-weighted imaging. Stroke; a journal of cerebral circulation, 40(11), pp.3504–3510.

Kellner, C.P. et al., 2020. Long-term functional outcome following minimally invasive endoscopic intracerebral hemorrhage evacuation. Journal of neurointerventional surgery, 12(5), pp.489–494.

Kellner, C.P. et al., 2018. The VITAL study and overall pooled analysis with the VIPS non-invasive stroke detection device. Journal of neurointerventional surgery, 10(11), pp.1079–1084.

Khaleeli, Z. et al., 2018. Remember the retina: retinal disorders presenting to neurologists. Practical neurology, 18(2), pp.84–96.

Khan, N.I. et al., 2018. Novel Algorithm to Help Identify Stroke Mimics. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 27(3), pp.703–708.

Khedr, A.A. et al., 2013. MRI and magnetic resonance angiography findings in patients with multiple sclerosis mimicked by stroke. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia, 20(8), pp.1163–1164.

Kidwell, C.S. & Wintermark, M., 2008. Imaging of intracranial haemorrhage. Lancet neurology, 7(3), pp.256–267.

Kidwell, C.S. et al., 2004. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA : the journal of the American Medical Association, 292(15), pp.1823–1830.

Kidwell, C.S. et al., 2000. Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS). Stroke; a journal of cerebral circulation, 31(1), pp.71–76.

Kleindorfer, D. et al., 2008. The challenges of community-based research: the beauty shop stroke education project. Stroke; a journal of cerebral circulation, 39(8), pp.2331–2335.

Kohn, M.A., 2014. HINTS to identify stroke in ED patients with dizziness. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine, 21(3), pp.347–347.

Koivunen, R.-J. et al., 2015. Incidence, risk factors, etiology, severity and short-term outcome of non-traumatic intracerebral hemorrhage in young adults. European journal of neurology : the official journal of the European Federation of Neurological Societies, 22(1), pp.123–132.

Koster, G.T. et al., 2018. A Reduction in Time with Electronic Monitoring In Stroke (ARTEMIS): study protocol for a randomised multicentre trial. BMJ open, 8(6), p.e020844.

Kothari, R.U. et al., 1999. Cincinnati Prehospital Stroke Scale: reproducibility and validity. Annals of emergency medicine, 33(4), pp.373–378.

Kotila, M. et al., 1999. Post-stroke depression and functional recovery in a population-based stroke register. The Finnstroke study. European Journal of Neurology, 6(3), pp.309–312.

Krebes, S. et al., 2012. Development and validation of a dispatcher identification algorithm for stroke emergencies. Stroke; a journal of cerebral circulation, 43(3), pp.776–781.

Krishnamoorthy, S. et al., 2021. Biomarkers in the Prediction of Hemorrhagic Transformation in Acute Stroke: A Systematic Review and Meta-Analysis. Cerebrovascular Diseases, pp.1–13.

Kuramatsu, J.B. et al., 2015. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA : the journal of the American Medical Association, 313(8), pp.824–836.

Kyrozis, A. et al., 2009. Incidence and predictors of post-stroke aphasia: the Arcadia Stroke Registry. European journal of neurology : the official journal of the European Federation of Neurological Societies, 16(6), pp.733–739.

Langhorne, P. et al., 2020. Stroke systems of care in high-income countries: what is optimal? Lancet, 396(10260), pp.1433–1442.

Lawes, C.M.M. et al., 2004. Blood pressure and stroke: an overview of published reviews. Stroke; a journal of cerebral circulation, 35(3), pp.776–785.

Lee, K.R. et al., 1996. Edema from intracerebral hemorrhage: the role of thrombin. Journal of neurosurgery, 84(1), pp.91–96.

Lees, K.R. et al., 2010. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet, 375(9727), pp.1695–1703.

Li, L., Scott, C.A. & Rothwell, P.M., 2022. Association of Younger vs Older Ages With Changes in Incidence of Stroke and Other Vascular Events, 2002-2018. JAMA : the journal of the American Medical Association, 328(6), pp.563–574.

Li, Qi et al., 2020. Ultra-Early Blood Pressure Reduction Attenuates Hematoma Growth and Improves Outcome in Intracerebral Hemorrhage. Annals of neurology, 88(2), pp.388–395.

Li, Qian et al., 2018. Ultrastructural Characteristics of Neuronal Death and White Matter Injury in Mouse Brain Tissues After Intracerebral Hemorrhage: Coexistence of Ferroptosis, Autophagy, and Necrosis. Frontiers in neurology, 9, p.581.

Li, T. et al., 2021. Prehospital time intervals and management of ischemic stroke patients. The American journal of emergency medicine, 42, pp.127–131.

Lima, F.O. et al., 2016. Field Assessment Stroke Triage for Emergency Destination: A Simple and Accurate Prehospital Scale to Detect Large Vessel Occlusion Strokes. Stroke; a journal of cerebral circulation, 47(8), pp.1997–2002.

Lindsberg, P.J. et al., 2003. Community-based thrombolytic therapy of acute ischemic stroke in Helsinki. Stroke; a journal of cerebral circulation, 34(6), pp.1443–1449.

Lindsberg, P.J. et al., 1996. Complement activation in the central nervous system following blood-brain barrier damage in man. Annals of neurology, 40(4), pp.587–596.

Lindsberg, P.J. et al., 2006. Door to thrombolysis: ER reorganization and reduced delays to acute stroke treatment. Neurology, 67(2), pp.334–336.

Lindsberg, P.J., Kuisma, M. & Mattila, O.S., 2017. How development of blood biomarkers could benefit prehospital management of acute stroke. Biomarkers in medicine, 11(12), pp.1043–1046.

Lippman, J.M. et al., 2016. Mobile Telestroke During Ambulance Transport Is Feasible in a Rural EMS Setting: The iTREAT Study. Telemedicine journal and e-health : the official journal of the American Telemedicine Association, 22(6), pp.507–513.

Lok, U. et al., 2013. Bilateral thalamic infarct as a diagnosed conversion disorder. The American journal of emergency medicine, 31(5), pp.889.e1–3.

Lord, A.S. et al., 2015. Time course and predictors of neurological deterioration after intracerebral hemorrhage. Stroke; a journal of cerebral circulation, 46(3), pp.647–652.

Lou, M. et al., 2008. The HAT Score: a simple grading scale for predicting hemorrhage after thrombolysis. Neurology, 71(18), pp.1417–1423.

Luger, S. et al., 2017. Glial Fibrillary Acidic Protein Serum Levels Distinguish between Intracerebral Hemorrhage and Cerebral Ischemia in the Early Phase of Stroke. Clinical chemistry, 63(1), pp.377–385.

Lyden, P. et al., 2009. National Institutes of Health Stroke Scale certification is reliable across multiple venues. Stroke; a journal of cerebral circulation, 40(7), pp.2507–2511.

Mac Grory, B. et al., 2018. Distinguishing Characteristics of Headache in Nontraumatic Subarachnoid Hemorrhage. Headache, 58(3), pp.364–370.

Mackay, M.T. et al., 2016. Differentiating Childhood Stroke From Mimics in the Emergency Department. Stroke; a journal of cerebral circulation, 47(10), pp.2476–2481.

Malomo, K. & Ntlholang, O., 2016. A Lesser Known Stroke Mimic: Posterior Reversible Encephalopathy Syndrome. European journal of case reports in internal medicine, 3(3), p.000376.

Manganotti, P. et al., 2019. CT perfusion and EEG patterns in patients with acute isolated aphasia in seizure-related stroke mimics. Seizure, 71, pp.110–115.

Martí-Fábregas, J. et al., 2018. SMASH-U versus H-ATOMIC: A Head-to-Head Comparison for the Etiologic Classification of Intracerebral Hemorrhage. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 27(9), pp.2375–2380.

Mata, J., Frank, R. & Gigerenzer, G., 2014. Symptom recognition of heart attack and stroke in nine European countries: a representative survey. Health expectations : an international journal of public participation in health care and health policy, 17(3), pp.376–387.

Mathern, R. & Calestino, M., 2020. An unusual presentation of hemiparesis: Rapidly progressing Streptococcal pneumoniae meningitis secondary to acute mastoiditis. IDCases, 21, p.e00831.

Mattila, O.S. et al., 2017. Ultra-acute diagnostics for stroke: Large-scale implementation of prehospital biomarker sampling. Acta neurologica Scandinavica, 136(1), pp.17–23.

Mayer, A.R., Quinn, D.K. & Master, C.L., 2017. The spectrum of mild traumatic brain injury: A review. Neurology, 89(6), pp.623–632.

Mayer, C.A. et al., 2013. Blood levels of glial fibrillary acidic protein (GFAP) in patients with neurological diseases. C. Kleinschnitz, ed. PLoS ONE, 8(4), p.e62101.

Mazya, M.V. et al., 2020. Implementation of a Prehospital Stroke Triage System Using Symptom Severity and Teleconsultation in the Stockholm Stroke Triage Study. JAMA neurology, 77(6), pp.691–699.

McCarron, M.O. & Nicoll, J.A.R., 2004. Cerebral amyloid angiopathy and thrombolysis-related intracerebral haemorrhage. Lancet neurology, 3(8), pp.484–492.

McClelland, G. et al., 2019. The frequency, characteristics and aetiology of stroke mimic presentations: a narrative review. European journal of emergency medicine : official journal of the European Society for Emergency Medicine, 26(1), pp.2–8.

Medcalf, R.L., 2017. Fibrinolysis: from blood to the brain. Journal of thrombosis and haemostasis : JTH, 15(11), pp.2089–2098.

Mellon, L. et al., 2014. Can a media campaign change health service use in a population with stroke symptoms? Examination of the first Irish stroke awareness campaign. Emergency medicine journal : EMJ, 31(7), pp.536–540.

Mendelow, A.D., 2015. Surgical Craniotomy for Intracerebral Haemorrhage. Frontiers of neurology and neuroscience, 37, pp.148–154.

Mendelow, A.D. et al., 2013. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. Lancet, 382(9890), pp.397–408.

Mendelson, S.J. & Prabhakaran, S., 2021. Diagnosis and Management of Transient Ischemic Attack and Acute Ischemic Stroke: A Review. JAMA : the journal of the American Medical Association, 325(11), pp.1088–1098.

Menon, B.K. et al., 2012. Risk score for intracranial hemorrhage in patients with acute ischemic stroke treated with intravenous tissue-type plasminogen activator., 43(9), pp.2293–2299.

Meretoja, A. et al., 2013. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. Neurology, 81(12), pp.1071–1076.

Meretoja, A. et al., 2020. Tranexamic acid in patients with intracerebral haemorrhage (STOP-AUST): a multicentre, randomised, placebo-controlled, phase 2 trial. Lancet neurology, 19(12), pp.980–987.

Meretoja, A. et al., 2011. Trends in treatment and outcome of stroke patients in Finland from 1999 to 2007. PERFECT Stroke, a nationwide register study. Annals of medicine, 43 Suppl 1(sup1), pp.S22–30.

Meretoja, A., Strbian, D., Mustanoja, S., et al., 2012. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. Neurology, 79(4), pp.306–313.

Meretoja, A., Strbian, D., Putaala, J., et al., 2012. SMASH-U: a proposal for etiologic classification of intracerebral hemorrhage. Stroke, 43(10), pp.2592–2597.

Merino, J.G. et al., 2013. Predictors of acute stroke mimics in 8187 patients referred to a stroke service. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 22(8), pp.e397–403.

Miyamatsu, N. et al., 2012. Effects of public education by television on knowledge of early stroke symptoms among a Japanese population aged 40 to 74 years: a controlled study. Stroke; a journal of cerebral circulation, 43(2), pp.545–549.

Mochari-Greenberger, H. et al., 2015. Racial/Ethnic and Sex Differences in Emergency Medical Services Transport Among Hospitalized US Stroke Patients: Analysis of the National Get With The Guidelines-Stroke Registry. Journal of the American Heart Association, 4(8), p.e002099.

Momjian-Mayor, I. & Baron, J.-C., 2005. The pathophysiology of watershed infarction in internal carotid artery disease: review of cerebral perfusion studies. Stroke; a journal of cerebral circulation, 36(3), pp.567–577.

Monbailliu, T., Goossens, J. & Hachimi-Idrissi, S., 2017. Blood protein biomarkers as diagnostic tool for ischemic stroke: a systematic review. Biomarkers in medicine, 11(6), pp.503–512.

Moreau, F. et al., 2016. Near-infrared measurements of brain oxygenation in stroke. Neurophotonics, 3(3), p.031403.

Morley, W., Jackson, K. & Mead, G.E., 2005. Post-stroke fatigue: an important yet neglected symptom. Age and ageing, 34(3), pp.313–313.

Mozaffarian, D. et al., 2015. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation, 131(4), pp.e29–322.

Mszar, R. et al., 2020. Association Between Sociodemographic Determinants and Disparities in Stroke Symptom Awareness Among US Young Adults. Stroke; a journal of cerebral circulation, 51(12), pp.3552–3561.

Mukherjee, D., Levin, R.L. & Heller, W., 2006. The cognitive, emotional, and social sequelae of stroke: psychological and ethical concerns in post-stroke adaptation. Topics in stroke rehabilitation, 13(4), pp.26–35.

National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995. Tissue plasminogen activator for acute ischemic stroke. The New England journal of medicine, 333(24), pp.1581–1587.

Newman-Toker, D.E. et al., 2008. Normal head impulse test differentiates acute cerebellar strokes from vestibular neuritis. Neurology, 70(24 Pt 2), pp.2378–2385.

Nguyen, T.T.M. et al., 2021. Comparison of Prehospital Scales for Predicting Large Anterior Vessel Occlusion in the Ambulance Setting. JAMA neurology, 78(2), pp.157–164.

Nogueira, R.G. et al., 2017. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. The New England journal of medicine, p.NEJMoa1706442.

Nor, A.M. et al., 2005. The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument. Lancet neurology, 4(11), pp.727–734.

Nouh, A., Remke, J. & Ruland, S., 2014. Ischemic posterior circulation stroke: a review of anatomy, clinical presentations, diagnosis, and current management. Frontiers in neurology, 5(3), p.30.

Ntaios, G. et al., 2012. An integer-based score to predict functional outcome in acute ischemic stroke: the ASTRAL score. Neurology, 78(24), pp.1916–1922.

O'Donnell, M.J. et al., 2010. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet, 376(9735), pp.112–123.

Ohshita, T. et al., 2015. Hypoglycemia with focal neurological signs as stroke mimic: Clinical and neuroradiological characteristics. Journal of the neurological sciences, 353(1-2), pp.98–101.

Oostema, J.A. et al., 2016. Dispatcher Stroke Recognition Using a Stroke Screening Tool: A Systematic Review. Cerebrovascular Diseases, 42(5-6), pp.370–377.

Pan, R. et al., 2017. Blood Occludin Level as a Potential Biomarker for Early Blood Brain Barrier Damage Following Ischemic Stroke. Scientific reports, 7(1), pp.40331–9.

Park, C.-H., Kou, N. & Ward, N.S., 2016. The contribution of lesion location to upper limb deficit after stroke. Journal of neurology, neurosurgery, and psychiatry, 87(12), pp.1283–1286.

Park, J.S. et al., 2022. Occlusion type and posterior communicating artery patency may predict favorable outcome after endovascular thrombectomy in selective basilar top occlusion. Frontiers in neurology, 13, p.1047971.

Parker, S.A. et al., 2020. Enhanced dispatch and rendezvous doubles the catchment area and number of patients treated on a mobile stroke unit. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 29(8), p.104894.

Parsons, M.W. et al., 2007. Identification of the penumbra and infarct core on hyperacute noncontrast and perfusion CT. Neurology, 68(10), pp.730–736.

Patel, A. et al., 2019. Awareness of Stroke Signs and Symptoms and Calling 9-1-1 Among US Adults: National Health Interview Survey, 2009 and 2014. Preventing chronic disease, 16, p.E78.

Perry, L.A. et al., 2018. Glial fibrillary acidic protein for the early diagnosis of intracerebral hemorrhage: Systematic review and meta-analysis of diagnostic test accuracy. International journal of stroke, 133, p.1747493018806167.

Persson, M. et al., 2014. Microwave-based stroke diagnosis making global prehospital thrombolytic treatment possible. IEEE transactions on biomedical engineering, 61(11), pp.2806–2817.

Pérez de la Ossa, N. et al., 2014. Design and validation of a prehospital stroke scale to predict large arterial occlusion: the rapid arterial occlusion evaluation scale. Stroke; a journal of cerebral circulation, 45(1), pp.87–91.

Pohl, M. et al., 2021. Ischemic stroke mimics: A comprehensive review. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia, 93, pp.174–182.

Pollack, C.V. et al., 2017. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. The New England journal of medicine, 377(5), pp.431–441.

Popkirov, S., Stone, J. & Buchan, A.M., 2020. Functional Neurological Disorder: A Common and Treatable Stroke Mimic. Stroke; a journal of cerebral circulation, 51(5), pp.1629–1635.

Potreck, A. et al., 2022. RAPID CT Perfusion-Based Relative CBF Identifies Good Collateral Status Better Than Hypoperfusion Intensity Ratio, CBV-Index, and Time-to-Maximum in Anterior Circulation Stroke. AJNR American journal of neuroradiology, 43(7), pp.960–965.

Power, C. et al., 2003. Intracerebral hemorrhage induces macrophage activation and matrix metalloproteinases. Annals of neurology, 53(6), pp.731–742.

Powers, W.J., Rabinstein, A.A., Ackerson, T., Adeoye, O.M., Bambakidis, N.C., Becker, K., Biller, J., Brown, M., Demaerschalk, B.M., Hoh, B., Jauch, E.C., Kidwell, C.S., Leslie-Mazwi, T.M., Ovbiagele, B., Scott, P.A., Sheth, K.N., Southerland, A.M., Summers, D.V. & Tirschwell, D.L., 2019a. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke; a journal of cerebral circulation, 50(12), pp.e344–e418.

Prodi, E. et al., 2022. Stroke Mimics in the Acute Setting: Role of Multimodal CT Protocol. AJNR American journal of neuroradiology, 43(2), pp.216–222.

Prospective Studies Collaboration et al., 2007. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet, 370(9602), pp.1829–1839.

Puolakka, T., Virtanen, P., Kinnunen, J., et al., 2021. Prehospital identification of large vessel occlusion using the FAST-ED score. Acta neurologica Scandinavica, 144(4), pp.400–407.

Puolakka, T., Virtanen, P., Kuisma, M., et al., 2021. Comparison of large vessel occlusion scales using prehospital patient reports. Acta neurologica Scandinavica.

Purrucker, J.C. et al., 2016. Early Clinical and Radiological Course, Management, and Outcome of Intracerebral Hemorrhage Related to New Oral Anticoagulants. JAMA neurology, 73(2), pp.169–177.

Qin, X. et al., 2017. Validation of simplified FABS scale to predict stroke mimics in a Chinese population undergoing intravenous thrombolysis. Clinical neurology and neurosurgery, 161, pp.1–5.

Quenardelle, V. et al., 2016. Stroke Mimics in a Stroke Care Pathway Based on MRI Screening. Cerebrovascular Diseases, 42(3-4), pp.205–212.

Qureshi, A.I. et al., 2016. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. The New England journal of medicine, 375(11), pp.1033–1043.

Qureshi, A.I. et al., 2001. Spontaneous intracerebral hemorrhage. The New England journal of medicine, 344(19), pp.1450–1460.

Rajendram, P. et al., 2020. Crisis Resource Management and High-Performing Teams in Hyperacute Stroke Care. Neurocritical care, 33(2), pp.338–346.

Reeves, M.J. et al., 2008. Changes in knowledge of stroke risk factors and warning signs among Michigan adults. Cerebrovascular Diseases, 25(5), pp.385–391.

Requena, M. et al., 2018. Predictors of Endovascular Treatment Among Stroke Codes Activated Within 6 Hours From Symptom Onset. Stroke; a journal of cerebral circulation, 49(9), pp.2116–2121.

Riedel, C.H. et al., 2011. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. Stroke; a journal of cerebral circulation, 42(6), pp.1775–1777.

RIGHT-2 Investigators, 2019. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. Lancet, 393(10175), pp.1009–1020.

Robertson, C.S. et al., 2010. Clinical evaluation of a portable near-infrared device for detection of traumatic intracranial hematomas. Journal of Neurotrauma, 27(9), pp.1597–1604.

Roquer, J. et al., 2020. Short- and long-term outcome of patients with aneurysmal subarachnoid hemorrhage. Neurology, 95(13), pp.e1819–e1829.

Rostami, E. et al., 2018. Early low cerebral blood flow and high cerebral lactate: prediction of delayed cerebral ischemia in subarachnoid hemorrhage. Journal of neurosurgery, 128(6), pp.1762–1770.

Rozanski, M. et al., 2017. Glial Fibrillary Acidic Protein for Prehospital Diagnosis of Intracerebral Hemorrhage. Cerebrovascular Diseases, 43(1-2), pp.76–81.

Runchey, S. & McGee, S., 2010. Does this patient have a hemorrhagic stroke?: clinical findings distinguishing hemorrhagic stroke from ischemic stroke. JAMA : the journal of the American Medical Association, 303(22), pp.2280–2286.

Sacco, R.L. et al., 2013. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke; a journal of cerebral circulation, 44(7), pp.2064–2089.

Sacco, R.L. et al., 1984. Subarachnoid and intracerebral hemorrhage: natural history, prognosis, and precursive factors in the Framingham Study. Neurology, 34(7), pp.847–854.

Saenger, A.K. & Christenson, R.H., 2010. Stroke biomarkers: progress and challenges for diagnosis, prognosis, differentiation, and treatment. Clinical chemistry, 56(1), pp.21–33.

Saloheimo, P. et al., 2006. Regular aspirin-use preceding the onset of primary intracerebral hemorrhage is an independent predictor for death. Stroke; a journal of cerebral circulation, 37(1), pp.129–133.

Saposnik, G. et al., 2011. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. Circulation, 123(7), pp.739–749.

Sattin, J.A. et al., 2006. An expedited code stroke protocol is feasible and safe. Stroke; a journal of cerebral circulation, 37(12), pp.2935–2939.

Schellinger, P.D. et al., 2010. Evidence-based guideline: The role of diffusion and perfusion MRI for the diagnosis of acute ischemic stroke: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology, 75(2), pp.177–185.

Schwamm, L.H. et al., 2013. Temporal trends in patient characteristics and treatment with intravenous thrombolysis among acute ischemic stroke patients at Get With The Guidelines-Stroke hospitals. Circulation. Cardiovascular quality and outcomes, 6(5), pp.543–549.

Sequeira, A.J., Fara, M.G. & Lewis, A., 2018. Ethical Challenges in Acute Evaluation of Suspected Psychogenic Stroke Mimics. The Journal of clinical ethics, 29(3), pp.185–190.

Siegal, D.M. et al., 2015. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. The New England journal of medicine, 373(25), pp.2413–2424.

Silvennoinen, H.M. et al., 2008. CT perfusion identifies increased salvage of tissue in patients receiving intravenous recombinant tissue plasminogen activator within 3 hours of stroke onset. AJNR American journal of neuroradiology, 29(6), pp.1118–1123.

Silver, F.L. et al., 2003. Advertising strategies to increase public knowledge of the warning signs of stroke. Stroke; a journal of cerebral circulation, 34(8), pp.1965–1968.

Snaphaan, L. et al., 2009. Post-stroke depressive symptoms are associated with post-stroke characteristics. Cerebrovascular Diseases, 28(6), pp.551–557.

Sprigg, N. et al., 2018. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. Lancet, 391(10135), pp.2107–2115.

Stanimirovic, D.B. & Friedman, A., 2012. Pathophysiology of the neurovascular unit: disease cause or consequence? Journal of Cerebral Blood Flow & Metabolism, 32(7), pp.1207–1221.

Staykov, D. et al., 2017. Efficacy and safety of combined intraventricular fibrinolysis with lumbar drainage for prevention of permanent shunt dependency after intracerebral hemorrhage with severe ventricular involvement: A randomized trial and individual patient data meta-analysis. Annals of neurology, 81(1), pp.93–103.

Steiner, T. et al., 2016. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. Lancet neurology, 15(6), pp.566–573.

Strand, T. et al., 1984. Brain and plasma proteins in spinal fluid as markers for brain damage and severity of stroke. Stroke; a journal of cerebral circulation, 15(1), pp.138–144.

Strbian, D., Engelter, S., et al., 2012. Symptomatic intracranial hemorrhage after stroke thrombolysis: the SEDAN score. Annals of neurology, 71(5), pp.634–641.

Strbian, D., Meretoja, A., et al., 2012. Predicting outcome of IV thrombolysis-treated ischemic stroke patients: the DRAGON score. Neurology, 78(6), pp.427–432.

Stroke Unit Trialists' Collaboration, 1997. Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. Stroke Unit Trialists' Collaboration. BMJ (Clinical research ed), 314(7088), pp.1151–1159.

Studnek, J.R. et al., 2013. Assessing the validity of the Cincinnati prehospital stroke scale and the medic prehospital assessment for code stroke in an urban emergency medical services agency. Prehospital emergency care : official journal of the National Association of EMS Physicians and the National Association of State EMS Directors, 17(3), pp.348–353.

Suwatcharangkoon, S. et al., 2016. Loss of Consciousness at Onset of Subarachnoid Hemorrhage as an Important Marker of Early Brain Injury. JAMA neurology, 73(1), pp.28–35.

Suzuki, J. et al., 2018. Ten-Year Evaluation of the TOYOTA Prehospital Stroke Scale for Tissue Plasminogen Activator Intravenous Therapy in the Real World. Cerebrovascular Diseases, 46(3-4), pp.184–192.

Tan, J. et al., 2021. Effectiveness of Public Education Campaigns for Stroke Symptom Recognition and Response in Non-Elderly Adults: A Systematic Review and Meta-Analysis. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 31(2), p.106207.

Tatu, L. et al., 1996. Arterial territories of human brain: brainstem and cerebellum. Neurology, 47(5), pp.1125–1135.

Tatu, L. et al., 1998. Arterial territories of the human brain: cerebral hemispheres. Neurology, 50(6), pp.1699–1708.

Thomalla, G. et al., 2018. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. The New England journal of medicine, 379(7), pp.611–622.

Thompson, B.B. et al., 2010. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. Neurology, 75(15), pp.1333–1342.

Tibæk, M. et al., 2016. Increasing Incidence of Hospitalization for Stroke and Transient Ischemic Attack in Young Adults: A Registry-Based Study. Journal of the American Heart Association, 5(5).

Troiani, Z. et al., 2021. Minimally invasive surgiscopic evacuation of intracerebral hemorrhage. Journal of neurointerventional surgery, 13(4), pp.400–400.

Tsivgoulis, G. et al., 2016. Risk of Symptomatic Intracerebral Hemorrhage After Intravenous Thrombolysis in Patients With Acute Ischemic Stroke and High Cerebral Microbleed Burden. JAMA neurology, 73(6), pp.675–9. Available at: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/jamaneurol.2016.0292.

Tu, T.M. et al., 2020. External validation of stroke mimic prediction scales in the emergency department. BMC Neurology, 20(1), pp.269–9.

Tuhrim, S. et al., 1999. Volume of ventricular blood is an important determinant of outcome in supratentorial intracerebral hemorrhage. Critical care medicine, 27(3), pp.617–621.

Valenzuela Espinoza, A. et al., 2016. Development and Pilot Testing of 24/7 In-Ambulance Telemedicine for Acute Stroke: Prehospital Stroke Study at the Universitair Ziekenhuis Brussel-Project. Cerebrovascular Diseases, 42(1-2), pp.15–22.

Vannucci, S.J., Maher, F. & Simpson, I.A., 1997. Glucose transporter proteins in brain: delivery of glucose to neurons and glia. Glia, 21(1), pp.2–21.

Varga, A. et al., 2019. Multidetector CT angiography of the Circle of Willis: association of its variants with carotid artery disease and brain ischemia. European radiology, 29(1), pp.46–56.

Verma, A., Jaiswal, S. & Sheikh, W.R., 2020. Acute thrombotic occlusion of subclavian artery presenting as a stroke mimic. Journal of the American College of Emergency Physicians open, 1(5), pp.932–934.

Virta, J.J. et al., 2021. Trends in Mortality after Intensive Care of Patients with Aneurysmal Subarachnoid Hemorrhage in Finland in 2003-2019: A Finnish Intensive Care Consortium study. Neurocritical care, pp.1–8.

Viswanathan, A. & Greenberg, S.M., 2011. Cerebral amyloid angiopathy in the elderly. Annals of neurology, 70(6), pp.871–880.

Vlak, M.H. et al., 2011. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet neurology, 10(7), pp.626–636.

Walsh, K.B., 2019. Non-invasive sensor technology for prehospital stroke diagnosis: Current status and future directions. International journal of stroke, 14(6), pp.592–602.

Walter, S. et al., 2010. Bringing the hospital to the patient: first treatment of stroke patients at the emergency site. PLoS ONE, 5(10), p.e13758.

Walter, S., Grunwald, I.Q., et al., 2018. Mobile Stroke Units - Cost-Effective or Just an Expensive Hype? Current atherosclerosis reports, 20(10), pp.49–6.

Walter, S., Zhao, H., et al., 2018. Air-Mobile Stroke Unit for access to stroke treatment in rural regions. International journal of stroke, 13(6), pp.568–575.

Wang, J., Zhang, P. & Tang, Z., 2020. Animal models of transient ischemic attack: a review. Acta neurologica Belgica, 120(2), pp.267–275.

Wareing, W., Dhotore, B. & Mahawish, K., 2015. Hyponatraemic encephalopathy: an unusual stroke mimic. BMJ case reports, 2015, p.bcr2014207397.

Weir, C.J. et al., 1994. Poor accuracy of stroke scoring systems for differential clinical diagnosis of intracranial haemorrhage and infarction. The Lancet, 344(8928), pp.999–1002.

Werner, R. & Woehrle, J.C., 2021. Prevalence of Mimics and Severe Comorbidity in Patients with Clinically Suspected Transient Global Amnesia. Cerebrovascular Diseases, 50(2), pp.171–177.

Whiteley, W., Tian, Y. & Jickling, G.C., 2012. Blood biomarkers in stroke: research and clinical practice. International journal of stroke, 7(5), pp.435–439.

Williams, O. & Noble, J.M., 2008. "Hip-hop" stroke: a stroke educational program for elementary school children living in a high-risk community. Stroke; a journal of cerebral circulation, 39(10), pp.2809–2816.

Wojner-Alexandrov, A.W. et al., 2005. Houston paramedic and emergency stroke treatment and outcomes study (HoPSTO). Stroke; a journal of cerebral circulation, 36(7), pp.1512–1518.

Wu, T.-C. et al., 2017. Telemedicine Can Replace the Neurologist on a Mobile Stroke Unit. Stroke; a journal of cerebral circulation, 48(2), pp.493–496.

Wu, T.C. et al., 2014. Prehospital Utility of Rapid Stroke Evaluation Using In-Ambulance Telemedicine: A Pilot Feasibility Study. Stroke; a journal of cerebral circulation, 45(8), pp.2342–2347.

Xi, G. et al., 1998. Role of blood clot formation on early edema development after experimental intracerebral hemorrhage. Stroke; a journal of cerebral circulation, 29(12), pp.2580–2586.

Xian, Y. et al., 2021. Achieving More Rapid Door-to-Needle Times and Improved Outcomes in Acute Ischemic Stroke in a Nationwide Quality Improvement Intervention. Stroke; a journal of cerebral circulation, p.STROKEAHA121035853.

Xu, L. et al., 2017. Portable near-infrared rapid detection of intracranial hemorrhage in Chinese population. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia, 40, pp.136–146.

Xue, M. et al., 2009. Relative importance of proteinase-activated receptor-1 versus matrix metalloproteinases in intracerebral hemorrhage-mediated neurotoxicity in mice., 40(6), pp.2199–2204.

Yang, J. et al., 2010. Validation of the ABCD2 score to identify the patients with high risk of late stroke after a transient ischemic attack or minor ischemic stroke. Stroke; a journal of cerebral circulation, 41(6), pp.1298–1300.

Yang, W.-S. et al., 2020. Hydrocephalus Growth: Definition, Prevalence, Association with Poor Outcome in Acute Intracerebral Hemorrhage. Neurocritical care, pp.1–10.

Yang, Z. & Wang, K.K.W., 2015. Glial fibrillary acidic protein: from intermediate filament assembly and gliosis to neurobiomarker. Trends in neurosciences, 38(6), pp.364–374.

Yassi, N. et al., 2015. The association between lesion location and functional outcome after ischemic stroke. International journal of stroke, 10(8), pp.1270–1276.

Younes, K. et al., 2019. Hepatic Encephalopathy Mimicking Acute Dominant Middle Cerebral Artery Ischemic Stroke: A Case Report. Case reports in neurology, 11(3), pp.304–311.

Young, C. & MacDougall, D., 2019. Portable Stroke Diagnosis Devices for Adults with Stroke Symptoms: A Review of Diagnostic Accuracy and Cost-Effectiveness.

Yuan, Z.H. et al., 2010. A meta-analysis of the efficacy and safety of recombinant activated factor VII for patients with acute intracerebral hemorrhage without hemophilia. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia, 17(6), pp.685–693.

Zand, R. et al., 2017. Cerebral Microbleeds and Risk of Intracerebral Hemorrhage Post Intravenous Thrombolysis. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 26(3), pp.538–544.

Zuurbier, S.M. et al., 2021. Be aware: COVID-19 the new stroke mimicker. Acta neurologica Belgica, 121(1), pp.309–310.