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ESSI RAATIKAINEN

Delayed Cerebral Ischemia and Blood Coagulation Changes After Aneurysmal Subarachnoid Hemorrhage

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ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the auditorium F114
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 31 March 2023, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Tampere University Hospital, Department of Intensive Care Medicine
Finland

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Cover design: Roihu Inc.

ISBN 978-952-03-2785-9 (print)
ISBN 978-952-03-2786-6 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-2786-6

Carbon dioxide emissions from printing Tampere University dissertations have been compensated.

PunaMusta Oy – Yliopistopaino
Joensuu 2023

ABSTRACT

Aneurysmal subarachnoid hemorrhage (aSAH), with a one-year mortality of up to 50%, remains a devastating disease with many survivors struggling with neurological and psychosocial impairment. Only 25% of aSAH survivors make a full recovery. A significant contributor to a poor outcome is delayed cerebral ischemia (DCI), which complicates recovery in approximately 30% of patients with aSAH. The risk period for DCI is typically 3-14 days after aSAH ictus. The pathophysiology of DCI is incompletely understood. It is thought that vasospasm in large cerebral arteries is one mechanism causing DCI (causing reduced blood flow in affected areas, ischemia, and infarction), but increasing knowledge supports that it is not the sole factor driving DCI. Postmortem studies have shown that cerebral microthrombosis is a common finding in aSAH patients, and the risk of DCI grows with the increasing amount of microclots. Studies have utilized various definitions of DCI in the past, e.g., angiographic vasospasm (where arterial narrowing is seen on imaging), symptomatic vasospasm (i.e., clinical worsening), vasospasm seen in transcranial doppler ultrasound and various definitions of delayed neurological deficits. Comparing studies has been difficult due to the multiple definitions; the 2010 consensus definition of delayed cerebral ischemia after aSAH sought to provide a clear description of DCI for studies to utilize and make comparing studies easier.

The main objective of this thesis is to evaluate the prognostic value of the 2010 consensus definition of DCI and to investigate the association of blood coagulation changes with DCI and neurological outcome in aSAH patients.

This thesis consists of three studies. Study I is an evaluation of the prognostic value of the 2010 consensus definition of DCI in a large retrospective cohort of aSAH patients. Fulfillment of the DCI criteria is found to be a strong and independent risk factor for an unfavorable neurological outcome at hospital discharge as defined by GOS (Glasgow Outcome Scale) scores of 1 to 3 (out of 5).

Study II evaluated the absolute platelet count and change in platelet count and an association with DCI during the 14-day study period. It also evaluated the association of treatment modality and anti-platelet therapy with DCI. The absolute platelet count or change in platelet count was not associated with DCI; neither were treatment modality nor the use of anti-platelet therapy.

Study III examined coagulation changes after aSAH are examined by rotational thromboelastometry (ROTEM), fibrinogen and D-dimer values in a prospective observational study of 60 consecutive aSAH patients. Patients with aSAH are found to be in a state of increased coagulation, with the patients with an unfavorable neurological outcome (measured with Glasgow Outcome scale extended [GOSe] at 90 days, unfavorable outcome defined as GOSe 1-4 [out of 8]) being more coagulable than those with a favorable outcome. However, this state of increased blood coagulation is not associated with DCI defined by the 2010 consensus definition.

In conclusion, fulfilling the 2010 consensus criteria of DCI leads to an increased risk for an unfavorable neurological outcome at hospital discharge. Absolute platelet values or the change in platelet values are not associated with DCI; neither is the use of anti-platelet therapy in patients treated with stent-assisted coiling. Patients with aSAH are in a state of increased blood coagulation, which is associated with poor neurological outcome but not DCI as defined according to the 2010 consensus criteria.

TIIVISTELMÄ

Aivovaltimon pullistuman repeämisestä johtuvaan lukinkalvonalaiseen verenvuotoon (subarachnoidaalivuoto, SA-vuoto) liittyvä kuolemanvaara on suuri, osa potilaista kuolee välittömästi ja vuoden kuluttua elossa on vain joka toinen sairastuneista. Eloon jääneillä on usein neurologisia ja psykososiaalisia ongelmia vuodon jälkeen ja vain 25 % toipuu täysin.

Viivästynyt aivoiskemia (delayed cerebral ischemia, DCI) vaikeuttaa noin 30 % SA-vuodon saaneiden potilaiden toipumista. DCI ilmaantuu tyypillisesti 3–14 vuorokautta vuodosta ja aiheuttaa lisävaurioita kuten tiedonkäsittelyn ja liikkumisen ongelmia sekä elämänlaadun heikentymistä. Tämän tarkkaa syntymekanismia ei tiedetä, mutta nykytiedon mukaan se on monitekijäinen. Aivoverisuonten supistumista on aiemmin pidetty merkittävimpänä tekijänä DCI:n taustalla (aiheuttaen supistuneen suonen vaikutusalueella verenkierron vähenemistä, iskemiaa ja infarktaatiota), mutta nykytietämyksen mukaan se on vain yksi osatekijä muiden joukossa. SA-vuodon sairastaneilla on ruumiinavauksissa todettu aivoverisuonten mikrohyytymiä, joiden lisääntynyt määrä on yhteydessä DCI:n ilmaantuvuuteen. SA-vuotoihin liittyvissä tutkimuksissa on käytetty monia eri määritelmiä DCI:stä, esimerkiksi angiografinen vasospasmi (jossa kuvantamisessa nähdään supistunut aivoverisuoni/suonia), oireinen vasospasmi (jolloin potilaalla on jokin neurologinen puutosoire), kallon päältä tehtävällä doppler-ultraäänellä nähtävä aivoverisuonen supistuminen, ja lukuisat muut määritelmät, jotka liittyvät viivästyneisiin neurologisiin puutosoireisiin. Nämä useat määritelmät ovat vaikeuttaneet eri tutkimusten välistä vertailua. Vuonna 2010 luotiin konsensusmääritelmä DCI:stä, jonka tavoitteena oli luoda yhteinen määritelmä DCI:stä, joka mahdollistaisi jatkossa tutkimusten luotettavamman vertailun.

Tämän väitöskirjan tavoitteena on arvioida SA-vuotopotilailla vuoden 2010 DCI:n konsensusmääritelmän ennustearvoa neurologiseen toipumiseen ja veren hyytymisen merkkiaineiden yhteyttä konsensusmääritelmän mukaisesti määritettyyn DCI:hin ja neurologiseen toipumiseen.

Tämä väitöskirja koostuu kolmesta osatyöstä. Osatyössä I arvioitiin vuoden 2010 DCI:n konsensusmääritelmän ennustearviota neurologiseen toipumiseen retrospektiivisessä SA-vuotopotilaiden kohortissa. DCI-määritelmän täyttyminen on

vahva itsenäinen riskitekijä huonoon neurologiseen toipumiseen mitattuna GOS-asteikolla (Glasgow outcome scale, huono toipuminen GOS 1-3 [maksimispistemäärä 5]) sairaalasta kotiutuessa.

Osatyössä II tutkittiin, onko verihiutaleiden määrällä tai määrän muutoksella yhteyttä DCI:n retrospektiivisessä SA-vuotopotilaiden kohortissa. Tutkimuksessa arvioitiin myös, onko valtimonpullistuman hoitomuodolla tai trombosyyttiestäjälääkityksellä vaikutusta DCI ilmaantuvuuteen. Verihiutaleiden määrällä tai määrän muutoksella ei ollut yhteyttä DCI ilmaantuvuuteen, ei myöskään valtimonpullistuman hoitomuodolla tai trombosyyttiestäjälääkityksellä.

Osatyössä III tutkittiin veren hyytymisen muutoksia SA-vuodon jälkeen 60 potilaan prospektiivisessa aineistossa. Potilailta katsottiin tromboelastometria (ROTEM)-, fibrinogeeni- ja D-dimeeritutkimukset ja arvioitiin niiden yhteyttä DCI:hin sekä neurologiseen toipumiseen mitattuna GOSe (Glasgow outcome scale extended) -asteikolla 90 päivän kohdalla vuodosta. SA-vuotopotilailla todettiin veren lisääntynyt hyytyminen ja tämä oli yhteydessä neurologiseen toipumiseen niin, että huonosti toipuneilla (GOSe 1-4 [maksimipistemäärä 8]) veren hyytyminen oli lisääntynyt paremmin toipuneita enemmän. Yhteyttä DCI:n ilmaantumiseen ei kuitenkaan todettu.

Yhteenvetona, SA-vuotoon sairastuneilla 2010 konsensuskriteeristöllä määritetty DCI oli vahva ja itsenäinen riskitekijä huonoon neurologiseen toipumiseen sairaalasta kotiutuessa. Trombosyyttiarvoilla tai niiden muutoksilla ei ollut yhteyttä DCI:n ilmaantuvuuteen, yhteyttä ei ollut myöskään pullistuman hoitomuodolla tai käytössä olleella trombosyyttiestäjälääkityksellä. SA-vuotopotilailla veren hyytyminen on lisääntynyt ja lisääntynyt hyytyminen on yhteydessä huonompaan neurologiseen toipumiseen, mutta ei DCI:hin.

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ABBREVIATIONS

A10	amplitude 10 minutes after CT
ADAMTS13	a disintegrin and metalloprotease with thrombospondin repeats-13
ADL	activities of daily living
ADP	adenosine diphosphate
AED	antiepileptic drugs
APACHE	acute physiology and chronic health evaluation score
APT	antiplatelet therapy
ASA	acetylsalicylic acid
aSAH	aneurysmal subarachnoid hemorrhage
AUC	area under the curve
BA	basilar artery
BUN	blood urea nitrogen
CFT	clot formation time
CI	confidence interval
CT	computed tomography
CT	clotting time
CTA	computed tomographic angiography
DAPT	dual antiplatelet therapy
DCI	Delayed cerebral ischemia
DIND	delayed ischemic neurologic deficit
DSA	Digital subtraction angiography
DVT	deep vein thrombosis
EACA	epsilon-aminocaproic acid
EBI	early brain injury
EEG	electroencephalogram
ERT	endovascular rescue therapy
EXTEM	assay measuring extrinsic pathway coagulation in ROTEM
F1+2	prothrombin fragments 1+2

FIBTEM	assay measuring clot formation after platelet inhibition in ROTEM
FOUR	The Full Outline of UnResponsiveness score
G	a transformation of the MA value representing clot strength
GCS	Glasgow coma scale
GOS	Glasgow outcome scale
GOSe	Glasgow outcome scale extended
H&H	Hunt and Hess scale grade
HIT II	heparin-induced thrombocytopenia type II
HMG-CoA	3-hydroxy-4-methyl-glutaryl coenzyme A
HR	Hazard ratio
IA	intra-arterial
ICH	intracerebral hemorrhage
ICP	intracranial pressure
ICU	intensive care unit
IL	interleukin
ISAT	The International Subarachnoid Aneurysm Trial
IVH	Intraventricular hemorrhage
K	kinetics time
κ	kappa value
LMWH	low-molecular-weight heparin
MA	maximum amplitude
MAP	mean arterial pressure
MCE	maximum clot elasticity
MCF	maximum clot firmness
MoCA	Montreal cognitive assessment
MRI	magnetic resonance imaging
mRS	modified Rankin scale
n/a	not applicable
NINDS	National Institute of Neurological Disorders and Stroke
NO	nitric oxide
OR	odds ratio
PAF	platelet-activating factor
PAI-1	plasminogen activator inhibitor-1
PaO2	arterial oxygen tension
PBD	post-bleed day

PE	pulmonary embolism
R	reaction time
ROTEM	rotational thromboelastometry
SAH	subarachnoid hemorrhage
SVS	symptomatic vasospasm
TAT	thrombin-antithrombin complex
TBI	traumatic brain injury
TCD	Transcranial doppler ultrasound
TEG	thromboelastography
TEG-PM	thromboelastography platelet mapping
TF	tissue factor
TG	a surrogate of trombin generation
tPA	tissue plasminogen activator
TXA	tranexamic acid
UFH	unfractionated heparin
ULvWF	ultra large von Willebrand factor
VTE	venous thromboembolism
vWF	von Willebrand factor
WBC	white blood cell
WFNS	World Federation Neurosurgical Score

ORIGINAL PUBLICATIONS

Publication I Raatikainen E., Vahtera A., Kuitunen A., Junttila E., Huhtala H., Ronkainen A., Pyysalo L. & Kiiski H. (2021). Prognostic value of the 2010 consensus definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. J. Neurol. Sci. 2021 Jan; 420:117261.

Publication II Raatikainen E., Kiiski, H., Kuitunen, A., Junttila, E., Huhtala, H., Ronkainen, A., Pyysalo, L., & Vahtera, A. (2022). Platelet count is not associated with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as defined by the 2010 consensus definition. J. Neurol. Sci. 2022 May; 436, 120227–120227.

Publication III Raatikainen E., Kiiski, H., Kuitunen, A., Junttila, E., Huhtala, H., Kallonen, A., Ala-Peijari, M., Långsjö, J., Saukkonen, J., Valo, T., Kauppila, T., Raerinne, S., Frösen, J. & Vahtera, A. Increased blood coagulation is associated with poor neurological outcome in aneurysmal subarachnoid hemorrhage. Submitted.

AUTHOR'S CONTRIBUTION

I, II	The author collected the study data and analyzed the data with the help of co-authors. The articles were written by the author with the help of co-authors. The author was the main author of the publications and submitted the article as well as acted as corresponding author in submission.
III	The author took part in the study design and process of applying for permissions to begin the study. The author was a part of the recruiting process as well as the daily follow-up of study patients. The author designed the REDCap study database and analyzed the data with the help of co-authors. The author wrote the article with the help of co-authors and was the main author of the publication. The author submitted the article and acted as corresponding author.

1 INTRODUCTION

Aneurysm rupture is the cause of more than 80% of spontaneous subarachnoid hemorrhage (SAH) cases, accounting for 2-7% of all strokes (Neifert et al. 2021). The annual incidence of aneurysmal subarachnoid hemorrhage (aSAH) has been relatively high in Finland, and it varies between 8-171 per 100 000 persons per year (Korja et al. 2013a), although the incidence seems to be declining (Korja et al. 2016). Risk factors for aSAH include non-modifiable factors (including female sex, Finnish or Japanese nationality, possibly Hispanic or African-American ethnicity) and modifiable factors (including smoking, hypertension, heavy alcohol use, and possibly cocaine use) (Neifert et al. 2021). Approximately 12% of patients with aSAH die immediately before admittance to hospital (Rinkel and Algra 2011).

The one-year mortality rate is up to 50% despite advances in neurocritical and neurosurgical care (Korja et al. 2013b). Many survivors of aSAH struggle with neuropsychological and neurological impairments (Connolly et al. 2012), and over 50% of survivors make an incomplete recovery (Andersen et al. 2019b). The recovery of approximately 30% of aSAH patients is complicated by delayed cerebral ischemia (DCI) (Macdonald 2012; Eagles et al. 2019), causing not only disturbances in cognitive function, memory, mood, and return to work, but also physical impairment (Hackett and Anderson 2000; Seule et al. 2020). The 2010 consensus definition of DCI aimed to provide a clear description of DCI for studies to utilize as an outcome measure and to make comparing studies easier (Vergouwen et al. 2010).

DCI occurs typically between post-bleed days 3 and 14 (Vergouwen et al. 2010; Rowland et al. 2012; Neifert et al. 2021). The pathophysiology of DCI remains incompletely understood, and previous research mainly focuses on large artery vasospasm, but that is not the sole cause of DCI (Rowland et al. 2012; Macdonald 2014). The pathophysiological processes behind DCI, according to current knowledge, include at least cerebral vasospasm, blood-brain barrier disruption, cerebral microthrombi, oxidative stress, and neuroinflammation (Dankbaar et al. 2009, 2010; Macdonald 2012; Rowland et al. 2012; Macdonald et al. 2014). The prevention of DCI and vasospasm has been widely studied, but nimodipine is

currently the only drug found to improve neurological outcome and reduce DCI (Neifert et al. 2021).

Microthrombosis and microcirculatory constriction are among the pathophysiological processes that are hypothesized to contribute to DCI (Macdonald 2014). The brain is a rich source of tissue factor (TF), and its activation after aSAH leads to the activation of the extrinsic clotting cascade and an increase in thrombin generation (Juvela and Siironen 2006; Stein et al. 2006). Blood in the subarachnoid space also causes endothelial cell activation and injury, leading to platelet and coagulation activation (Stein et al. 2006). As a conclusion, aSAH patients have been found to be in a state of increased blood coagulation after ictus and with this, of increased coagulation correlating with poor neurological outcome (Frontera et al. 2012, 2017; Ramchand et al. 2016; Lauridsen et al. 2019).

The purpose of this thesis is to evaluate the prognostic value of the 2010 consensus definition of DCI and to investigate the association of blood coagulation changes measured with platelet count, rotational thromboelastometry (ROTEM) and D-dimer with DCI and neurological outcome in aSAH patients.

2 REVIEW OF THE LITERATURE

2.1 Delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage

2.1.1 Pathophysiology and incidence

Early brain injury (EBI) and DCI are the two main mechanisms that affect patients' outcomes after aSAH (Macdonald 2014). EBI occurs during the first 72 hours after aSAH and is an important determinant of clinical outcomes (Ahn et al. 2018). The mechanisms of EBI are not well understood, ischemia possibly being one mechanism through the low or absent intracranial blood flow caused by transiently elevated intracranial pressure (ICP) (which exceeds mean arterial pressure) at the time of aneurysm rupture (Frontera et al. 2015). Cerebral edema and acute impairment of cerebral autoregulation are also strongly linked to EBI, as are inflammation and oxidative stress caused by the extravasated blood (Rowland et al. 2012). Aneurysm rupture also causes endothelial damage leading to activation of the coagulation cascade (Rowland et al. 2012). Patients have also been found to have cortical spreading depolarizations, leading to depression of evoked and spontaneous activity on an electroencephalogram (EEG) (Rowland et al. 2012). The pathophysiological changes associated with EBI are thought to influence the likelihood and severity of later ischemic complications in aSAH patients (Rowland et al. 2012).

The initial clinical presentation after admission reflects the severity of EBI and is the most important predictor of neurological outcome (Frontera et al. 2015, 2017). The initial clinical presentation may be measured by the Hunt and Hess scale (H&H) or the World Federation Neurosurgical Score (WFNS) (Oshiro et al. 1997; Rosen and Macdonald 2005; Ahn et al. 2018). Oshiro et al examined the H&H scale and WFNS score in a cohort of aSAH patients and discovered that both the H&H scale and WFNS score were predictors of neurological outcome at hospital discharge (odds ratio [OR] 2.585, p=0.0001 and OR 2.262, p=0.0001, respectively) (Oshiro et al. 1997). Both the H&H scale and WFNS scores were highly predictive of mortality

(OR 3.391, p=0.0001, and OR 2.560, p=0.0001, respectively) (Oshiro et al. 1997), Table 1.

Table 1. Hunt and Hess scale and World Federation Neurosurgical Score

Grade	Hunt and Hess	Mortality (%)	WFNS	Mortality (%)
I	Asymptomatic or minimal headache, alert and oriented, mimimal (if any) neck stiffness	1.4	GCS 15, no motor deficit	4.9
II	Moderate to severe headache, neck stiffness, no motor deficiency except cranial nerve palsy	5.4	GCS 13 to 14, no motor deficit	9.3
III	confusion, drowsiness, mild focal neurological deficits	18.8	GCS 13 to 14 with motor deficit	20.0
IV	Stupor, moderate to severe hemiparesis	41.9	GCS 7 to 12, with or without motor deficit	33.3
V	Deep coma, decerebrate rigidity, moribund appearance	76.9	GCS 3 to 6, with or without motor deficit	76.5

Abbreviations: GCS, Glasgow coma score;
Modified from Rosen and Macdonald 2005; Oshiro et al 1997

The severity of the initial hemorrhage is also a significant determinant of outcome (Grasso et al. 2017); this is most commonly quantified using the Fisher scale or modified Fisher scale. The Fisher score was developed in the 1980s to quantify the amount of blood seen on computed tomography (CT) (Fisher et al. 1980). It was also proposed to predict cerebral vasospasm after aSAH (Rosen and Macdonald 2005) with the modified Fisher score found to show a stronger association with symptomatic vasospasm (SVS) than the original score (Frontera et al. 2006), Table 2. The modified Fisher score is also a predictor of in-hospital mortality (OR 1.25, 95% CI 1.0-1.5, p=0.03) (Lantigua et al. 2015). The Hijdra sum score can also be used to quantify the severity of the initial hemorrhage. The grading scale was proposed in 1990 by Hijdra et al. and evaluates the amount of blood in 10 basal cisterns/fissures and in 4 ventricles separately, Table 3 (Hijdra et al. 1990). A recent study comparing radiographic scores in predicting DCI, unfavorable outcome and in-hospital mortality found that the Hijdra sum score had the largest area under the curve (AUC) of all the radiological scores studied with a clinically relevant cut-off at ≥ 15 points (Said et al. 2022).

Table 2. Fisher grading scale

Grade	Fisher grade	percent within grade with SVS	modified Fisher grade	percent within grade with SVS
1	Focal thin SAH	21	Focal or diffuse thin SAH, no IVH	24
2	Diffuse thin SAH	25	Focal or diffuse thin SAH, with IVH	33
3	Thick SAH	37	Thick SAH present, no IVH	33
4	Focal or diffuse thin SAH, with significant ICH or IVH	31	Thick SAH present, with IVH	40

Modified from Frontera et al 2006

Abbreviations: SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SVS, symptomatic vasospasm

Table 3. Hijdra sum score

Step	Action
1	**Separately grade each of the 10 basal cisterns and fissures according to the amount of extravasated blood: *#**
	No blood = 0
	Small amount = 1
	Moderately filled = 2
	Completely filled = 3
2	**Grade the amount of blood in the four ventricles**
	No blood = 0
	Sedimentation in posterior part = 1
	Partly filled = 2
	Completely filled = 3
3	**Calculate the sum score from step 1 by adding the 10 scores, range 0-30**
4	**Calculate the sum score from step 2 by adding the 4 scores, range 0-12**
5	**Hijdra sum score = the sum from steps 3 and 4, range 0-42**

* clots that expanded the original size of a cistern or fissure are graded as 3; # an average score of the other cisterns/fissures is used for inadequately visualized cisterns or fissures
modified from Hijdra et al. 1990

DCI occurs from days 3 to 14 after aSAH (Rowland et al. 2012) and complicates the recovery of approximately 30% of patients with aSAH (Foreman 2016), causing survivors to struggle with neurological and psychosocial impairment (Connolly et al. 2012). Common issues survivors struggle with include memory problems, disturbances in mood, speech problems, and physical impairment (i.e., dependence in activities of daily living or ADL) (Hackett and Anderson 2000). Other reported problems are attention deficits, mental slowness, increased rates of symptoms of anxiety and depression, and even post-traumatic stress disorder (Rinkel and Algra 2011). A study that conducted neuropsychological evaluation at the 3-month follow-up as part of the study evaluated 90 patients (36% of surviving study population) and found that normal cognitive function was observed in 31 (34%) patients, mild cognitive deficit in 27 (30%) of patients and moderate to severe deficit in 32 (36%) patients (Roquer et al. 2020). However, delayed functional recovery after one year

has been reported in approximately 20% of high-grade aSAH patients and warrants outcome assessment beyond the first year after aSAH (Seule et al. 2020).

Cerebral vascular dysfunction includes both the micro- and macrovascular systems of the brain. Macrovascular systems have historically been the main focus of investigations because cerebral vasospasm was thought to be the primary mechanism of DCI (Foreman 2016). However, because the drug clazosentan (a nonpeptide endothelin receptor A antagonist) failed to improve functional outcomes despite reducing vasoconstriction, DCI's cause has been thought to be multifactorial (Macdonald et al. 2007; Rowland et al. 2012). The processes behind DCI are currently considered to be cerebral vascular dysfunction, microthrombosis, spreading cortical depolarizations, and neuroinflammation (Geraghty and Testai 2017).

Postmortem studies have shown cerebral microthrombosis in patients with aSAH (Suzuki et al. 1990; Stein et al. 2006). However, only some of these patients had developed symptoms of DCI (Stein et al. 2006). Microemboli have also been detected using transcranial doppler ultrasound (TCD) in 70% of aSAH patients (Rowland et al. 2012). The contact of blood with the extracellular matrix during aneurysm rupture is thought to initiate the activation of blood coagulation and fibrinolysis (Juvela and Siironen 2006). Numerous studies have found that aSAH patients are in a state of increased blood coagulation after ictus (Juvela and Siironen 2006; Ramchand et al. 2016; Lauridsen et al. 2019).

The development of DCI in aSAH patients also likely involves inflammatory processes (Vergouwen et al. 2008). Inflammatory reactions promote blood coagulation and the formation of microthrombi through the induction of blood coagulation and downregulation of anticoagulatory pathways (Vergouwen et al. 2008). Several proinflammatory cytokines (interleukin [IL]-1, IL-6, and IL-8) have been found to be associated with vasospasm and DCI after aSAH, although the mechanism of cytokines leading to vasospasm is not entirely understood (Vergouwen et al. 2008).

2.1.2 Definition of DCI

2.1.2.1 Previous definitions of DCI

Cerebral vasospasm is an important complication after aSAH. However, various means of defining vasospasm have been used throughout the aSAH literature,

including angiographic vasospasm, SVS, DCI, and transcranial doppler vasospasm (Frontera et al. 2009). Delayed ischemic neurological deficits (DIND) is also frequently used to explain the manifestation of vasopasm in aSAH research (Andersen et al. 2019a).

Angiographic vasospasm, defined as arterial narrowing seen on digital subtraction angiography (DSA) or computed tomographic angiography (CTA), occurs in about 70% of aSAH patients 3-12 days after the initial hemorrhage (Sehba et al. 2012; Brown et al. 2013). It was thought that the vasospasm of the cranial arteries is the cause of DCI because this timeframe coincides with the appearance of DCI's appearance (Fisher et al. 1977; Sehba et al. 2012). However, only 30% develop DCI, which may involve a completely different vascular territory from the spasm (Geraghty and Testai 2017). Improvements in clinical outcomes, including cerebral infarction, were also not achieved in clinical trials with the reduction of vasospasm (Macdonald et al. 2008, 2011).

SVS refers to clinical neurological worsening and occurs in 20-40% of aSAH patients (Frontera et al. 2009). Those patients with a lower level of consciousness are problematic; thus, clinical examination in detecting this decline is limited (Schmidt et al. 2008).

TCD is commonly used to detect vasospasm in cerebral arteries; its sensitivity is adequate for detecting angiographic spasm of the middle cerebral artery. However, its sensitivity is poor for the anterior and distal cerebral arteries (Frontera et al. 2009). An increase in blood flow velocity can be seen, the increase in velocity brought on by either a decrease in vessel diameter or through the increase in volume flow when the vessel diameter stays the same (Grosset et al. 1993). However, in a human brain, the collateral flow will also influence the velocity (Grosset et al. 1993).

TCD is not without its problems, because the proportion of false negatives was between 20 and 55% even with qualified neurosonographers, depending on the artery under observation (Suarez et al. 2002). The usefulness of TCD in monitoring aSAH requires serial and daily assessments to detect clinical vasospasm (Suarez et al. 2002). TCD velocities may increase due to hypertension, hypervolemia, and hemodilution therapy in patients without vasospasm and may not increase in patients with vasospasm with systemic hypertension or raised ICP (Gross et al. 2014).

The definition of DIND varies slightly with each study, but according to a review of the outcome measures utilized in aSAH research, 40% of studies described an outcome measure with some sort of clinical deterioration combined with DCI (Andersen et al. 2019a). Some required a combination of radiological and clinical

findings to define DIND, while others were purely clinical or radiological, and some provided no definition at all (Andersen et al. 2019a).

Table 4 presents the definitions of DCI used in clinical aSAH research.

Table 4. Definitions of delayed cerebral ischemia used in clinical aSAH research

term	definition
SVS	clinical worsening after other possible causes for neurological deterioration have been eliminated
angiographic vasospasm	cerebral arterial narrowing seen on DSA or CTA
TCD vasospasm	the detection of vasospasm in cerebral arteries using TCD, seen as an increase in blood flow velocity
DIND	definitions vary, but most studies use an outcome measure with some sort of clinical deterioration combined with DCI
Consensus definition of DCI	a decrease of at least 2 points on the GCS or a focal neurological deficit (e.g. aphasia, apraxia, hemianopia, or neglect) lasting for at least one hour and is not apparent immediately after aneurysm occlusion and cannot be attributed to any other causes. Radiological DCI: an infarction seen on cerebral imaging that cannot be attributed to the neurosurgical procedure or aSAH

Abbreviations: SVS, symptomatic vasospasm; DSA, digital subraction angiography; CTA, computed tomographic angiography; GCS, Glasgow Coma Scale; DCI, delayed cerebral ischemia; TCD, transcranial doppler ultrasound; aSAH, aneurysmal subarachnoid hemorrhage

2.1.2.2 Consensus definition of DCI

Various definitions of DCI have been utilized in aSAH clinical trials and observational studies, making comparing studies difficult. In 2010 a multidisciplinary research group proposed a consensus definition of DCI to be used as an outcome measure in future studies (Vergouwen et al. 2010). They proposed that the clinical definition of DCI is a decrease of at least 2 points on the Glasgow Coma Scale (GCS) or a focal neurological deficit (e.g. aphasia, apraxia, hemianopia, or neglect) lasting for at least one hour and is not apparent immediately after aneurysm occlusion and cannot be attributed to any other causes (Vergouwen et al. 2010). The exclusion criteria were further clarified in a study on the interrater agreement in the DCI diagnosis and are ICP repeatedly over 20 mmHg, rebleeding, acute hydrocephalus,

new infection, acute metabolic abnormality, association with sedative medication, seizure confirmed on EEG, and causality related with a neurosurgical procedure within 24 hours (Zafar et al. 2016). Table 5 presents the criteria for acute metabolic abnormalities.

Table 5. Acute metabolic abnormalities as exclusion criteria for delayed cerebral ischemia

Parameter	lower limit	upper limit	change (within 24 hours)
P-Sodium, mmol/l	130	155	+ or - 10
P-BUN, mg/dl	n/a	60	+ 20
B-Glucose, mg/dl	40	>300	+ 100
B-Hemoglobin g/dl	7	n/a	- 2
aB-PaO2, mmHg	60	n/a	- 20
B-WBC 10^9/l	n/a	20	+ 10

Abbreviations: BUN, blood urea nitrogen; n/a, not applicable; WBC, white blood cell; PaO2 arterial oxygen tension
modified from Zafar et al 2016

The proposed definition for cerebral infarction due to DCI is the presence of cerebral infarction on the CT/magnetic resonance imaging (MRI) brain scan that is not explained by aneurysm occlusion (Vergouwen et al. 2010; Zafar et al. 2016). The consensus definition further states that the infarction should be present on imaging within six weeks of aSAH or on the latest imaging before death within six weeks of aSAH or proven in autopsy (Vergouwen et al. 2010). A study focusing on the interrater agreement in the DCI diagnosis also clarifies additional radiologic signs of infarction; Table 6 presents these (Zafar et al. 2016). If any of these criteria for radiological delayed infarction are met, the infarction is seen as caused by DCI. Zafar et al. found excellent overall interobserver agreement using consensus definitions of DCI (Zafar et al. 2016).

Table 6. The criteria for radiological delayed infarction

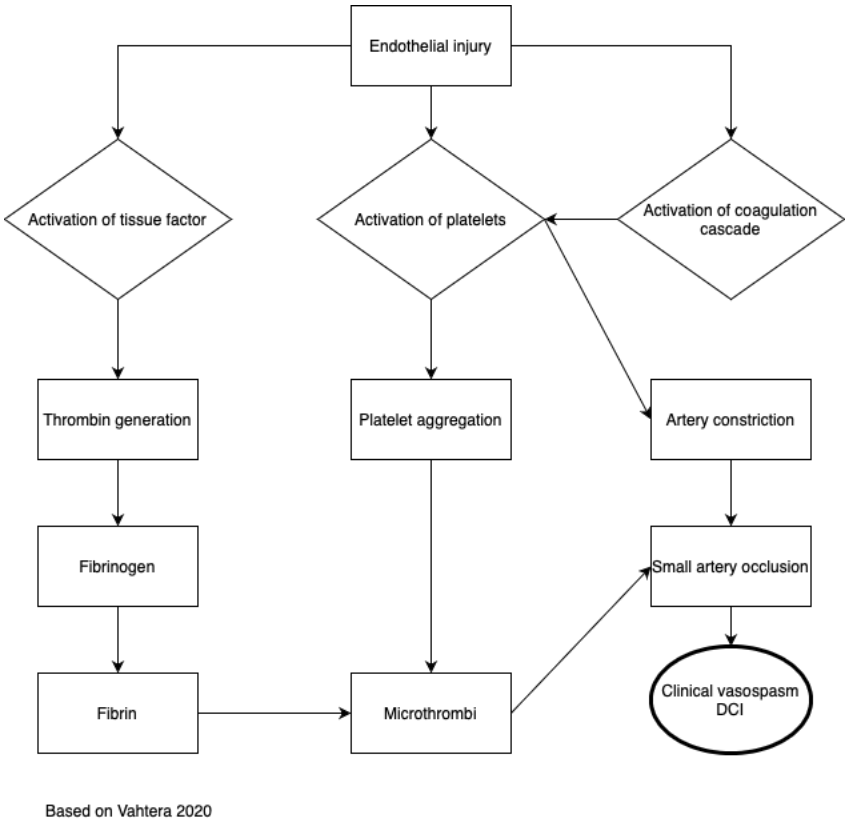
Infarction on imaging satisfying one of the following criteria:
- Seen > 48 hours after any intracranial procedure and absent on intervening imaging
- Seen > 48 hours after any intracranial procedure without intervening imaging in a location distant from the operative site and not considered to be caused by a procedure
- Seen < 48 hours after an intracranial procedure in a setting of severe vasospasm
- Seen < 48 hours after an intracranial procedure in a vascular or watershed territory distinct from operative site and not considered to be caused by a procedure

modified from Zahar et al. 2016

Studies still use varying definitions of DCI despite this consensus definition of DCI, making it difficult to pool data from various studies (Rigante et al. 2022). Some study groups still rely on vasospasm-based definitions of DCI while others use various definitions of delayed neurological decline, such as DIND.

2.1.3 Blood coagulation changes in aSAH and the relationship with DCI

Blood pours into the subarachnoid space at aneurysm rupture, sometimes also into brain parenchyma and ventricles (Macdonald 2014). The volume of the blood clot and the amount of blood in contact with the extravascular matrix correlates with the size of the rupture defect (Peltonen et al. 1997; Rowland et al. 2012), leading to activation of both blood coagulation and fibrinolysis (Ettinger 1970). Microcirculatory constriction and microthrombosis are among the pathophysiological processes that are hypothesized to contribute to DCI, Figure 1 (Macdonald 2014).



Abbreviations: DCI, delayed cerebral ischemia

Figure 1. Blood coagulation in the pathophysiology of delayed cerebral ischemia

The brain, especially the astrocytes in the gray matter and the adventitial surfaces of cerebral arterioles, is a rich source of TF (Antovic et al. 2002; Stein et al. 2006). TF activation at aSAH leads to the activation of the extrinsic clotting cascade and an increase in thrombin generation, namely a rise in levels of thrombin-antithrombin complex (TAT) and prothrombin fragments 1+2 (F1+2) (Juvela and Siironen 2006; Stein et al. 2006). Blood in the subarachnoid space also causes endothelial cell activation and injury, which creates an environment for platelet and coagulation activation and leads to emboli formation (Stein et al. 2006).

2.1.3.1 Tissue factor

SAH leads to a significant elevation in plasma TF, with a significant further increase relating to DCI onset (Bell et al. 2017). Hirashima et al. also found that the membrane-bound TF, which has a more potent procoagulant activity, was increased in aSAH (Hirashima et al. 1997).

2.1.3.2 Thrombin-antithrombin complex

Studies have shown that TAT levels are significantly higher in aSAH patients than controls (patients surgically treated for unruptured aneurysms) (Peltonen et al. 1997). Ilveskero et al. found that the TAT levels decreased during the 10-day study period (Ilveskero et al. 2005). The increase in TAT levels paralleled the severity of the neurological state of the patients at admission, and high TAT levels were associated with unfavorable outcomes (Nina et al. 2001). Fujii et al. found that the TAT levels were increased with the amount of subarachnoid clot and the severity of the neurological grade and that TAT levels were significantly higher in patients with a poor outcome (Fujii et al. 1995). However, Fujii et al. did not find any significant difference in the TAT levels of patients with and without DIND. They did, however, find that on post-bleed day (PBD) 6, patients with a high TAT level ($\geq$ 20 ng/ml) had a significantly higher frequency of DINDs compared to patients with a relatively low TAT level < 20 ng/ml) (Fujii et al. 1997).

2.1.3.3 Prothrombin fragments 1+2

F1+2 are released from prothrombin during the conversion of prothrombin to thrombin (Páramo et al. 2004). Measurement of levels of F1+2 has been considered a specific marker of thrombin generation in vivo (Páramo et al. 2004).

Peltonen et al. found that unlike TAT levels, the F1+2 levels did not differ between the aSAH and control groups (control group patients had unruptured intracranial aneurysms); however, the patients with infarctions detectable on imaging obtained three months after aSAH had significantly increased F1+2 levels during the first postoperative day compared with those without infarctions (despite similar grade at sampling) (Peltonen et al. 1997). F1+2 levels decreased during the 10-day study period equally in patients treated with enoxaparin postoperatively and in patients treated with placebo (Ilveskero et al. 2005)., Fujii et al. found no statistical

difference in F1+2 levels when comparing patients with and without DIND (Fujii et al. 1997).

2.1.3.4 Fibrinogen

Xie et al. found that aSAH patients had a higher fibrinogen level at admission compared to healthy individuals (3.3 ± 1.1 vs. 2.65 ± 0.53 g/l), and aSAH patients with poor-grade aSAH (H&H grade V) had a higher level of fibrinogen compared to the good-grade aSAH (Xie et al. 2020). The fibrinogen level elevated beyond its normal limit on PBD 3 after aSAH and gradually decreased after PBD 6, returning to the normal range by PBD 30 (Fujii et al. 1997). Tseng et al. also found that the fibrinogen levels increased from admission to PBD 3 and that a higher fibrinogen level was sustained during the 14-day study period (Tseng et al. 2007). Some studies found little or no increase in fibrinogen levels (Ameriso et al. 1992; Ilveskero et al. 2005).

Frontera et al. found no association between fibrinogen and admission clinical scores (measured with H&H), but elevated fibrinogen levels correlated with worse 14-day and 3-month functional independence (Frontera et al. 2012). Xie et al. also found that an admission fibrinogen level of < 2.5 g/l was an independent predictor of mortality and that an admission fibrinogen level < 2.5 g/l was associated with DCI (Xie et al. 2020). Hou et al. found that fibrinogen levels were associated with unfavorable outcomes (measured with the modified Rankin Scale, mRS), with the levels of patients with poor outcomes being higher (Hou et al. 2022). A higher level of fibrinogen or a larger increase of fibrinogen on PBD 3 was associated with vasospasm, and patients with larger increases of fibrinogen developed DIND (Tseng et al. 2007). Fujii et al. also reported this higher fibrinogen level on PBD 3 in patients who later developed DIND (Fujii et al. 1997).

2.1.3.5 D-dimer

D-dimer levels have been shown to be higher in patients with aSAH compared to patients with unruptured aneurysms at admission, first postoperative day and 7. postoperative day, with the effect of surgery being similar in both groups (Peltonen et al. 1997). According to one study, D-dimer levels in aSAH patients increased after ictus, reached a peak on PBD 6, decreased on PBD 14, and returned to near admission level on PBD 30, with levels on PBD 3, PBD 6 and PBD 14 significantly

higher than admission (Fujii et al. 1997). In contrast, Tseng et al. found no significant changes in D-dimer levels during their study period (Tseng et al. 2007). One study found no significant relationship between elevated levels of D-dimer and clinical grade at admission (Nina et al. 2001), whereas another found that on admission the WFNS grade was significantly related to D-dimer (Peltonen et al. 1997). Ilveskero et al. also reported that aSAH patients had high D-dimer levels that were significantly correlated with clinical status at admission and at the end of treatment timepoint in their study and outcome at three months (Ilveskero et al. 2005).

Patients who developed DIND after aSAH had a significantly higher D-dimer level on PBD 3 and PBD 14, and the D-dimer level on day 6 was also higher in patients with DIND but without statistical significance (Fujii et al. 1997). Ameriso et al. found no significant elevation of D-dimer level in the aSAH patients who later developed DIND; however, the D-dimer was already elevated in patients who presented with ischemic deficits at admission (Ameriso et al. 1992)., Tseng et al., despite finding no significant changes in D-dimer levels during their study period, found that a smaller increase in D-dimer on PBD 3 or PBD 6 correlated with an aggravating effect toward severe vasospasm and that patients who developed DIND had larger reductions in D-dimer (Tseng et al. 2007). A recent study found that high D-dimer levels at admission were associated with long-term mortality (hazard ratio [HR] 3.01, 95% confidence interval [CI] 2.49-3.63; AUC 0.66, 95% CI 0.59-0.72), with an optimal cut-off value for D-dimer as a predictor for long-term outcome determined as 2.36 mg/l (Fang et al. 2022). Juvela et al. found that postoperative D-dimer values did not predict DCI, but higher levels were found at discharge in the patients with ischemia than in those without it (Juvela and Siironen 2006). They also found a high correlation between D-dimer values and outcome scales on the first postoperative day and at discharge, with patients with poor outcomes having higher D-dimer values (Juvela and Siironen 2006), as did Peltonen et al. (Peltonen et al. 1997). Similar findings were reported by Nina et al., with very high D-dimer levels (>1mg/ml) in patients with unfavorable outcomes and a strong association between significant D-dimer elevation and severe delayed ischemic deficit (Nina et al. 2001).

2.1.3.6 Plasminogen activator inhibitor-1 and tissue plasminogen activator

The plasminogen activator inhibitor-1 (PAI-1) is the most important inhibitor of tissue plasminogen activator (tPA) (Ameriso et al. 1992). Peltonen et al. found that neither PAI-1 nor TPA differed between the two groups when comparing PAI-1 levels in patients with aSAH against the control group of patients without SAH

undergoing craniotomy for unruptured aneurysm (Peltonen et al. 1997). The aSAH patients with more severe bleeding had higher PAI-1 levels on admission than those with less severe bleeding, and the WFNS grade was significantly related to the PAI-1 level (Peltonen et al. 1997). Ilveskero et al. found that PAI-1 antigen, PAI-1 activity, and tPA levels were associated with clinical condition at admission, and tPA levels at admission also correlated with outcome at three months (Ilveskero et al. 2005). The tPA antigen levels rose significantly during the 10-day follow-up period (Ilveskero et al. 2005).

Ameriso et al. found no significant correlations between PAI-1 levels and the development of delayed ischemic deficit (Ameriso et al. 1992). Symptomatic brain ischemia and ischemia on imaging at three months post-aSAH also led to a significant increase in PAI-1 levels, as well as elevated levels of PAI-1 at admission and on the first postoperative day in patients with an unfavorable outcome at three months (Peltonen et al. 1997).

2.1.3.7 Von Willebrand factor and ADAMTS13

Von Willebrand factor (vWF) is a glycoprotein that mediates the initial attachment of platelets to subendothelium through binding to platelet glycoprotein Ib (GPIb) (Weiss et al. 1989; Vergouwen et al. 2009). vWF can also bind to adenosine diphosphate (ADP) or thrombin-stimulated platelets through the platelet membrane receptor GPIIb-IIIa (Weiss et al. 1989). vWF is secreted from the vascular endothelium and alfa-granules of platelets as ultra-large von Willebrand factor (ULvWF) multimers ; under normal circumstances, a protease called a disintegrin and metalloprotease with thrombospondin repeats-13 (ADAMTS13) cleaves ULvWF (Vergouwen et al. 2009). ADAMTS13 cleaves ULvWF into lower molecular weight vWF form with reduced adhesive and aggregation potential; thus, a deficiency in ADAMTS13 leads to a higher concentration of ULvVF, resulting in microthrombosis (Vergouwen et al. 2009). The vWF propeptide is linked to vWF; equal amounts of both are released upon activation, but the propeptide has a shorter half-life than vWF (Frijns et al. 2006).

Patients with aSAH have a higher concentration of vWF than healthy controls, and aSAH patients with DIND had significantly higher concentrations of vWF than patients without DIND (Hirashima et al. 1997). Nina et al. also reported a rise in vWF in all tested aSAH patients (Nina et al. 2001). aSAH patients with DCI had a more profound decrease of ADAMTS13 in the first few days after aSAH, and the vWF antigen, vWF propeptide, and vWF activity also showed a greater increase in

the same timeframe (Vergouwen et al. 2009). Frijns et al. found that aSAH patients with vWF ≥ 94.5 nmol/l had an increased risk of poor outcome (OR 4.6, 95% CI 2.0-10.9), and this association stayed statistically significant after multivariate adjustment (OR 3.3, 95% CI 1.1-9.8) (Frijns et al. 2006). There was also a positive association between vWF concentration and ischemic events from any cause, but after multivariate analysis, this association was no longer statistically significant (adjusted HR 1.8, 95% CI 0.8-3.9) (Frijns et al. 2006). A trend toward a positive association with vWF and DCI was weakened after adjustment in the multivariate analysis (HR 2.2, 95% CI 0.5-9.8) (Frijns et al. 2006).

2.1.3.8 Platelet activating factor

The platelet activating factor (PAF) is a chemical mediator of inflammation; it can be produced by various cells including neutrophils, basophils, platelets, monocytes, macrophages, endothelial cells, and neurons (Hirashima et al. 1993). PAF induces activation of platelets, causes direct damage to nerve cells, and has contractile activity on vessel smooth muscle (Abe et al. 2002).

The involvement of PAF in vasospasm was studied in a rabbit model of SAH. Rabbits injected with autologous blood and PAF had aggravated neurological deficiencies in a dose-dependent manner and produced vasoconstriction in the basilary artery (BA) (Hirashima et al. 1993). Neurological deterioration was prevented with intracisternal administration of either anti-PAF IgG or PAF antagonist, and BA vasoconstriction was also reduced with PAF IgG administration (Hirashima et al. 1993).

PAF concentration in aSAH patients was in a higher range as compared to a control group of healthy individuals and another control group of other neurosurgical patients (e.g. dural arteriovenous fistula, arteriovenous malformation or epilepsy due to brain tumor) during the 14-day observation period ($p<0.01$) (Hirashima et al. 1997). Patients with DIND (defined as delayed transient or permanent neurologic deterioration) had a significantly higher PAF concentration between PBD 5 and 9 ($p<0.05$) but not between PBD 0-4 and PBD 10-14 (Hirashima et al. 1997). PAF concentrations in aSAH patients with cerebral infarction were also greater than in aSAH patients without cerebral infarction (Hirashima et al. 1994).

2.1.3.9 Platelets

Platelets initiate blood vessel constriction through the release of vasoconstricting factors, In addition to being a crucial mediator of hemostasis by promoting clotting, and participate in inflammation through the release of chemokines/cytokines and by interactions with immune cells (Dienel et al. 2021).

Platelet activation after aSAH is achieved through an increase of PAF, vWF, inflammatory cytokines, and platelet-derived factors (thrombin, thromboxane) (Dienel et al. 2021). Using a murine model with fluorescence microscopy and laser doppler flowmetry, Ishikawa et al. reported that platelets adhere directly to the cerebral vessel wall early after aSAH, closely followed by leukocyte recruitment and platelet-leukocyte adhesion, with an increase of platelet-endothelial cell adhesion observed between 2 to 8 hours after aSAH (Ishikawa et al. 2009). These platelet-leukocyte-endothelial cell interactions occurred in the whole brain after aSAH, not just in the hemorrhage location (Ishikawa et al. 2009). According to prior studies, these forming platelet aggregates in the brain's microvasculature disrupt and reduce cerebral blood flow, leading to microthrombosis and capillary obstruction either directly or by reduced platelet inhibition (Dienel et al. 2021). Based on autopsy studies, microthrombosis is a common finding in aSAH patients, and the increasing number of microclots is associated with DCI (Suzuki et al. 1990; Stein et al. 2006). Analysis of the composition of these microthrombi reveals that they consist of aggregated platelets and fibrin, sometimes mixed with leukocytes (Suzuki et al. 1990). Sabri et al. found that in a murine model of SAH, cell membrane P-selectin increased in the mice with SAH, and the concentration of nitric oxide (NO) concurrently decreased, leading to constricted microvessels and thrombosis due to constricted vessels as opposed to emboli (Sabri et al. 2012).

Platelets are reported to cause prolonged cerebral vasospasm in experimental SAH through a proposed mechanism of elevated levels of vasoconstricting factors (thromboxane A2 and platelet-derived growth factor-ß) (Dienel et al. 2021). Out of these, thromboxane A2 has also been highlighted in clinical studies as being involved in the development of vasospasm and DCI pathogenesis (Dienel et al. 2021). Platelets also play a role in microvessel constriction after aSAH, although the mechanisms behind this are still unknown, possibly through P-selectin binding or the release of vasoactive factors (Dienel et al. 2021).

The platelet count in aSAH patients first decreases and then rises to levels greater than the admission level (Hirashima et al. 2005; Schebesch et al. 2007). Lower platelet counts have also been found in patients with more severe hemorrhage; the

mechanism is thought to be a result of thrombogenicity of cerebral blood because of aSAH (Rzepliński et al. 2021). Platelet consumption has also been found to be greater in aSAH patients with vasospasm in an Asian population (Hirashima et al. 2005); however, in a Caucasian population there was no correlation between vasospasm or DIND and platelet count (Schebesch et al. 2007). Rzepliński et al. found no correlation between DCI (defined according to the consensus criteria) and platelet count (Rzepliński et al. 2021), whereas Kasius et al. (using the same DCI definition) found that aSAH patients who develop DCI had significantly larger increases in platelet counts than patients without DCI (Kasius et al. 2010).

Coated platelets are a subset of activated platelets, which retain high levels of several procoagulant proteins on the cell surface (Prodan et al. 2013) and can be used as a surrogate marker for platelet-mediated thrombogenicity (Ray et al. 2018).
The levels of coated platelets are significantly higher in aSAH patients during PBDs 1-4 when comparing aSAH patients to age, race and gender matched controls (Ray et al. 2018). Lower coated-platelet levels were associated with increased 1-month mortality following aSAH (Prodan et al. 2013). Ray et al. found that coated platelet levels rose until PBD 4 and then started decreasing (Ray et al. 2018). aSAH patients who developed DCI (defined according to the consensus criteria) had lower coated-platelet levels at admission than patients without DCI, but the levels in patients with DCI rose more steeply and remained higher than in patients without DCI (Ray et al. 2018). A similar trend is seen in patients with more severe bleed (modified Fisher 3-4) compared to those with less severe bleed (Ray et al. 2018). However, they could not ascertain whether the rise is due to activation of circulating platelets or an increased production of coated platelets in the bone marrow and cannot establish causality between coated platelets and DCI (Ray et al. 2018).

2.1.3.10 Blood coagulation changes shown with thromboelastography and rotational thromboelastometry

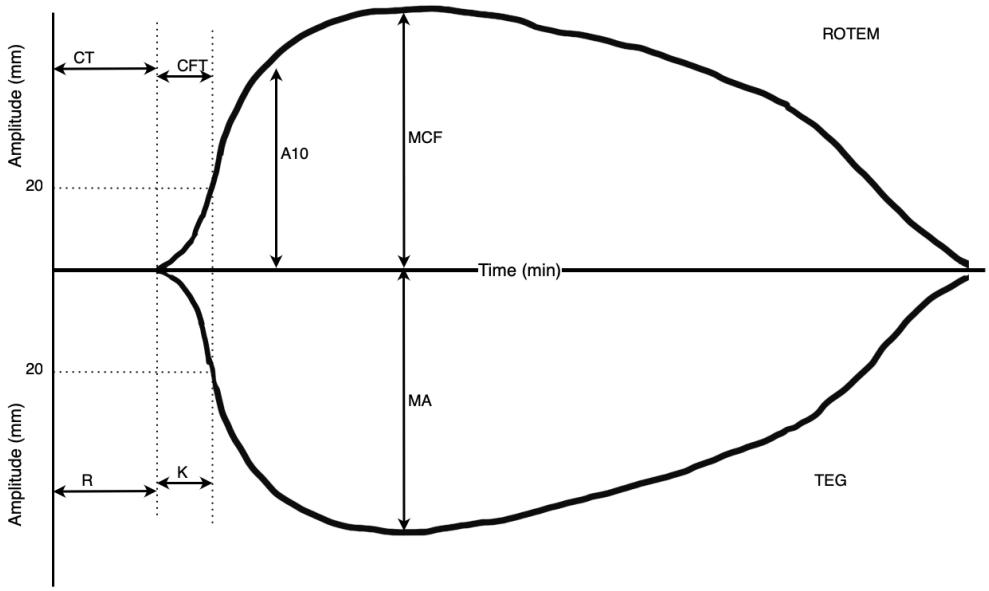
Thromboelastography (TEG) and rotational thromboelastography (ROTEM) are point of care viscoelastic tests that measure clot formation, clot strength and clot dissolution using whole blood samples (Whiting and DiNardo 2014; Ramchand et al. 2016), Table 7. ROTEM and TEG provide the same information on clot formation kinetics and strength, but the results are not interchangeable because of operating characteristics (Whiting and DiNardo 2014). The tests also use different nomenclature for describing the same parameters (Whiting and DiNardo 2014), Figure 2 and Table 8.

Table 7. Comparison of variables from rotational thromboelastometry and thromboelastography

ROTEM test variable	TEG test variable	Definition	Physiological significance
Clotting time (CT)	Reaction time (R)	Time until clot amplitude of 2 mm is reached	Measure of time taken to initiate coagulation
Clot formation time (CFT)	Kinetics time (K)	Time until clot amplitude of 20 mm is reached (from 2 mm amplitude)	The amount of time it takes to reach a certain clot strength
Alpha angle (α)	Alpha angle (α)	Angle between central horizontal line and a tangent to the curve through the 20 mm amplitude point	Rate of clot formation and strengthening (kinetic measurement of fibrin-platelet interaction)
Amplitude 10 min after CT (A10)	n/a	Amplitude at 10 min after clotting time	Measure of clot strength
Amplitude 30 min after CT (A30)	n/a	Amplitude at 30 min after clotting time	Measure of clot strength
Maximum clot firmness (MCF)	Maximum amplitude (MA)	Peak amplitude of clot	Measure of clot strength
Maximum lysis (ML)	n/a	Maximum percentage reduction in MCF	Measure of clot stability (fibrinolytic-induced dissolution of the fibrin-platelet bond)
n/a	Lysis at 30 min (ML30)	Percentage decrease in clot strength at 30 min after MA	Measure of clot stability (fibrinolytic-induced dissolution of the fibrin-platelet bond)
n/a	Lysis at 60 min (ML60)	Percentage decrease in clot strength at 60 min after MA	Measure of clot stability (fibrinolytic-induced dissolution of the fibrin-platelet bond)

Abbreviations: n/a, not applicable

Modified from Cannata 2021



Abbreviations: ROTEM, rotational thromboelastometry; TEG, thromboelastography; CT, clotting time; CFT, clot firmness time; A10, amplitude at 10 minutes; MCF, maximum clot firmness; R, reaction time; K, kinetics time; MA, maximum amplitude

Figure 2. Basic principles of rotational thromboelastometry and thromboelastography

Table 8. Standard thromboelastography and rotational thromboelastometry assays

TEG	Activator	ROTEM	Activator	Interpretation
Standard TEG	Kaolin	INTEM	ellagic acid	clot formation via the contact phase
n/a	n/a	EXTEM	tissue factor	extrinsic pathway (platelets and fibrinogen)
Rapid TEG (rTEG)	kaolin and tissue factor	n/a	n/a	both the tissue factor-initiated and contact pathway-initiated coagulation
Heparinase TEG (hTEG)	kaolin and tissue factor	HEPTEM	ellagic acid and lyophilized heparinase (for neutralizing unfractionated heparin)	can assess heparin's effect when assessed together with standard TEG/INTEM
Functional fibrinogen TEG (FLEV-TEG)	tissue factor and abcizimab	FIBTEM	tissue factor and cytochalasin D	clot formation after platelet inhibition
n/a	n/a	APTEM	aprotinin	discrimination between fibrinolysis and platelet-mediated clot retraction
TEG platelet mapping (TEG-PM)	ADP or arachidonic acid	n/a	n/a	assess platelet function and the effect of antiplatelet agents

abbreviations: ROTEM, rotational thromboelastometry; TEG, thromboelastography; n/a, not applicable; ADP, adenosine diphosphate
Modified from Selby 2020

Patients with SAH were more coagulable by TEG parameters than controls when comparing aSAH patients to healthy controls (Ramchand et al. 2016). Maximum amplitude (MA), G (a transformation of the MA value that represents clot strength), alpha angle and TG (a surrogate of thrombin generation) were significantly higher in aSAH patients on PBD 3, PBD 5, PBD 7, and PBD 10 when compared to controls, whereas none of these variables differed from controls on PBD 1 (Ramchand et al. 2016). Higher clot strength (indicated by higher maximum clot firmness [MCF] in ROTEM assays EXTEM, INTEM and FIBTEM) was observed in patients with SAH compared to healthy controls (Lauridsen et al. 2019).

The MA in TEG is analogous to MCF in ROTEM, and elevated MA/MCF indicates platelet activation (Frontera et al. 2012). Significantly higher MA was found in poor grade (H&H 4-5) SAH compared to good grade patients (H&H 1-3) (Frontera et al. 2012). SAH patients with poor neurological outcome also had significantly higher MA values (Frontera et al. 2012, 2017; Ramchand et al. 2016). aSAH patients who developed DCI (defined as a new focal neurologic deficit or decrease in the level of consciousness, with identified cerebral infarction CT/MRI not relating to procedures) had a higher median admission FIBTEM MCF than patients without DCI (p=0.02) (Lauridsen et al. 2019). aSAH patients with higher MA within 72 hours of ictus had a higher likelihood of developing DCI later during their hospital stay (median MA 66.6 mm in patients with DCI vs.>64.9 mm in patients without DCI, OR for developing DCI 1.1, 95% CI 1.0-1.2, p=0.02) (Frontera et al. 2017).

2.1.4 Prevention and management of DCI

2.1.4.1 Treatment modality

Clipping of ruptured aneurysms in craniotomy was historically performed 7 to 9 days after aSAH, depending on the patient's neurological function and the severity of meningeal signs (i.e., neck stiffness, intolerance to bright light and headache) (Sundt et al. 1982). Surgical clipping has also been favored because partial or complete removal of blood from the subarachnoid space might prevent vasospasm; however, this is based on data from experimental SAH and animal studies mainly on primates (Dehdashti et al. 2004). The optimal timing of the surgical intervention was published in 1989 in a prospective randomized trial by Öhman and Heiskanen, which stated that operating in the acute stage (within 72 hours of aSAH) yields better results than in a later stage because acute surgery was not associated with higher mortality or morbidity rates, and a trend toward better results was observed in the acute surgery group (Öhman and Heiskanen 1989). Current guidelines recommend that aneurysm occlusion occur as early as feasible or within 72 hours of aSAH to reduce the risk of rebleeding (Rawal et al. 2017). A meta-analysis of the timing of endovascular treatment suggests that very early (< 1 day) endovascular aneurysm treatment may reduce the likelihood of poor outcome; however this group included only a subset of patients highly selected based on age and clinical condition on

admission (Rawal et al. 2017). No difference was found compared to later treatment if the definition of early treatment is treatment in <2 or <3 days (Rawal et al. 2017).

The International Subarachnoid Aneurysm Trial (ISAT) found a significant reduction in the relative risk of death or dependency of 23.9% (12.4-33.9) comparing endovascular coiling to neurosurgical clipping (Molyneux et al. 2005). The absolute risk reduction (7.4%, 3.6-11.2) means that 74 patients avoid death or dependency at one year for every 1000 patients treated (Molyneux et al. 2005), shifting the treatment strategies to favor endovascular treatment of aneurysms (Grasso et al. 2017).

Gross et al. found, when comparing treatment modalities and the appearance of vasospasm, that 60% of patients had moderate-severe vasospasm after clipping compared with 38% after coiling (OR 2.32, 95% CI 1.21-4.47, p=0.01) and that the appearance of delayed radiographic infarction was also more common in patients treated with clipping (17% vs. 6%, multivariate OR 3.66, 95% CI 1.06-12.71, p=0.04) (Gross et al. 2014). Differing results have also been reported where the treatment modality does not lead to a statistical difference in the appearance of vasospasm (Charpentier et al. 1999).

Gross et al. found a trend towards more DCI in patients treated with clipping (16% vs. 6%, multivariate OR 3.11, 95% CI 0.89-10.86, p=0.07), but found no statistically significant difference when assessing DCI (Gross et al. 2014). The most recent Cochrane review of coiling versus clipping in aSAH patients found that coiling is associated with a better outcome, and patients treated with coiling had less DCI than those treated with surgical clipping (RR 0.84, 95% CI 0.74-0.96) (Lindgren et al. 2018).

A recent retrospective study comparing treatment methods in a large cohort of aSAH patients found that the patients treated with surgical clipping have more in-hospital complications (including hypoproteinemia, anemia, and pneumonia, 2 [IQR 1-3] vs. 1 [IQR 0-2], p=0.001) and higher incidences of DCI (31.3% vs. 20.1%, p=0.001), with DCI defined according to the consensus definition (Li et al. 2022). Patients in the surgical clipping group also had a longer hospital stay (14 [IQR 11-18] vs. 10 [IQR 5-14] days, p<0.001) and a higher incidence of unfavorable outcome at discharge (46.5% vs. 33.1%, p<0.001) and at 90 days (19.6% vs. 13.8%, p=0.046) (Li et al. 2022). No significant difference in mortality was found between treatment modalities at hospital discharge or 90 days after discharge (Li et al. 2022).

2.1.4.2 Pharmacological measures

Numerous medications have been studied to find a drug that will prevent vasospasm or DCI and result in a favorable outcome in aSAH patients.

A systemic inflammatory response is common after aSAH and markers of inflammation are increased in the cerebrospinal fluid; these may be associated with vasospasm (Mohney et al. 2018). High-dose glucocorticoids prevented vasospasm and improved outcomes in experimental studies (Behrouz and Sadat-Hosseiny 2015). Gomis et al. studied intravenous placebo and methylprednisolone 16 mg/kg daily for three days starting 6 hours after angiographic diagnosis of aneurysm rupture and found that the incidence of symptomatic vasospasm was the same in both groups, but the methylprednisolone group had significantly reduced poor outcomes at 1-year follow-up (Gomis et al. 2010). Mohney et al. studied dexamethasone starting at 4 mg every 6 hours, then tapering down by 1 mg every 24 hours until discontinuation, and found that patients who received dexamethasone were less likely to have a poor functional outcome (mRS >3) at discharge (Mohney et al. 2018). No significant association with DCI or infection was found (Mohney et al. 2018).

At least in vivo, magnesium is found to have neuroprotective qualities, and it also functions as a noncompetitive antagonist of voltage-dependent calcium channels, leading, at least in theory, to a decrease in cerebral vasospasm (Golan et al. 2013). Hypomagnesemia is also relatively common in aSAH patients, and observational studies have found hypomagnesemia to be associated with poor outcomes (Golan et al. 2013). Van den Bergh et al. found hypomagnesemia 2-12 days after aSAH to predict DCI (van den Bergh et al. 2003). However, a systematic review and meta-analysis found that prophylactic intravenous magnesium substitution does not improve the incidence of good neurologic outcome or decrease the risk of cerebral infarction or mortality, although it did decrease the incidence of DCI (Golan et al. 2013).

Clazosentan is a nonpeptide endothelin receptor A antagonist, which in experimental SAH reduced vasospasm (Macdonald et al. 2008). The CONSCIOUS-1 (clazocentan to overcome neurological ischemia and infarction after subarachnoid hemorrhage) study found a dose-dependent reduction of moderate and severe vasospasm in the clazosentan group and a trend for reduction in vasospasm-related morbidity and mortality (Macdonald et al. 2008). However, the reduction of angiographic vasospasm seen in the CONSCIOUS-1 study did not lead to a decrease in morbidity or mortality in the CONSCIOUS-2 study (Macdonald et al. 2011). Patients treated with clazosentan had pulmonary complications, anemia, and

hypotension more commonly than those in the placebo group (Macdonald et al. 2011). A prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group phase 3 study is currently ongoing to assess the efficacy and safety of clazosentan in preventing DCI in aSAH patients (REACT), ClinicalTrials.gov, NCT03585270.

The use of antiepileptic drugs (AEDs) after aSAH is not heavily endorsed in current literary evidence; the evidence shows a lack of efficacy, and some studies also associated worse functional outcomes (Smith 2021). AEDs have also been found to impair cognitive function in healthy volunteers and patients with brain impairment (Rosengart et al. 2007). A recent observational multicenter study of AED usage in Australia and New Zealand found that 40% of patients (144/357) were prescribed an AED, and the leading agent used was levetiracetam (107/144), followed by phenytoin (10/144) and sodium valproate (4/144) (Carnegie et al. 2022). The study found that patients receiving AEDs had a higher clinical and radiological grade aSAH, higher median acute physiology and chronic health evaluation (APACHE) III score, and had their aneurysm clipped; the median duration of AED administration was eight days (IQR 4.5-12.5) (Carnegie et al. 2022). Surprisingly only 75% of patients with a witnessed prehospital seizure received AED (Carnegie et al. 2022). Carnegie et al. found no significant association between their primary outcome death or disability (mRS≥4) and the use of AEDs when the considerable amount of variability of AED prescription was taken into account within the intensive care unit (ICU) (Carnegie et al. 2022). A retrospective study comparing the incidence of delayed seizures, DCI and poor outcome with levetiracetam vs. phenytoin in aSAH patients found that the choice of AED was not associated with DCI, the rate of delayed seizures or poor functional outcome (Karamchandani et al. 2014).

Tranexamic acid (TXA) was widely used in the 1960s and 1970s to prevent the aneurysm thrombus's dissolution and thus prevent rebleeding (Behrouz and Sadat-Hosseiny 2015). The routine long-term use of TXA was abandoned after studies found associations with high cerebral vasospasm, infarction, and hydrocephalus rates (Behrouz and Sadat-Hosseiny 2015)., Ren et al. found in a recent meta-analysis of TXA randomized controlled trials that TXA does not reduce overall mortality in patients with aSAH, nor does it increase the incidence of DCI; it can reduce the incidence of rebleed (Ren et al. 2022). It needs to be noted that while long-term TXA therapy significantly reduced the incidence of rebleed, short-term (<24h) TXA therapy did not (Ren et al. 2022). Hydrocephalus is slightly more common in patients with TXA therapy, probably because TXA reduces plasminogen activity in

cerebrospinal fluid, leading to poor absorption of intraventricular hemorrhage (Ren et al. 2022). A study of an antifibrinolytic drug, epsilon-aminocaproic acid (EACA), found increased rates of deep vein thrombosis (DVT) but not pulmonary embolism (PE) in patients treated with EACA (Starke et al. 2008).

Statins theoretically provide neuroprotection, improvement in vasospasm, improved endothelial vasomotor function, and reduction of inflammation by inhibition of HMG-CoA (3-hydroxy-4-methyl-glutaryl coenzyme A) reductase (Behrouz and Sadat-Hosseiny 2015). A systematic review and meta-analysis of randomized controlled trials of statins found they significantly reduce cerebral vasospasm and DIND (defined here as the clinical symptoms and signs of new ischemic neurologic deficits not attributable to other causes), but no significant decrease in mortality or poor neurological outcome was achieved (Akhigbe et al. 2017). Pravastatin was used in patients with early good neurological status in a recent study: Treatment with pravastatin for 14 days was associated with better neurological outcome, with the control group being historical controls without statin treatment (Mazard et al. 2022). Again, no difference in DCI incidence was found between groups (Mazard et al. 2022).

Calcium channel blockers reduce the influx of calcium into the cell, thereby decreasing the rate of vasospasm (Dorhout Mees et al. 2007b). In a Cochrane review on calcium antagonists, calcium antagonist trials suggested a reduction of poor outcomes and the reduction of the frequency of secondary ischemia (Dorhout Mees et al. 2007b). Oral nimodipine improves the overall outcome of aSAH patients and reduces the frequency of secondary ischemia (Dorhout Mees et al. 2007b). The intravascular administration of these calcium antagonists does not improve outcome; this is also the case with intravascularly administered nimodipine (Dorhout Mees et al. 2007b). However, the review notes that none of the studies included had aSAH patients treated by endovascular coiling, so information on that patient group is missing (Dorhout Mees et al. 2007b). Nimodipine is currently the only drug on the Neurocritical Care Society's multidisciplinary consensus on the critical care management of aSAH patients (Diringer et al. 2011) and the European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid hemorrhage (Steiner et al. 2013) list of recommendations to reduce DCI (60 mg every 4 hours orally for 21 days post-aSAH). Alternative dosing regimens of nimodipine have also been studied, mainly because some patients are more prone to hypotension after oral nimodipine (Mahmoud et al. 2022). Mahmoud et al. studied a modified dosing regimen of 30 mg nimodipine every 2 hours, with the modified dosing regimen being utilized more frequently in women, patients with

vasospasm, and patients requiring vasopressors (Mahmoud et al. 2022). They found that the modified dosing regime was associated with vasospasm but not a worse outcome or DCI (Mahmoud et al. 2022).

Orally-administered nimodipine is currently the only drug with evidence of improving outcome and reducing DCI in aSAH patients (Neifert et al. 2021).

2.1.4.3 Hemodynamic considerations

The triple-H therapy (i.e., hemodilution, hypertension, hypervolemia) was a cornerstone of DCI management over decades (Diringer et al. 2011). Kassell et al. used intravascular volume expansion, administered antidiuretics and vasopressor agents and blocked the vagal depressor response and reversed the neurological deterioration in 47 out of 58 patients (Kassell et al. 1982). This therapy was not without complications: Pulmonary edema, dilutional hyponatremia, aneurysmal rebleeding, coagulopathy, hemothorax, and myocardial infarction were mentioned as complications (Kassell et al. 1982). Muench et al. studied the triple-H therapy on regional cerebral blood flow, ICP, and brain tissue oxygenation in aSAH patients and found that triple-H therapy failed to improve regional cerebral blood flow more than hypertension alone (Muench et al. 2007). The hypervolemia and hemodilution did lead to a negative effect on brain tissue oxygenation (Muench et al. 2007).

The triple-H therapy is reduced to only induced hypertension in current practice, with multiple studies showing an increase in cerebral blood flow and a neurological improvement in the majority of patients treated (Diringer et al. 2011). However, there is no evidence from randomized controlled trials on the use of induced hypertension, so the European Stroke Organization guidelines do not recommend the use of induced hypertension (Steiner et al. 2013). However, they state that in all aSAH patients (not differentiating patients with or without DCI), if blood pressure lowering is needed, the mean arterial pressure (MAP) should be kept at least above 90 mmHg (Steiner et al. 2013).

A 14-day MAP target of $\geq$ 95 mmHg was independently associated with DCI-related infarction and poor outcome in patients with vasospasm but not in patients without vasospasm in a recent retrospective study of blood pressure targets on DCI-related infarction and outcome in aSAH patients (Darkwah Oppong et al. 2022). The study also found that the higher MAP target was not attained by a high dosage of vasopressors in individuals with cerebral vasospasm; they concluded that the MAP increase could be partially related to autoregulatory mechanisms (Darkwah Oppong et al. 2022).

2.1.4.4 Invasive procedures for the treatment of vasospasm

The European Stroke Organization guidelines do not give any recommendations on endovascular rescue therapies (ERT) for vasospasm-related DCI (Steiner et al. 2013), whereas the Neurocritical Care Society guidelines state that ERTs may be considered for vasospasm-related DCI (Diringer et al. 2011). Angioplasty, intra-arterial (IA) vasodilator therapy, and a combination of these have been studied.

The patients who received IA-vasodilators did not have less DCI than the patients who did not receive treatment in a recent retrospective study of the angiographic treatment of asymptomatic cerebral vasospasm (Rebeiz et al. 2022). Another retrospective study into ERT found that patients with DCI achieved better functional outcomes when treated with ERT compared to patients treated without ERT (Mielke et al. 2022). The ERTs utilized in this study were IA-nimodipine, balloon dilation, and a combination of both (Mielke et al. 2022).

Continuous IA-nimodipine infusion has also been studied as a rescue therapy for intracranial vasospasm, with microcatheters placed in the patient's extracranial internal carotid and/or vertebral artery and a continuous nimodipine infusion (0.5-2.0 mg/h) administered through these (Kramer et al. 2022). In this study, 17 patients received a continuous IA-nimodipine infusion for a median duration of 5 (IQR 1-13) days, with treatment onset at a median of 9 (IQR 3-13) days (Kramer et al. 2022). This treatment led to a favorable outcome (Glasgow outcome scale [GOS] 4-5) in 13 patients (76%) within one year of aSAH (Kramer et al. 2022).

The optimum ERT timing is also a complex matter; ERT would ideally be performed before the development of permanent ischemic damage (Diringer et al. 2011). Rosenwasser et al. found that ERT performed within a 2-hour window of a patient developing DCI or vasospasm symptoms lead to a sustained clinical improvement (Rosenwasser et al. 1999). Prophylactic treatments have not been found to affect DCI or outcome significantly but can be associated with potential risks (Mielke et al. 2022). The main risks related to ERT include wire perforation, vessel dissection, and ischemic stroke (Tsogkas et al. 2020).

2.1.4.5 Heparins and anti-platelet medication

Patients with aSAH are at risk of venous thromboembolism (VTE, encompassing both DVT and PE) through the established risk factors (Kshettry et al. 2014), ICU-acquired risk factors (Viarasilpa et al. 2020), and the increased coagulation relating to the aSAH itself (Ramchand et al. 2016; Lauridsen et al. 2019). The incidence of

VTE in aSAH patients ranges from 1.5 to 18%, with the higher incidence related to DVT ultrasound screening in aSAH patients (Diringer et al. 2011; de Oliveira Manoel et al. 2014; Hantsche et al. 2021). This incidence can be reduced by VTE prophylaxis; however, the method and timing of this prophylaxis has been debated (de Oliveira Manoel et al. 2014).

A recent retrospective study into early anticoagulation after aSAH found that early anticoagulation did not increase in the intracranial rebleeding rate; however, delaying anticoagulation significantly increases the incidence of systemic ischemia (e.g., VTE, PE, or other ischemia or thrombi) ($p=0.009$), with the OR being 1.013 (95% CI 1.001-1.024) per hour (Hantsche et al. 2021). There was also a trend towards an improved outcome in patients who had VTE prophylaxis started early, but this did not reach statistical significance (Hantsche et al. 2021).

Heparins (i.e., unfractionated heparin, UFH and low-molecular-weight heparins, LMWHs) have also been studied as potential drugs to reduce DCI. This is based on the extravascular effects of heparin, mainly preventing inflammation and restoring blood-brain barrier integrity (Hayman et al. 2017). Some studies have found the use of UFH or enoxaparin to reduce the incidence of clinical vasospasm and DCI after aSAH (Bruder et al. 2017; Kole et al. 2021), while others have not (Siironen et al. 2003).

The use of acetylsalicylic acid (ASA) has also been studied as a measure for reducing DCI. ASA has anti-inflammatory and analgesic effects and is an inhibitor of platelet aggregation; it is suggested that the anti-inflammatory effects lead to lower adjusted odds of aSAH (Dasenbrock et al. 2017). The MASH study, a randomized, placebo-controlled trial, aimed to assess whether ASA would reduce DIND (defined as the occurrence of a new, spontaneous hypodense lesion on CT that was accompanied by new clinical features of DIND, e.g., focal deficits, decreased level of consciousness); the researchers found that ASA started after aneurysm occlusion did not reduce the incidence of DIND in aSAH patients (van den Bergh 2006). They did find a tendency toward a decreased risk of poor outcome and DIND with ASA after endovascular treatment (van den Bergh 2006). A Cochrane review on anti-platelet drugs observed a trend for ASA to reduce the occurrence of poor outcome in aSAH patients; they also indicated a reduction of the occurrence of secondary ischemia (Dorhout Mees et al. 2007a). A slight increase in hemorrhagic complications was indicated; however, there was no effect on case fatality (Dorhout Mees et al. 2007a). ASA use was independently associated with reduced DCI risk (adjusted OR 0.41, 95% CI 0.25-0.65, $p<0.001$) and favorable outcome (adjusted OR 1.78, 95% CI 1.06-2.98, $p=0.02$) in a recent retrospective case-control study in

Germany (Darkwah Oppong et al. 2019). ASA was associated with only minor bleeding complications (Darkwah Oppong et al. 2019).

Dual anti-platelet therapy (DAPT) for patients treated with stent-assisted coiling has also been studied, especially because platelet activation has been found to play a role in the pathophysiology of DCI and vasospasm (Sun et al. 2020). Sun et al. performed a retrospective study in aSAH patients treated with stent-assisted coiling and receiving DAPT compared to patients treated with simple or balloon-assisted coiling (which do not require DAPT); they found the incidence of symptomatic vasospasm to be lower in the DAPT group (p=0.010) (Sun et al. 2020). DAPT also lead to a lower incidence of DCI (p=0.029) (Sun et al. 2020). A meta-analysis of patients treated with anti-platelet therapy (APT) (including ASA and DAPT) showed no significant beneficial effect of anti-platelet drugs on the occurrence of DCI (Cagnazzo et al. 2019). However, long-term (>2 weeks) APT tended to be associated with a reduction of DCI in the group treated endovascularly (Cagnazzo et al. 2019). They also found that patients receiving APT had a better clinical outcome (OR 1.36, p=0.002) and a lower mortality rate (OR 0.65, p=0.01) (Cagnazzo et al. 2019). Ditz et al. found that in aSAH patients treated endovascularly, post-interventional APT (ASA or ASA+clopidogrel) led to a better functional outcome after three months (p=0.021) (Ditz et al. 2021). They found no significant difference in intracranial bleeding events in APT patients versus the no-APT patients (6% vs. 7%, p=0.114) (Ditz et al. 2021). Nagahama et al. retrospectively studied the association of DAPT to the risk of clinical vasospasm and DCI in aSAH patients treated with coiling (no-DAPT group) and stent-assisted coiling (DAPT group); they found the risk of clinical vasospasm and DCI to be significantly lower in patients receiving DAPT (OR 0.244, CI 95% 0.097-0.615, p=0.003 and OR 0.056, CI 95% 0.01-0.318, p=0.001, respectively) (Nagahama et al. 2018). The rates of hemorrhagic complications were similar in both groups (4% vs. 2%, p=0.9) (Nagahama et al. 2018). Contrary to Ditz et al. and Nagahama et al., Wallace et al. found no difference between ASA monotherapy and DAPT groups in the incidence of DCI, symptomatic vasospasm, or good clinical outcome at six months (4.9 vs. 10.5%, p=0.32, 13.0 vs. 15.8%, p=0.74 and 73.3 vs. 66.7%, p=0.56, respectively) (Wallace et al. 2020). A trend toward more bleeding complications was observed in the DAPT group (0.8 vs. 5.3%, p=0.13), and the DAPT group had a higher incidence of in-hospital mortality (21 vs. 5.7%, p=0.02), although DAPT was not independently predictive of this in regression analysis (Wallace et al. 2020). Li et al. studied whether individualized APT based on TEG-PM parameters might reduce the bleeding risks associated with DAPT. The risk of minor bleeding events was significantly lower in

patients with adjusted therapy (1.1 vs.9.6%, p=0.02), but the rate of major bleeding events (p=0.35) and rates of thromboembolic events (22.6 vs. 28.8, p=0.42) were similar in both groups (Li et al. 2021). No statistical difference in favorable outcome was observed between groups (95.7 vs. 96.2, p=1.0) (Li et al. 2021).

2.1.5 Determining functional outcome

Outcome measures employed vary widely and, along with the varying definitions of DCI, hinder aSAH research progress (Andersen et al. 2019a). An international collaboration in recent years between the National Institute of Neurological Disorders and Stroke (NINDS), Neurocritical Care Society and the National Library of Medicine sought to provide a common structure for future aSAH research (Stienen et al. 2019). This multidisciplinary panel of experts classified outcome measures as common data elements by priority into "core," "supplemental – highly recommended," "supplemental," and "exploratory" (Stienen et al. 2019). Over 50 outcome elements were identified, of which none were classified as core, and the mRS and Montreal Cognitive Assessment (MoCA) were classified as supplemental – highly recommended (Stienen et al. 2019). GOS, Glasgow Outcome Scale extended (GOSe), and death were classified as supplemental (Stienen et al. 2019). All other outcome measures were classified as exploratory (Stienen et al. 2019). They also proposed that studies interested in long-term outcomes carry out the outcome assessments at 3 and 12 months after aSAH, and standardized dichotomizations are also recommended (Stienen et al. 2019). Some studies have also found that outcome assessment beyond the first year after aSAH might be beneficial, especially because delayed functional recovery occurs in up to 20% of patients in high-grade aSAH (Wilson et al. 2013; Seule et al. 2020).

The most used scales for measuring disability in aSAH research are the mRS, GOS, and GOSe, Table 9.

Table 9. Measuring disability with the modified Rankin Scale, Glasgow outcome scale and Glasgow outcome scale extended

	mRS		GOS		GOSe	
Favorable Outcome	0	no symptoms	5	good recovery	8	upper good recovery: full recovery or minor symptoms that do not affect daily life
	1	no significant disability, able to carry out all usual duties and activities despite symptoms			7	lower good recovery: minor physical or mental deficits that affect daily life
	2	slight disability, unable to carry out all usual duties and activities, but able to look after own affairs without assistance	4	moderate disability	6	upper moderate disability: some disability exists but can partly resume work or previous activities
	3	moderate disability, requiring some help but able to walk without assistance			5	lower moderate disability: independent, but cannot resume work/school or all previous social activities
Unfavorable Outcome	4	moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance	3	severe disability	4	upper severe disability: needs partial assistance in ADL
					3	Lower severe disability: needs full assistance in ADL
	5	severe disability: bedridden, incontinent and requiring constant nursing care and attention	2	vegetative state	2	vegetative state
	6	death	1	Death	1	death

Abbreviations: ADL, Activities of daily living; mRS, modified Rankin scale; GOS, Glasgow outcome scale; GOSe, Glasgow outcome scale extended

Adapted from Banks and Marotta 2007, Wilson et al 2021

The mRS, introduced by Dr. John Rankin in 1957, it has been in its current form since the 1980s after modification by Charles Warlow and others as part of the UK-

TIA trial (Broderick et al. 2017). It measures global disability (in particular, physical disability) and the need for assistance (Banks and Marotta 2007). Its reliability and validity have been demonstrated in stroke research, with strong correlations to stroke pathology (e.g. infarct volumes) and agreement with other stroke scales (Broderick et al. 2017). It has been criticized for the subjective determination between categories and the inter-rater reliability as well as test-retest reliability (Broderick et al. 2017). Banks and Marotta performed a literature review on the validity and reliability of the mRS: They found that the test-retest reliability was strong and that the inter-rater agreement ranged from moderate to nearly perfect (Banks and Marotta 2007). The use of structured interviews improves the inter-rater reliability further (Banks and Marotta 2007). There is, however, an important consideration to take into account when using the mRS: Patient comorbidities, surgery and socioeconomic factors on physical functioning, the cognitive abilities of the patient, and the overall health status of the patient may impact the mRS if not taken into account by the clinician in determining the mRS (Banks and Marotta 2007).

The GOS was developed in the 1970s as an outcome measure by Jennett and Bond for use after traumatic brain injury (TBI) (Jennett and Bond 1975). The original GOS had five outcome categories: death, vegetative state, severe disability, moderate disability, and good recovery (Weir et al. 2012). The GOS has been criticized for having only five outcome categories; those are thought to be too few to represent the wide range of mental and physical disabilities patients have after TBI (Weir et al. 2012). The upper categories have also been criticized as ambiguous because of the multidimensional nature of the upper levels of the GOS (Wilson et al. 1998). The GOS has traditionally been assigned based on a short interview, often unstructured, perhaps sometimes leading to variable results among assessors and an impressionistic use of the scale (Wilson et al. 1998). There is also evidence of systematic bias between different professional groups, with the general practitioners tending to make more optimistic assessments than psychologists (Anderson et al. 1993). Another critique of GOS has been that no guidelines are in place to deal with the effects of extracranial injury, epilepsy, and preinjury unemployment (Wilson et al. 1998).

The GOSe scale was later expanded into an 8-point scale to increase the sensitivity of GOS (Wilson et al. 2021). The good recovery, moderate disability, and severe disability categories were divided into "better" and "worse" (McMillan et al. 2016). However, in studies assessing the reliability of GOS and GOSe, the GOS was found to be superior (McMillan et al. 2016). A study using both the GOS and GOSe found considerable disagreement among assessors, even using the 5-point GOS

(Maas et al. 1983). Maas et al. found that the main reasons for observer disagreement were observer bias, different interpretations of the patient's condition among various observers, and errors in recording data (Maas et al. 1983). There is frequently a bias particularly if the outcome is assessed by those responsible for early treatment (who know the severity of the initial injury); therefore, outcome should preferably be assessed by physicians not involved in the previous treatment and who do not know the severity of the initial injury or preceding scores (Maas et al. 1983).

3 AIMS OF THE STUDY

The main aim of this thesis was to study the prognostic potential of the 2010 consensus definition of DCI in aSAH patients and to assess the correlation of blood coagulation changes and the incidence of DCI when using the 2010 consensus definition.

The more detailed objectives were:

1. To assess the prognostic potential of the 2010 consensus definition of DCI

2. To investigate whether the absolute platelet count or change in platelet count was associated with the incidence of DCI. To assess correlation of treatment modality and use of anti-platelet drugs to DCI

3. To analyze the blood coagulation after aSAH using ROTEM and D-dimer measurements and assess the correlation with DCI and neurological outcome at 90 days

4 MATERIALS AND METHODS

4.1 Studies I and II

4.1.1 Study design

Studies I and II were based on a retrospective cohort of adult aSAH patients from the Tampere University Hospital Intensive care unit from January 2010 to December 2014. The inclusion criteria were admission within 48 hours of aSAH. Patients admitted after 48 hours of ictus or those with an unknown time of onset of aSAH symptoms were excluded. Moribund patients and those admitted to the ICU solely based on organ donation were also excluded.

4.1.2 Assessment of DCI

Recorded patient data were used to retrospectively evaluate each patient for the development of DCI using Vergouwen et al.'s DCI definition (Vergouwen et al. 2010) that was clarified further by Zafar et al. (Zafar et al. 2016). The data were evaluated daily by one of three investigators (ER, AK, AV) from 48 hours to 14 days after ictus. Patient data were retrieved from the ICU electronic database (Centricity Critical Care Clinisoft; GE Healthcare, Barrington, IL, USA) and the electronic medical records. The data were thoroughly evaluated by all three investigators, and a consensus decision was achieved in case of any doubt.

4.1.3 Blood sampling (II)

Platelet count was performed at admission and daily thereafter during the ICU stay. Platelet count was performed according to clinical need after transfer to the ward. The average was analyzed if a day contained more than one platelet count. Only the platelet count obtained in the morning was used when assessing the effect of the platelets' circadian rhythm.

4.1.4 Assessment of other clinical factors and neurological outcome

We collected the aneurysm location, treatment modality, H&H grade, and Fisher scale score from the neurosurgical aneurysm database. The neurological outcome was assessed with GOS at hospital discharge; this was also collected from the neurosurgical aneurysm database.

The aSAH severity was evaluated by a neurosurgeon from the initial head-computed tomographic scan with the Fisher scale, and the Hunt and Hess grading scale assessed the severity of EBI at hospital admission. The Fischer scale was dichotomized as non-severe (Fisher scores: 1-2) and severe (Fisher scores: 3-4). The EBI severity at admission was dichotomized as mild (H&H grades: 1-3) and severe (H&H grades: 4-5). The neurological outcome was dichotomized as favorable (GOS scores: 4-5) and unfavorable (GOS scores: 1-3).

Study II also recorded the use of anti-platelet drugs in patients treated with stent-assisted coiling. All patients treated with stent-assisted coiling in our institution receive aspirin 100 mg and an ADP receptor inhibitor (clopidogrel, ticagrelor). Abciximab (a glycoprotein IIb/IIIa inhibitor) is temporarily used after stent placement until an ADP receptor inhibitor is initiated.

4.2 Study III

4.2.1 Study design

Study III was a single-center, prospective observational study from July 2019 to December 2021. Sixty consecutive aSAH patients were enrolled. The inclusion criteria were aneurysmal subarachnoid hemorrhage diagnosed by CT and/or digital subtraction angiography, age ≥ 18 years, admission to ICU within 24 hours from the onset of aSAH symptoms and expected treatment time of at least five days in the Tampere University Hospital. Patients with known pregnancy, any long-term anticoagulant or antithrombotic medication (except ASA less than 150 mg/day), known active cancer, cirrhotic liver disease, or end-stage renal disease requiring renal replacement therapy were excluded.

Patients were treated per a standardized in-house protocol based on international guidelines during their ICU stay (Diringer et al. 2011; Steiner et al. 2013). Tinzaparin 4500 IU once a day was used as VTE prophylaxis, started on the day of the

intravascular treatment or the first postoperative day after craniotomy. Patients treated with stent-assisted coiling received ASA 100 mg and an ADP inhibitor (ticagrelor). Patients temporarily receive abciximab, a glycoprotein IIb/IIIa inhibitor, after stent placement until an ADP receptor inhibitor is initiated.

Patients were monitored with continuous EEG, which was commenced after aneurysm occlusion and continued up to ICU discharge or the 14-day study period.

Anonymized study data were collected and managed using Tampere University hosted REDCap (Research Electronic Data Capture) electronic data capture tools.

4.2.2 Blood sampling

Blood samples were obtained from patients via heparin-naïve arterial line during the ICU stay and via vene puncture during ward stay. ROTEM samples (EXTEM and FIBTEM assays), fibrinogen and fibrin D-dimer were obtained from patients at ICU admission and on PBDs 2-3, 4-5, 7-8, and 11-12. An average of the biomarker was used for each timepoint if applicable.

A plasma sample was used to analyze D-dimer using a particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Cobas 8000-series c702 analyzer). STA-Liquid Fib (Stago) reagents on a Stagon STA-R Max analyzer were used to analyze fibrinogen from a plasma sample.

4.2.3 Rotational thromboelastometry

The central laboratory of the Tampere University Hospital performed the standard assays of EXTEM and FIBTEM using a ROTEM delta analysis system (TEM Innovations GmbH, Munich, Germany) and single-use reagents. The samples were analyzed within four hours of acquirement and measured the following parameters: clotting time (CT), clot formation time (CFT) and MCF.

4.2.4 Assessment of DCI

DCI was assessed daily by study group members using the criteria presented by Vergouwen et al. (Vergouwen et al. 2010) from 2 days to 14 days post-aSAH. The DCI exclusion criteria were based Zafar et al.'s study (Zafar et al. 2016). The neuroradiological imaging of patients was reviewed by a radiologist using the DCI-

related criteria to determine whether new infarctions were considered DCI related. The investigators thoroughly evaluated the patient history and made a consensus decision if any doubt arose.

4.2.5 Assessment of clinical and outcome measures

The clinical severity of aSAH was reviewed at hospital admission using the H&H grading scale and the WFNS score. These were further dichotomized as non-severe (H&H grades 1-3, WFNS grades 1-3) and severe (H&H grades 4-5, WFNS grades 4-5). The primary head CT was used to evaluate the bleeding severity using the Fisher scale. The aneurysm location was dichotomized into anterior and posterior circulation.

Neurological outcome was assessed using the GOSe scale at 90 days and was further dichotomized as favorable (GOSe 5-8) and unfavorable (GOSe 1-4).

Bleeding events were recorded and divided into major (defined as a decrease of hemoglobin of more than 20 g/l or transfusion of more than 2 units of packed red blood cells) and minor (defined as any other bleeding episode). A bilateral ultrasound of the lower extremities was performed once on days 3-7 to assess an asymptomatic DVT. Differentiations between DVT (defined as thrombosis in the deep veins of the lower extremities) and superficial venous thrombosis (defined as a thrombosis in the more superficial veins of the lower extremities) were made. A CT pulmonary angiography was performed on clinical need to detect PE.

4.3 Statistical methods

4.3.1 Studies I and II

The continuous variables (age, platelet count) were normally distributed and are presented as means with standard deviation. The t-test was used to compare between groups. The Pearson chi-square test was used to evaluate associations between categorical variables and DCI. Associations of categorical variables and age with unfavorable neurological outcomes in univariate analysis were performed with binary logistic regression. A multivariate logistic regression model was created to identify independent predictors of unfavorable neurological outcomes. Cox proportional

hazards regression was used to examine the association of platelet count with DCI; time-dependent covariates were made up of daily platelet counts, and missing platelet count values were imputed with the last-known platelet count. The association between platelet count and treatment modality was evaluated using analysis of variance.

Statistical analyses were performed using R version 3.6.3 or version 4.0.3 (The R Foundation, Vienna Austria) or SPSS software version 27 (IBM Corp, Armonk, NY, USA).

4.3.2 Study III

Study III's primary endpoint was MCF (mm) by FIBTEM assay in ROTEM. The sample size was calculated using previous results (Vahtera et al. 2019a). Accordingly, at least sixty patients would be needed to achieve 80% power to detect a clinically meaningful increase from 20.3 to 25.7 mm (SD 4.8 mm) in MCF with a p-level of 0.05.

The formula described by Solomon et al. (Solomon et al. 2015) was used to calculate maximum clot elasticity (MCE) for FIBTEM and EXTEM: MCE=(100 x MCF)/(100-MCF). The contribution of platelets to the clot strength was calculated as platelet MCE= EXTEM MCE – FIBTEM MCE (Solomon et al. 2015).

Chi-square (X^2) was used to evaluate associations of categorical variables with unfavorable neurological outcomes and DCI. The biomarker data was distributed non-normally in most biomarkers, so the descriptive data of biomarker levels were presented as median with IQR with 95% CI, age as mean with SD. The association of biomarker levels and neurological outcome was evaluated using the Mann-Whitney U-test at admission, PBD 2-3, PBD 4-5, PBD 7-8, and PBD 11-12.

Maximal D-dimer levels were selected to a multivariate logistic regression model based on the findings in the time-series analysis to identify whether it was an independent predictor of unfavorable neurological outcomes. Other selected factors for multivariate analysis (age, WFNS, Fisher grade) were chosen based on statistical significance in univariate logistic regression analysis for plausible risk factors for unfavorable neurological outcomes.

The Cox proportional hazard model was used to calculate the temporal association of biomarkers to DCI. The temporal resolution in this study was one day. Missing daily values were imputed by replacement with the previous existing value, and the event column is defined as positive on the first instance of a DCI

event. The temporal association of the biomarkers to the first DCI event was evaluated by hazard ratios for each biomarker.

Statistical analyses were performed using R version 4.2.1 (The R Foundation, Vienna, Austria) or Python version 3.10.6.

4.4 Ethical aspects

4.4.1 Studies I and II

The study design was approved by the local ethics committee of Pirkanmaa (approval no. R115508S). No informed consent was required because only medical records were used to collect data. Anonymized data were used for analysis.

Study II utilized blood samples collected on a clinical need during the 14-day study period.

4.4.2 Study III

The study was approved by the local ethics committee of Pirkanmaa (approval no. R18110) and the study was registered in the ClinicalTrials.gov database (ClinicalTrials.gov, NCT03985176). The study was conducted in accordance with the amended Declaration of Helsinki. All patients or their next of kin provided written informed consent, and electronic consent from next of kin was utilized (if necessary) from November 2020 onwards.

The blood samples were obtained from an arterial line already in place during the ICU stay and from vene-puncture during ward stay. Ward samples are taken at the same time routine samples are drawn. A total of approximately 110 ml of blood was taken during the study period. This amount of blood can be considered insignificant.

A compression ultrasound of the lower extremities, a non-invasive procedure with minimal complication risk, was performed once during the study period. The treating physician was informed if a DVT was detected, and the treatment was started accordingly.

EEG monitoring was placed after written consent and securing of the aneurysm. EEG-monitoring is non-invasive and complication risks mainly involve irritation of the skin on the patient's scalp.

5 RESULTS

5.1 Studies I and II

A total of 439 consecutive patients with aSAH admitted to the ICU were evaluated, of whom 99 patients were excluded. Figure 3 illustrates the study flowchart.

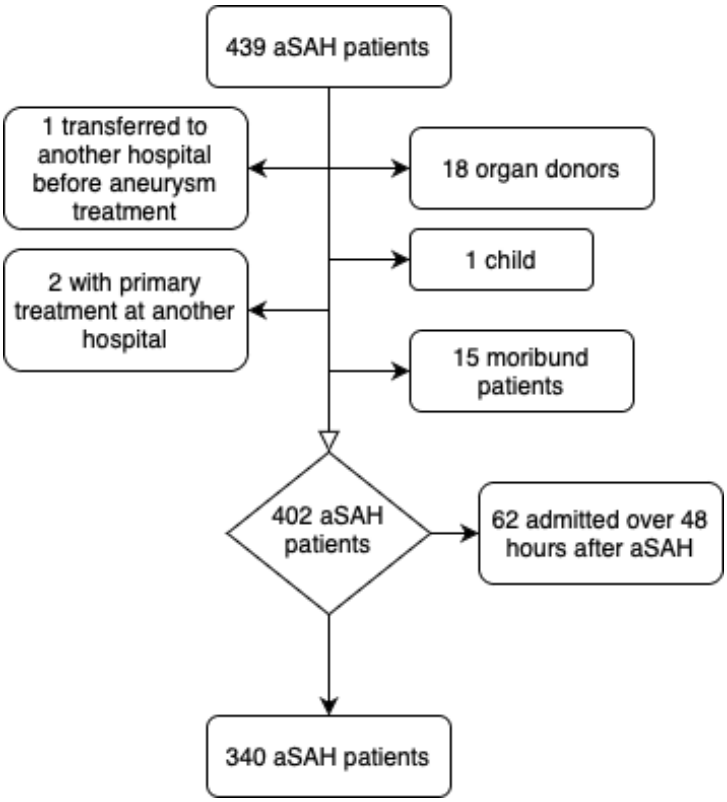


Figure 3. Flowchart of the study (studies I and II)

Table 10 shows the baseline characteristics of the study population.

Table 10. Baseline characteristics of the study population for studies I and II

	DCI (n=126)	%	No DCI (n=214)	%	p-value
Mean age, years (SD)	55.7 ± 12.7		56.8 ± 12.2		0.5
Gender					
Male	47	37.0	87	40.7	0.6
Female	79	62.7	127	59.3	
Aneurysm location					
Anterior circulation	105	83.3	170	79.4	0.5
Posterior circulation	21	16.7	44	20.6	
Treatment modality					
Surgical clipping	58	46.0	101	47.2	1.0
Endovascular coiling	58	46.0	96	44.9	
Endovascular stent-assisted coiling	10	7.9	17	7.9	
Anti-platelet medication*					
Aspirin	10	100.0	17	100.0	0.7
ADP receptor inhibitors	10	100.0	17	100.0	
Glycoprotein IIb/IIIa inhibitors	8	80.0	12	70.6	
Hunt and Hess scale					
Grade 1–3	80	63.5	150	70.1	0.3
Grade 4–5	46	36.5	64	29.9	
Fisher scale					
Grade 1–2	6	4.8	20	9.3	0.2
Grade 3–4	120	95.2	194	90.7	
Glasgow Outcome Scale at discharge					
Score 1–3	84	66.7	92	43.0	<0.001
Score 4–5	42	33.3	122	57.0	

*only in stent-assisted coiling patients

Abbreviations: DCI, delayed cerebral ischemia; SD, standard deviation;

ADP, adenosine diphosphate

The DCI criteria as defined by the 2010 consensus definition were met in 126/340 patients (37.1%) during the 14-day observation period. The interval from the primary ictus to DCI was 97 hours (IQR 68-151 hours). Most patients (113/126, 89.7%) who fulfilled the DCI criteria did so by neurological deterioration (i.e., decline in GCS score, new focal deficit, or both). Neuroradiological imaging was the

basis of DCI criteria fulfilment in 13 patients. Fulfilment of the DCI criteria was not associated with the H&H grade, Fisher score, aneurysm location, treatment modality or sex (Table 8).

DCI, age, the Fisher score, and the H&H grade showed significant (all $p<0.001$) associations with unfavorable neurological outcomes when analyzed using univariate binary logistic regression. The same variables were also independent risk factors in multivariate analysis, Table 11.

Table 11. Predicting an unfavorable neurological outcome using binary logistic regression. * p<0.001

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
DCI						
yes	2.65	1.69–4.22	*	3.23	1.90–5.60	*
no	1			1		
Age (years)	1.06	1.04–1.08	*	1.06	1.04–1.08	*
Sex						
Male	1.26	0.81–1.95		1.65	0.98–2.83	
Female	1			1		
Hunt and Hess scale grade						
4–5	6.46	3.83–11.26	*	5.8	3.30–10.59	*
1–3	1			1		
Fisher scale score						
3–4	6.66	2.48–23.17	*	4.4	1.43–17.43	*
1–2	1			1		
Aneurysm location						
Anterior circulation	1.13	0.66–1.95		1.33	0.70–2.56	
Posterior circulation	1			1		
Treatment modality						
Endovascular	1.14	0.75–1.75		1.21	0.72–2.05	
Surgical	1			1		

Abbreviations: CI, confidence interval; DCI, delayed cerebral ischemia; OR, odds ratio.

The mean platelet count reached a minimum on day 3 after the ictus in both the DCI and no-DCI-groups ($196 \pm 51.7 \times 10^9$/l vs. $196 \pm 50.4 \times 10^9$/l), then increased to exceed the count at admission after PBD 6. The mean platelet count was slightly higher in the no-DCI group on PBD 14, but the difference was not significant

(p=0.2). The platelet count was not significantly different between the groups at any day during the 14-day observation period. There was no time-dependent association of daily platelet count and DCI (HR 1.00; 95% CI 1.00-1.00). There was no time-dependent association of platelet count and DCI when considering the platelets' circadian rhythm (HR 1.00; 95% CI 1.00-1.00).

There was a significant difference in the mean platelet count PBD 9 between the endovascular coiling without stent assistance (273 ± 83.5 x 10^9/l), stent-assisted coiling (304 ± 52.7 x 10^9/l) and surgical clipping (308 ± 80.6 x 10^9/l) groups (p=0.020). However, only 180 (52.9%) patients had platelet count data on PBD 9. The DCI incidence did not differ significantly between the treatment modalities (stent-assisted coiling 37.0% vs. coiling without stent assistance 37.7% vs. surgical clipping 36.5%). There was a significant decline in platelet count on PBD 1 and 2 in patients with severe aSAH ($p<0.05$), but this was not seen on other days. The patients with a favorable neurological outcome had significantly higher platelet counts on PBD 1-6 compared to the patients with an unfavorable outcome ($p<0.05$).

5.2 Study III

Sixty aSAH patients were included and 124 patients were excluded (Figure 4) in this study after evaluating 184 patients.

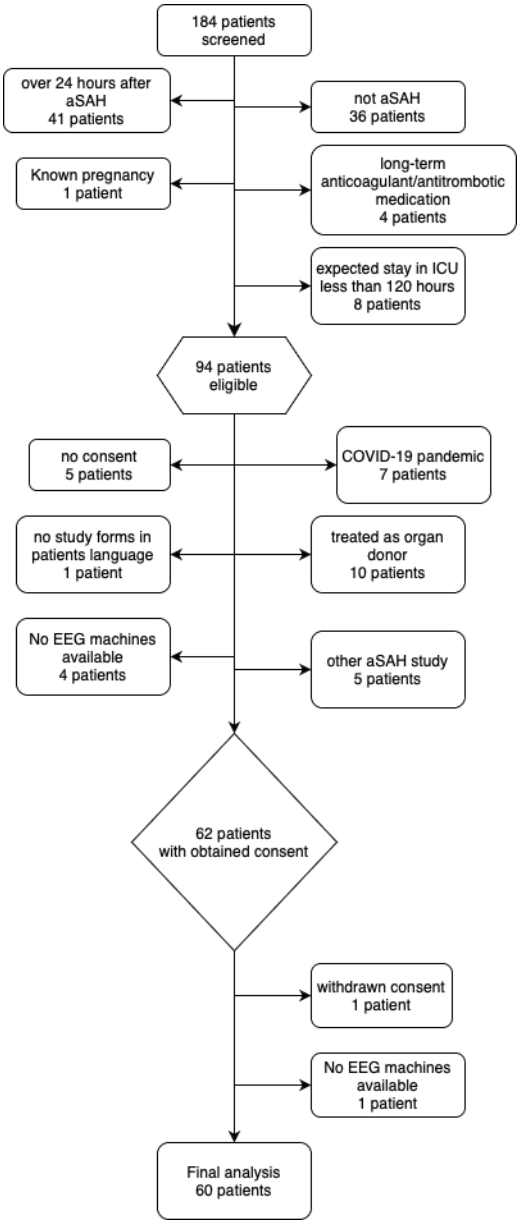


Figure 4. Flowchart of the study (study III)

Table 12 shows the baseline characteristics of the study population.

Table 12. The baseline characteristics of the study population of study III

	TOTAL		DCI		NO DCI	
	n=60	%	n=25 (41.7%)	%	n=35 (58.3%)	%
Mean age, years, ±SD, range	59.1 ± 14.1 (31–82)		57.5 ± 15.7 (31–78)		60.2 ± 12.9 (32–82)	
Female	47	78.3	18	72.0	29	82.9
Hypertension	21	35.0	9	36.0	12	34.3
Diabetes	5	8.3	1	4.0	4	11.4
Low-dose aspirin	4	6.7	2	8.0	2	5.7
Smoking						
Yes	20	33.3	8	32.0	12	34.3
No	22	36.7	9	36.0	13	37.1
unknown	18	30.0	8	32.0	10	28.6
Fisher scale						
3	31	51.7	11	44.0	20	57.1
4	28	46.7	14	56.0	15	42.9
Hunt&Hess scale						
1–3	37	61.7	14	56.0	23	65.7
4–5	23	38.3	11	44.0	12	34.3
WFNS scale						
1–3	33	55.0	12	48.0	21	60.0
4–5	27	45.0	13	52.0	14	40.0
Aneurysm location						
Anterior circulation	44	73.3	21	84.0	23	65.7
Posterior circulation	16	26.7	4	16.0	12	34.3
Treatment modality						
Endovascular	38	63.3	20	80.0	18	51.4
Stent-assisted coiling	8	13.3	2	8.0	6	17.1
Surgical	13	21.7	3	12.0	10	28.6
No treatment	1*	1.7	0	0	1	2.9
Neurological outcome at hospital discharge						
GOSe 1–4	28	46.7	13	52.0	15	42.9
GOSe 5–8	32	53.3	12	48.0	20	57.1
Venous thromboembolism						
DVT	7	11.7	2	8.0	5	14.9
Superficial venous thrombosis	3	5.0	2	8.0	1	2.9
PE	2	3.3	1	4.0	1	2.9

* one patient had a thrombosed aneurysm that was not treated because of the patient's poor neurological status

Abbreviations: DCI, delayed cerebral ischemia; GOSe, Glasgow Outcome Scale extended; SD, standard deviation; DVT, deep vein thrombosis; PE, pulmonary embolus; WFNS, World Federation Neurosurgical score

All patients had severe bleeds (Fisher scale 3-4) and DCI defined according to the 2010 consensus criteria was diagnosed in 24 (41.7%) of patients. Favorable neurological outcome (GOSe 5-8) at three months was achieved in 32 (53.3%) of patients, mortality at 90 days was 20.0%. VTE incidence was 20.0%. The H&H grade, Fisher scale score, WFNS score, and aneurysm location were not associated with the fulfillment of the DCI criteria. An unfavorable outcome was associated with H&H grade, Fisher scale score and WFNS score, but not DCI.

EXTEM-MCF was 63.0 mm (IQR 60.0-65.0 mm) at admission in the whole cohort, reaching its maximum of 70.5 mm (IQR 68.0-74.0 mm) on PBD 11-12. FIBTEM-MCF was 14.0 mm (IQR 10.8-16.5 mm) at admission, reaching its maximum of 23.0 mm (IQR 17.0-26.0 mm) on PBD 4-5. The platelet count first declined on PBD 2-3, then reached values higher than admission from PBD 7-8. Platelet MCE was 153.7 mm (IQR 132.2-165.3 mm) at admission and reached its maximum 209.9 mm (IQR 188.6-248.1 mm) on PBD 11-12.

None of the analyzed ROTEM parameters (i.e., EXTEM-MCF, EXTEM-CT, EXTEM-CFT, FIBTEM-MCF, FIBTEM-CT) or D-dimer were associated with DCI at any of the studied time points when analyzing associations with DCI.

An unfavorable neurological outcome (GOSe 1-4) was associated with EXTEM-CFT on PBDs 4-5 and 7-8, with values significantly lower in patients with an unfavorable outcome (unfavorable 78 s [IQR 68.0-96.0 s] vs. favorable 89.5 s [IQR 80.2-102.8 s], $p=0.02$ and 70.0 s [IQR 60.0-83.0 s] vs. 81.5 s [IQR 73.0-88.0 s], $p=0.02$, respectively). Patients with an unfavorable neurological outcome had a significantly higher FIBTEM-MCF on PBD 4-5 (25 mm [IQR 20.0-27.0 mm] vs. 20.0 mm [IQR 17.0-25.0], $p=0.04$), PBD 7-8 (26.0 mm [IQR 21.0-29.0 mm] vs. 21.5 mm [IQR 19.8-26.0 mm], $p<0.05$), and PBD 11-12 (28.0 mm [IQR 20.0-33.0 mm] vs. 21.0 [IQR 18.0-26.0 mm], $p=0.03$). Platelet MCE was not associated with an unfavorable neurological outcome at any of the studied time points.

D-dimer was associated with unfavorable neurological outcomes at all studied time points ($p<0.05$), with patients with unfavorable outcomes having higher D-dimer values. The platelet count was associated with unfavorable neurological outcomes on PBD 2-3 and PBD 4-5 ($p=0.04$ and $p=0.02$, respectively), with patients with an unfavorable outcome having lower platelet values than those with a favorable outcome at all studied time points.

Independent risk factors for unfavorable neurological outcomes identified in multivariate analysis were the maximum D-dimer OR 1.45 (95% CI 1.08–2.07) and Fisher scale grade OR 4.34 (95% CI 1.07–21.13).

6 DISCUSSION

6.1 Fulfillment of the 2010 DCI consensus criteria in studies I, II and III

Studies I and II evaluated the 2010 international panel of experts' consensus definition of DCI was evaluated in a large retrospective cohort of aSAH patients. Study III utilized the DCI consensus criteria in a prospective cohort of 60 aSAH patients. The incidence of DCI was high in both patient cohorts: 37.1% of patients in studies I and II and 41.7% in study III fulfilled the DCI criteria.

The incidence of DCI was high in both cohorts compared to previous literature in which the incidence has ranged from 11 to 57% in patients (van der Steen et al. 2019), with the most commonly reported incidence being approximately 30% (Macdonald 2012; Rowland et al. 2012).

The median time from aSAH ictus to DCI occurrence was 97 hours in studies I and II. Assessment of focal deficits in patients is usually relatively simple, especially if deficiencies are clear (e.g., hemiparesis). Assessment is more difficult if the patient is not cooperating or is in a state of altered consciousness. GCS decline was the sole criterion for DCI criteria fulfillment in 7.9% of patients in studies I and II. However, GCS decline led to the fulfillment of DCI criteria in 17/24 (70.8%) patients in study III. aSAH patients have mild fluctuations of the GCS score commonly in the ICU environment; agitation and delirium are also common in aSAH patients leading to fluctuation of consciousness (Reznik et al. 2018). Using the GCS score to assess consciousness is prone to interrater variability (Reith et al. 2016), and the GCS score is unreliable in intubated patients (Kornbluth and Bhardwaj 2011).

The 2010 consensus statement recommends that neuroradiological imaging should be performed between 24 and 48 hours after treatment of the aneurysm to rule out possible iatrogenic brain lesions (Vergouwen et al. 2010). Neuroradiological imaging was performed based on a clinical need in all three studies included in this thesis. A radiologist reviewed all the neuroradiological imaging performed on patients in study III to determine whether possible infarctions were related to the aSAH itself, neurosurgical procedures, or DCI. None of the DCI criteria fulfillments in study III are from an infarction in neuroradiological imaging, whereas 27/60

(45%) of patients had infarctions identified in neuroradiological imaging that were radiologically seen to be related to the aSAH or neurosurgical procedure. It can be argued that it can complicate the assessment of the etiology of the infarctions when neuroradiological imaging is not performed systematically. However, because aSAH patients are usually younger, the effect of radiation exposure during CT imaging must be taken into consideration. The most widely used CTA imaging technique, helical mode, does not support acquisition of CT perfusion images at the same time but instead requires a separate imaging to acquire perfusion images (Smith et al. 2022). The patient also requires contrast for these imaging modalities, and although the risk for a single dose of contrast to cause kidney failure is low, it needs to be noted that aSAH patients usually require multiple exams and contrast administrations during their hospitalization (Smith et al. 2022). Increased imaging could also lead to discovery of asymptomatic cerebral infarctions (when patients have no symptoms relating to the infarction), which could lead to treatment with induced hypertension and vasoactive drug use to reach this higher MAP target, especially if some sort of penumbra is seen in perfusion imaging. Induced hypertension, especially using vasoactive drugs, is not without complications, because high blood pressure has been linked with increased cardiac- and kidney-related complications (Gathier et al. 2018).

The Vergouwen et al.'s report recommendations is to use serial MRI and magnetic resonance angiogram scans in the follow-up of aSAH patients (Vergouwen et al. 2010). This could probably lead to a clearer knowledge of the amount and size of infarctions in aSAH patients but would lead to a large increase in the demand for MRI scans, which it is not feasible without an increase in MRI resources.

6.2 Predictors of DCI and unfavorable neurological outcomes

Study I found the fulfillment of the DCI criteria to be a robust and independent risk factor for an unfavorable neurological outcome (GOS 1-3) at hospital discharge. Studies I and III also found other well-known risk factors for an unfavorable neurological outcome identified previously, such as the H&H grade, the Fisher score and increasing age (Galea et al. 2017; van Donkelaar et al. 2017; Rubbert et al. 2018; Zafar et al. 2018). The treatment modality or use of anti-platelet drugs (used after stent-assisted coiling) were not associated with DCI in study II.

Meeting the DCI consensus criteria during the first 14 days after aSAH made patients prone to an unfavorable neurological outcome at hospital discharge. A large

registry-based study previously reported similar results; however, a detailed description of the DCI diagnosis was missing (Galea et al. 2017).

The high H&H grade and Fisher scores were prognostic for an unfavorable neurological outcome in studies I and III, but the H&H grade and Fisher score were not associated with the fulfillment of the 2010 consensus criteria. The Fisher scale, modified Fisher scale, and Hijdra sum scores were found to be associated with DCI in a previous systematic review (van der Steen et al. 2019). Most of the studies evaluated in this review utilized definitions other than the 2010 consensus definition. Thus, it seems that the DCI definition affects how it is associated with scales representing the severity of EBI (i.e., H&H and Fisher scales). The Fisher scale was developed in the 1980s and used to predict angiographic vasospasm from how much blood is visualized on the initial head CT scan (Fisher et al. 1980). The consensus definition does not require angiographic vasospasm for the DCI diagnosis to be made, which could explain the weaker association between the Fisher score and DCI. It also needs to be noted that all the patients were graded 3 or 4 on the Fisher scale in study III, probably at least partly because the imaging quality increase in head CT scans has been tremendous since the 1980s.

Treatment modality was not associated with DCI in study II. The ISAT trial compared DCI incidence between patients treated with endovascular coiling and surgical clipping and found the odds of DCI were 25% higher in the surgical group (95% CI, 1.01-1.51) (Dorhout Mees et al. 2012).

The use of anti-platelet medications has been suggested to reduce the risk of DCI by preventing microclot formation (Dorhout Mees et al. 2007a; Nagahama et al. 2018; Darkwah Oppong et al. 2019; Sun et al. 2020; Dienel et al. 2021; Ditz et al. 2021), although the use of anti-platelet therapy was not associated with a reduced incidence of DCI in study II. Previous studies regarding DAPT have been conflicting, with DAPT (ASA + clopidogrel/ticagrelor) not associated with reduced DCI (Dorhout Mees et al. 2012; Wallace et al. 2020) and DAPT (ASA + clopidogrel) lowering the incidence of DCI (Sun et al. 2020). A recent review suggested two main reasons for the lack of clinical benefit from anti-platelet agents: 1) difficulty in predicting which patients develop DCI and 2) lack of understanding of the DCI mechanisms (Dienel et al. 2021). Several studies reported more frequent bleeding complications after DAPT (Dorhout Mees et al. 2012; Wallace et al. 2020). Comparison of studies was again hindered by the various DCI definitions.

6.3 The correlation of the platelet count to DCI and unfavorable neurological outcomes

Study II evaluated the association of the absolute platelet count and change in platelet count with DCI, and neither was associated with DCI incidence when defining DCI according to the 2010 consensus criteria. Significantly, patients with an unfavorable neurological outcome (GOS 1-3) had a lower platelet count on PBD 1-6 than patients with a favorable outcome; lower platelet counts on PBD 1 and 2 were also found in patients with severe aSAH on initial computed tomography (Fisher grade 3-4). Study III found that the platelet count was associated with unfavorable neurological outcome (GOSe 1-4) on PBDs 2-3 and 4-5, with the patients with an unfavorable outcome having lower platelet counts.

Previous studies on aSAH patients found the platelet count increased compared with baseline during the development of DCI (Kasius et al. 2010), while Hirashima et al. found that platelet consumption (i.e., the ratio of the lowest platelet count and the admission count greater than 0.7) was an independent risk factor for symptomatic vasospasm (Hirashima et al. 2005). Schebesch et al. performed a study with a protocol similar to Hirashima et al.'s, but no association between the platelet count and symptomatic vasospasm or clinical outcome was found in a Caucasian population (Schebesch et al. 2007). They postulated that genetic differences between Asians and Caucasians were responsible for the discrepancy (Schebesch et al. 2007). Rzepliński et al. found no association between the platelet count and DCI when defining DCI according to the 2010 consensus definition (Rzepliński et al. 2021).

The hemostatic system has been found to show a significant circadian variation, with platelet counts typically increasing in the afternoon (Montagnana et al. 2009). Study II showed that there was no time-dependent association with the daily platelet count and DCI when considering the circadian rhythm. Platelet variability between subjects seems to be greater than the variability within subjects.

Platelet counts in both studies II and III were found to be associated with unfavorable neurological outcomes: in study II on PBD 1-6 and in study III on PBDs 2-3 and 4-5. Kasius et al. found no association between platelet counts and neurological outcome using the mRS as an outcome measure (Kasius et al. 2010). Rzepliński et al. found no association with the platelet count and neurological outcome (measured with mRS) or 90-day mortality (Rzepliński et al. 2021)

Study II showed that patients with more severe (Fisher 3-4) aSAH had significantly lower platelet counts than patients with non-severe (Fisher 1-2) aSAH. However, only 26 patients made up the group of non-severe aSAH. Previous studies

have, however, reported similar findings. Rzepliński et al. reported lower platelet counts in patients with Fisher grade 3-4 aSAH compared to patients with Fisher grade 1-2 aSAH (Rzepliński et al. 2021). This could possibly be a result of platelet consumption due to the more severe bleed, with Rzepliński reporting the platelet count to correlate with the volume of hemorrhage (Rzepliński et al. 2021).

6.4 The correlation of D-dimer to DCI and unfavorable neurological outcomes

Study III found no association between D-dimer and DCI was found. However, D-dimer was associated with unfavorable neurological outcomes (GOSe 1-4) at all studied time points with patients with an unfavorable outcome having higher D-dimer levels.

D-dimer was not associated with DCI in the study III cohort. Previous studies have had mixed results when studying associations between D-dimer and DCI. Juvela et al. found significantly higher D-dimer levels in patients who had DCI than those who did not; however, DCI or permanent ischemic lesions visible on imaging were not independently predicted with D-dimer (Juvela and Siironen 2006). Other studies found that D-dimer was elevated from the baseline, but did not predict DCI (Ameriso et al. 1992) and that even though D-dimer positively correlated with WFNS, it did not predict the occurrence of cerebral infarcts (DCI was not reported on as such) (Ilveskero et al. 2005). Patients with DIND (defined as both the clinical neurological deterioration and the presence of an ischemic area on imaging responsible for the deterioration) had higher D-dimer values on PBD 3 and PBD 14 than those without DIND (Fujii et al. 1997). Poor study quality and a small number of studies lead a systematic review to show a weak level of association of D-dimer and DCI, although patients with DCI were shown to have a higher plasma level of D-dimer on PBD 11 to 14 compared to patients without DCI (Boluijt et al. 2015), and no such findings were seen in this cohort.

The D-dimer was found to be associated with poor neurological outcome at all studied time points in study III. This finding is in line with previous studies. Higher D-dimer on the first postoperative day and at hospital discharge was associated with a poor neurological outcome (Juvela and Siironen 2006), and higher D-dimer values were found in non-surviving patients (Lauridsen et al. 2019). Ilveskero et al. found D-dimer was associated with a poor outcome (measured with GOS) at all four measured points during the 10-day study period and additionally that enoxaparin

used as thromboprophylaxis was not sufficient to down-regulate D-dimer generation (Ilveskero et al. 2005).

Overall, the D-dimer is a non-specific marker of thrombosis with levels being raised due to age, trauma, surgery, VTE, etc. Study III's cohort had a 20% incidence of VTE, which is high compared to the previous literature in which incidence in a doppler-screened cohort of aSAH patients was 4.5% (Mack et al. 2008). Studies utilizing ROTEM and TEG in VTE patients have been conflicting, with some showing no differences between normal controls and patients with VTE (Lim et al. 2019), while a large systematic review in orthopedic trauma patients indicated that MA>65 mm is an independent predictor of developing VTE (Brown et al. 2020).

6.5 The correlation of ROTEM parameters to DCI and unfavorable neurological outcomes

None of the studied ROTEM parameters were associated with DCI in study III, and EXTEM-CFT was associated with poor neurological outcomes on PBDs 4-5 and 11-12, FIBTEM-MCF on PBDs 4-5, 7-8 and 11-12. The platelet MCE was not associated with unfavorable neurological outcomes at any of the studied time points.

Patients who developed DCI had a slightly higher FIBTEM-MCF, although it was without statistical significance. No association was found between DCI and FIBTEM-MCF. This is in contrast with previous ROTEM studies in which FIBTEM-MCF was significantly greater in patients with DCI compared to patients without DCI when measured early after aSAH ictus (Lauridsen et al. 2019; Vahtera et al. 2019b). Frontera et al. had a similar result: A higher MA (in TEG) led to a higher likelihood of DCI later during hospitalization (Frontera et al. 2017). Ramchand et al. found no significant difference in the occurrence of DCI when comparing patients with high and low MA. Prospective assessment of DCI criteria fulfillment was only performed in this study; Vahtera et al. (Vahtera et al. 2019a) did use the consensus criteria, but analyzed their DCI data retrospectively. Ramchand et al. (Ramchand et al. 2016) used a vasospasm-based definition of DCI, while Frontera et al. defined DCI as a clinical neurological deterioration but also required evidence of vasospasm in imaging or an infarction due to vasospasm detected in imaging (Frontera et al. 2017).

The length of follow-up also varied, whereas Lauridsen et al. (Lauridsen et al. 2019), Frontera et al. (Frontera et al. 2017) and Vahtera et al. (Vahtera et al. 2019a)

focused on the 72 hours after ictus. Study III continued ROTEM measurements up to PBD 12 covering the typical onset period of DCI.

Study III showed that in the cohort of aSAH patients, all patients are in a state of increased blood coagulation, but the patients with an unfavorable neurological outcome are more coagulable than those with a favorable outcome. Previous studies have also shown this state of increased blood coagulation and fibrinolysis (Peltonen et al. 1997; Ramchand et al. 2016; Lauridsen et al. 2019). The increased blood coagulation in this cohort is shown by higher FIBTEM-MCF and shorter EXTEM-CFT. The increase in platelet contribution to clot strength is also seen in the rise of platelet MCE during the study period. Increased fibrinolysis is shown by higher D-dimer. The rise in FIBTEM-MCF levels signifies an increase in fibrin formation and polymerization, which are essential contributors to clot strength. An association between higher FIBTEM-MCF levels and unfavorable neurological outcomes was seen on PBDs 4-5, 7-8, and 11-12. Patients with an unfavorable outcome have stronger clots (measured with FIBTEM-MCF), formed in a shorter time (measured by EXTEM-CFT) and platelet contribution to clot formation is greater (measured by platelet MCE)., Ramchand et al. previously found that patients with a poor outcome (mRS≥3) had a significantly elevated MA in the 10-day study period and a higher G (representing clot strength) on day 10, with a higher MA being an independent predictor for a poor outcome in multivariate regression analysis (Ramchand et al. 2016). Frontera et al. also found a trend for an association of higher MA and worse outcome (mRS), but their findings lacked statistical significance (Frontera et al. 2017). No association was found between platelet MCE and DCI (Lauridsen et al. 2019; Vahtera et al. 2019a) or mortality (Lauridsen et al. 2019) in previous studies.

6.6 The 2010 consensus definition of DCI

The 2010 consensus definition of delayed cerebral ischemia is the product of an international ad hoc panel of experts who, through a consensus building approach, proposed a definition of DCI to be used as an outcome measure in clinical trials and observational studies (Vergouwen et al. 2010). The panel consisted of experts from different disciplines (neurology, neurosurgery, interventional neuroradiology and neurocritical care), with a description of this consensus building described in the report by Vergouwen et al. (Vergouwen et al. 2010). The authors state that, although based on past aSAH research and as such having a scientific basis, the preference for

some of the terms used in the definition is based on their subjective judgements (Vergouwen et al. 2010). The consensus definition in the Vergouwen et al. report is divided into two parts: 1) clinical deterioration due to DCI and 2) cerebral infarction, with the authors suggesting that clinical deterioration should only be a secondary measure of outcome and speculating that the attribution of clinical deterioration to the occurrence of DCI is subjective (Vergouwen et al. 2010).

Zafar et al. aimed to clarify the consensus definition and thus came up with three DCI classifications: 1) delayed cerebral infarction (infarction seen on imaging), 2) DIND type 1 (defined as focal neurologic decline) and 3) DIND type 2 (a global decline in arousal), with clearly listed exclusion criteria for the DCI diagnosis (Zafar et al. 2016). They studied the inter-rater reliability of this clarified definition of DCI retrospectively and found an excellent overall agreement regarding the presence or absence of any of the three DCI classifications (Zafar et al. 2016). However, there was only moderate agreement on the DIND type 1 events (kappa value, κ=56.58%) and DIND type 2 events (κ=48.66%) (Zafar et al. 2016). Contrary to the recommendation of the original Vergouwen et al consensus criteria for DCI, Zafar et al. found that clinical episodes of DIND were more reliably diagnosed than radiological DCI, but even at its best, the inter-rater agreement is only moderate (Zafar et al. 2016). Confounding effects of sedated and intubated patients as well as patients with poor baseline examinations (leading to hard-to-detect changes in clinical status) can lead to disagreement among raters, as does applying the complex exclusion criteria (Zafar et al. 2016).

This high incidence of DCI in both cohorts, and most DCI criteria fulfillments being from neurological decline solely in study III, could reflect the oversensitivity of the 2010 consensus criteria. However, the DCI incidence is mostly based on the literature that uses varying definitions of DCI. It remains to be seen whether this higher incidence is a true finding, or merely mirrors the oversensitive criteria.

The Full Outline of UnResponsiveness (FOUR) score is equivalent to or even superior to GCS in predicting outcomes after traumatic brain injury (Zeiler et al. 2017). The FOUR score can be assessed in all patients, especially those unable to verbally communicate, because it provides a structured objective scoring for aspects of brainstem function (Zeiler et al. 2017). The FOUR score has been studied in the aSAH patient population, and the admission FOUR score was better at predicting the one and six month mortality (AUC 0.762, p=0.009 and AUC 0.823, p=0.004, respectively) compared to all other admission scoring systems (GCS, H&H, Fisher, WFNS) (Zeiler et al. 2017). The PBD 7 FOUR score was associated with GOS at one and six months in addition to mortality; the PBD 14 score was associated with

GOS at six months (Zeiler et al. 2017). The FOUR score has showed excellent inter-rater agreement scores (Kramer et al. 2012); in fact, the inter-rater agreement surpasses that of the GCS (Zeiler et al. 2017). Perhaps substituting the GCS component of the 2010 consensus definition of DCI with a FOUR score component could help to alleviate the problems seen with the GCS score?

6.7 Studied blood coagulation markers and their correlation to DCI and unfavorable neurological outcomes

None of the studied blood coagulation markers were found to be associated with DCI in studies II and III. However, the results from studies II and III show that all the studied blood coagulation markers are associated with an unfavorable neurological outcome. Previous studies have had mixed results, as discussed in previous chapters. The interpretation of previous results has been complicated with varying definitions of DCI, while the results in study III may have been muddled with DCI criteria that are possibly oversensitive. The oversensitive DCI criteria possibly led to the higher incidence of DCI, with the association with outcomes reflecting the true findings. Thus, more prospective studies are needed, especially utilizing ROTEM, to show whether there is, in fact, an association of coagulation markers with DCI.

6.8 Limitations

These studies have some limitations that need to be addressed.

6.8.1 Studies I and II

First, the studies were based on the same retrospective population from a single center: Although a fairly large cohort, it still limits the generalizability of the results. However, patients from only one center does reduce the bias from interpreting the DCI criteria. Second, some of the known risk factors for DCI (e.g., smoking) could not be included in the logistic regression analysis because of the study's retrospective nature. Third, neuroradiological imaging was only performed based on clinical need, which complicates the assessment of infarct etiology and can leave case

ascertainment open to interpretations. Fourth, platelet count data was unavailable for every patient on each day, because patients with better neurological status were discharged from the ICU and thus underwent less frequent laboratory testing. Fifth, data regarding patients' past medical history, previous use of antiplatelet drugs, bleeding events and platelet transfusions were unavailable. Sixth, platelet function testing was not performed because it is not a part of the aSAH treatment protocol in our hospital. Finally, the neurological outcome was assessed at hospital discharge, which hinders the conclusions about the long-term neurological outcome of patients.

6.8.2 Study III

First, the 2010 DCI consensus definition recommends using serial imaging with CT/MRI/digital subtraction angiography combined with clinical monitoring, but the imaging was performed on clinical need in this study. However, all neuroimaging done on study patients was reviewed by a radiologist to assess whether possible infarctions were due to neurosurgical procedures or DCI. Second, although effort was put into enquiring about smoking habits of patients, there is an unfortunate lack of smoking data in 30% of study patients. Third, the use of TXA in study patients was not recorded, most patients coming from further away in the catchment area probably received at least one dose. However, there is no clear guideline in place to guide TXA administration besides the international guidelines. Fourth, the results of multivariate regression analysis showing D-dimer levels during follow-up and higher Fisher scale grading to be the only risk factors for unfavorable neurological outcomes need to be interpreted with caution due to multicollinearity of the variables in the model. The cohort size was also found to be small for reliable multivariate models. The sample size was based on a previous ROTEM study, in which the sample acquirement was based on a slightly different schedule and although using the 2010 consensus definition of DCI, the DCI data were acquired retrospectively. Fifth, we could not assess the effect of treatment modality on the laboratory values, but the sample size was not calculated to make any conclusions from possible findings in this relation anyway.

6.9 Future perspectives

The neurological outcome of aSAH patients is impacted by the presence of DCI, which usually develops between 3 to 14 days after the onset of aSAH. Gaining a more thorough understanding of DCI pathophysiology could lead to treatment options in the future.

There now is a consensus definition of DCI for studies to use, but it is not without problems. The 2010 consensus definition of DCI in its current form may be too sensitive, especially as seen in study III. Future studies could see whether using the FOUR score instead of the GCS score in assessing global decline could lead to more consistent results.

Blood coagulation changes are seen in aSAH patients after ictus, but the relationship between these changes and the incidence of DCI is still unclear. Future studies with larger sample sizes are needed to evaluate this relationship. Other coagulation markers (e.g., TAT, thrombin generation) also need to be evaluated in an aSAH patient cohort in the future. Blood coagulation changes were not associated with DCI but were associated with unfavorable neurological outcomes in study III. The sample size proved too small for more complex multivariate analyses, so future studies with a larger sample size are needed to evaluate this relationship further.

7 CONCLUSIONS

The following conclusions can be drawn based on this thesis:

1. Fulfillment of the 2010 consensus criteria of DCI is an independent predictor of an unfavorable neurological outcome at hospital discharge.
2. The incidence of DCI observed is high compared to previous literature, possibly due to oversensitivity of the 2010 consensus criteria of DCI. Most patients fulfilling the DCI criteria did so with neurological decline (i.e., with a decline in GCS) in study III.
3. Platelet values in aSAH patients with unfavorable neurological outcomes are lower than those with favorable outcomes. Platelet values in severe bleeds showed a trend of being lower than in non-severe bleeds.
4. The treatment modality is not associated with DCI; neither is the use of anti-platelet therapy in patients treated with stent-assisted coiling.
5. aSAH patients with unfavorable neurological outcomes have higher D-dimer values; however, D-dimer is a non-specific marker of thrombosis with raised levels possible due to many factors, possibly partly because of the high incidence of VTE in study III.
6. aSAH patients are in a state of increased blood coagulation after ictus, shown with higher FIBTEM-MCF and shorter EXTEM-CFT in ROTEM. Patients with unfavorable neurological outcomes have stronger clots (measured with FIBTEM-MCF) formed in a shorter time (measured with EXTEM-CFT) and have a greater platelet contribution to clot strength (measured with platelet MCE).

8 ACKNOWLEDGEMENTS

This doctoral study was conducted in the Department of Anesthesiology and Intensive Care at Tampere University Hospital. The work would not have been possible without financial support from the Finnish Society of Anesthesiology, the Päivikki and Sakari Sohlberg foundation, the Finnish Society of Intensive Care, the research funding provided by the Tampere University Hospital and Tampere University Support Foundation, as well as the Competitive State Research Financing of the Expert Resposibility area of Tampere University Hospital.

First, I would like to extend my gratitude to my supervisors. Docent Anne Kuitunen, your support and guidance have been invaluable in helping me reach this important milestone in my academic journey. Professor Jukka Peltola, I thank you for valuable comments and help along the way.

Extra special thanks must be given to Doctors Annukka Vahtera and Heikki Kiiski, with whom many hours have been spent planning, discussing, and writing. You have given invaluable insights and support during this whole process; your constructive feedback has been critical in shaping my work and refining my ideas. Your willingness to read and provide feedback on my drafts, and your encouragement and motivation have been a source of strength throughout the journey. Your friendship and camaraderie have also made this experience a memorable one.

Docent Sari Karlsson and Doctor Ville Jalkanen for making sure that taking research leaves were possible to further one's academic goals alongside clinical work.

I would like to express my deepest appreciation to Docent Melissa Rahi and Doctor Teemu Luostarinen for their careful external review of my dissertation and constructive comments. I am very grateful for Docent Jussi Posti for honoring my work by being my opponent in my public defense of this dissertation.

To the team behind the SAV-DCI study, Marika Ala-Peijari, Jaakko Långsjö, Juhana Frösen, Eija Junttila, Maija Kalliomäki and study nurses Sanna Ristimäki, Sanna Mäkinen and Helka Tervas, I am truly grateful for your contributions and support during the study process.

To co-authors Antti Ronkainen and Liisa Pyysalo, thank you for your valuable comments and suggestions to my manuscripts.

Heini Huhtala, I am very grateful for your insights into the statistics of my research, no question was too dumb to ask.

To my colleagues at the ICU of Tampere University Hospital, thank you for your support in making studies like this possible, for keeping in mind all the ongoing studies on top of all the other things going on. Thank you to all the other colleagues at the Anesthesiology department who participated in the recruitment of study patients.

I am also very grateful for the group of friends from medical school, Kati, Sylvia, Eeva-Kaisa and Kerttu, who have managed to get together more or less often despite busy schedules to this day.

Finally, my family, my mum Ulla, and my sister Tiina, thank you for your support in this project and unconditional belief in me. I am also grateful for the support and guidance of my late father who unfortunately never got to see the finished dissertation.

Nokia, February 2023

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PUBLICATIONS

PUBLICATION I

Prognostic value of the 2010 consensus definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

Raatikainen E., Vahtera A., Kuitunen A., Junttila E., Huhtala H., Ronkainen A., Pyysalo L. & Kiiski H.

Journal of the neurological sciences, 2021, Vol.420, p.117261-117261
DOI: 10.1016/j.jns.2020.117261

Journal of the Neurological Sciences 420 (2021) 117261

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Prognostic value of the 2010 consensus definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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ARTICLE INFO

Keywords:
Aneurysmal subarachnoid hemorrhage
Outcome
Delayed cerebral ischemia
Intensive care unit

ABSTRACT

Background and purpose: Delayed cerebral ischemia (DCI) complicates the recovery of approximately 30% of patients with aneurysmal subarachnoid hemorrhage (aSAH). The definition of DCI widely varies, even though a consensus definition has been recommended since 2010. This study aimed to evaluate the prognostic value of the 2010 consensus definition of DCI in a cohort of patients with aSAH.

Methods: We conducted a single-center, retrospective, observational study that included consecutive adult patients with aSAH who were admitted to the intensive care unit from January 2010 to December 2014. DCI was evaluated 48 h to 14 days after onset of aSAH symptoms using the 2010 consensus criteria and outcome was assessed by the Glasgow Outcome Scale (GOS) at discharge from hospital.

Results: A total of 340 patients were analyzed and the incidence of DCI was 37.1%. The median time from primary hemorrhage to the occurrence of DCI was 97 h. Neurological deterioration was observed in most (89.7%) of the patients who fulfilled the DCI criteria. The occurrence of DCI was strongly associated with an unfavorable outcome (GOS 1–3) at hospital discharge (OR 2.65, 95% CI 1.69–4.22, $p < 0.001$).

Conclusions: The incidence of DCI after aSAH is high and its occurrence is strongly associated with an unfavorable neurological outcome. This finding adds to the previous literature, which has shown that DCI appears to be a major contributor affecting the functional ability of survivors of aSAH. To further advance reliable knowledge of DCI, future studies should adhere to the consensus definition of DCI.

1. Introduction

Despite advances in neurocritical care, aneurysmal subarachnoid hemorrhage (aSAH) remains a devastating disease with a 1-year mortality rate up to 50% [1]. Additionally, many survivors of aSAH struggle with neurological and psychosocial impairment [2]. Only 25% of survivors report a complete recovery [3]. A major contributor to a poor outcome is delayed cerebral ischemia (DCI), which complicates recovery in approximately 30% patients with aSAH [4]. The typical risk period for DCI is 3–14 days after onset of aSAH [4,5]. In part, DCI is a continuum of pathophysiological mechanisms that are initiated during early brain injury, which is usually defined as injury in the first 72 h after aSAH [6–8]. The specific pathophysiology of DCI is still incompletely understood, but it appears to be multifactorial. Ischemia from vasospasm in cerebral arteries is one of the mechanisms that causes DCI, but contrary to historical dogma, it is not the sole contributory factor [5]. Patients can deteriorate neurologically because of DCI without angiographic vasospasm [9] and they can also have angiographic vasospasm without DCI [10]. Other biochemical processes that might be involved in DCI include blood–brain barrier disruption, cerebral microthrombi, oxidative stress, and inflammation [4,5,11].

The terminology used for DCI varies, which makes comparison of studies challenging [12,13]. Increasing knowledge of the pathophysiology of DCI requires validation and standardization of definitions and

Abbreviations: DCI, delayed cerebral ischemia; aSAH, aneurysmal subarachnoid hemorrhage; GOS, Glasgow Outcome Scale.

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https://doi.org/10.1016/j.jns.2020.117261
Received 14 July 2020; Received in revised form 17 November 2020; Accepted 3 December 2020
Available online 7 December 2020

terminology of DCI. To address this problem of heterogeneity of definitions, an international panel of experts in aSAH developed and proposed a definition of DCI to be used as an outcome measure in future clinical trials and observational studies [12]. A recent preprint of a systematic review indicated a steady increase in publications referring to the 2010 consensus definition of DCI. However, the majority of cohort studies and clinical trials omitted the consensus definition [14].

Therefore, this study aimed to evaluate the prognostic value of the 2010 consensus definition of DCI using a large cohort of patients with aSAH.

2. Methods

2.1. Study design

We conducted a single-center, retrospective, observational study. The local ethics committee of Pirkanmaa approved the study design (approval no. R115508S). No informed consent was required because the data were retrospectively obtained from medical records.

The study population consisted of consecutive adult patients with aSAH who were admitted to the intensive care unit (ICU) of Tampere University Hospital from January 2010 to December 2014. Tampere University Hospital is one of five tertiary referral centers in Finland serving a population of approximately 1 million inhabitants. All patients requiring neurointensive care in the catchment area of Tampere University Hospital are treated at the Tampere University Hospital intensive care unit. All aSAH patients admitted to the Tampere University Hospital, unless deemed moribund, are initially treated in the ICU.

2.1.1. Selection of patients

The onset of symptoms associated with aSAH was registered from the patients' records. We excluded patients with an unknown time of onset of symptoms and those whose admission was longer than 48 h after the onset of symptoms. Additionally, patients who were admitted to the ICU solely on the basis of organ donation, and moribund patients with unsecured aneurysms were excluded. All patients received neurointensive care in accordance with a standardized in-house protocol on the basis of international multidisciplinary consensus guidelines [15,16].

2.1.2. Assessment of DCI

DCI was evaluated independently by 3 of the investigators (AK, AV, and ER) from the ICU database (Centricity Critical Care Clinisoft; GE Healthcare, Barrington, IL, USA) and electronic medical records at 48 h to 14 days from the onset of aSAH symptoms using the criteria defined by Vergouwen et al. [12] In case of any doubt, all investigators thoroughly evaluated the patient's history and a consensus decision was made. Accordingly, DCI was defined as follows: neurological deterioration and a reduction in the Glasgow coma scale (GCS) score by $\geq$2 points, which was sustained for longer than 1 h (within a 4-h window), a new focal neurological deficit, which lasted longer than 1 h, or a new ischemic episode on neuroimaging data that was not related to the primary aSAH or neurosurgery. The specific criteria for DCI-related infarction on neuroradiological imaging are shown in Supplementary Table I. The exclusion criteria for DCI were based on a previous study that focused on the interrater agreement in the diagnosis of DCI [13] and were as follows: rebleeding, intracranial cerebral pressure repeatedly >20 mmHg, acute hydrocephalus, acute metabolic abnormality, new infection, a seizure confirmed on electroencephalogram, association with sedative medication, and causality related to a neurosurgical procedure within 24 h. The detailed exclusion criteria are shown in Supplementary Table II. These exclusion criteria were evaluated from the ICU database and medical records. The data in the ICU database is gathered in a prospective manner during patient care.

2.1.3. Assessment of other clinical factors and neurological outcome

We collected the following information from the neurosurgical aneurysm database: Glasgow Outcome Scale (GOS) score [17], aneurysm location, treatment modality, Hunt and Hess scale grade [18], and Fisher scale score [19].

Neurological outcome was assessed with the GOS at discharge from hospital. The neurological outcome was further dichotomized as favorable (GOS scores: 4–5) and unfavorable (GOS scores: 1–3). The severity of aSAH in an initial head computed tomographic scan was evaluated by a neurosurgeon with the Fisher scale and the severity of early brain injury at hospital admission was assessed with the Hunt and Hess grading scale. The Fisher scale was dichotomized as non-severe (Fisher scores: 1–2) and severe (Fisher scores: 3–4). The severity of early brain injury at admission was dichotomized as mild (Hunt and Hess grades: 1–3) and severe (Hunt and Hess grades: 4–5).

2.1.4. Statistical methods

Age was normally distributed in our study population. Therefore, the *t*-test was used to test differences in age between patients with and without DCI. The associations of categorical variables and DCI were evaluated using the Pearson chi-square test. Binary logistic regression was used to evaluate associations of categorical variables and age with unfavorable neurological outcome in univariate analysis. A multivariate logistic regression model was created to identify independent predictors of unfavorable neurological outcome. All statistical analyses were performed using R version 3.6.3 (The R Foundation, Vienna Austria).

3. Results

A total of 439 consecutive patients with aSAH who were admitted to the ICU were evaluated and 99 patients were excluded (Fig. 1). The characteristics of the remaining 340 patients are shown in Table 1. The

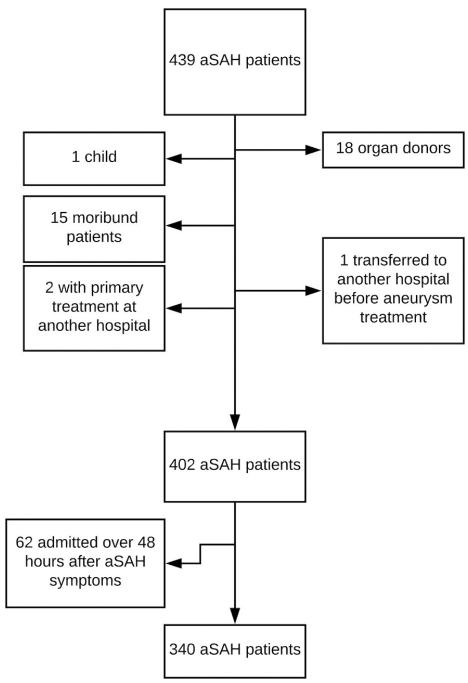

Fig. 1. Flowchart of the study.
A total of 439 consecutive patients with aSAH who were admitted to Tampere University Hospital intensive care unit between January 2010 and December 2014 were evaluated, and 99 patients were excluded.

Table 1
Demographics and baseline characteristics of the study population.

Variable	DCI ($n = 126$)	%	No DCI ($n = 214$)	%	p value
Mean age, years (± SD)	55.7 ± 12.7		56.8 ± 12.2		0.474
Sex					
Male	47	37.0	87	40.7	0.620
Female	79	62.7	127	59.3	
Aneurysm location					
Anterior circulation	105	83.3	170	79.4	0.460
Posterior circulation	21	16.7	44	20.6	
Treatment modality					
Endovascular treatment	69	54.8	113	52.8	0.813
Surgical clipping	57	45.2	101	47.2	
Hunt and Hess scale grade					
Non-severe (1–3)	80	63.5	150	70.1	0.256
Severe (4–5)	46	36.5	64	29.9	
Fisher scale score					
Non-severe (1–2)	6	4.8	20	9.3	0.185
Severe (3–4)	120	95.2	194	90.7	
Neurological outcome					
Unfavorable (GOS score: 1–3)	84	66.7	92	43.0	< 0.001
Favorable (GOS score: 4–5)	42	33.3	122	57.0	

Abbreviations: DCI, delayed cerebral ischemia; GOS, Glasgow Outcome Scale; SD, standard deviation.

majority (60.6%) of patients were women and the mean (SD) age was 56.4 ± 12.4 years. Ruptured anterior circulation aneurysms (80.9%) had a clear over-representation compared with posterior circulation aneurysms. Endovascular aneurysm occlusion (53.5%) was slightly more common than surgical clipping.

During the 14-day observational period, 126/340 (37.1%) patients met the DCI criteria as defined by the 2010 consensus definition. The median interval from the primary ictus to DCI was 97 h (interquartile range, 68–151 h). Neurological deterioration (i.e., decline in GCS score, new focal neurological deficit, or both) was observed in most of the patients (113/126, 89.7%). In 13 patients, fulfillment of the DCI criteria was based solely on neuroradiological imaging (Table 2). The Hunt and Hess scale grade, Fisher scale score, aneurysm location, treatment modality, and sex were not associated with fulfillment of the 2010 consensus DCI criteria (Table 1). The occurrence of DCI was strongly associated with an unfavorable neurological outcome at hospital discharge (OR 2.65, 95% CI 1.69–4.22, $p < 0.001$Table 3).

In univariate binary logistic regression analysis, DCI, age, the Fisher scale score, and the Hunt and Hess scale grade showed significant associations (all $p < 0.001$) with an unfavorable neurological outcome (Table 3). In multivariate analysis, these same variables were also independent risk factors (DCI, OR 3.23, CI 1.90–5.60; age[years], OR 1.06, CI 1.04–1.08; Fisher scale score, OR 4.4, CI 1.43–17.43; Hunt & Hess scale grade, OR 5.8, CI 3.30–10.59, all $p < 0.001$) for an unfavorable neurological outcome (Table 3).

Table 2
Description of the diagnosis for DCI and timing of each diagnosis in hours.

Criteria for DCI diagnosis (n = 126)	N	%	Median	IQR
Decline in GCS score alone	10	7.9	69.8	61.1–134.8
Focal deficit alone	12	9.5	117.4	104.1–132.4
Decline in GCS score and focal deficit	18	14.3	83.0	59.1–93.3
Decline in GCS score, focal deficit, and new infarction	30	23.8	94.4	63.9–146.1
Decline in GCS score and new infarction	18	14.3	84.0	59.2–96.7
Focal deficit and new infarction	25	19.8	118.0	77.0–165.2
New infarction alone	13	10.3	171.3	115.4–210.5

Abbreviations: DCI, delayed cerebral ischemia; GCS, Glasgow coma scale; IQR, Interquartile range.

4. Discussion

Our study evaluated the prognostic potential of the 2010 international panel of experts' consensus definition of DCI [12] in a large retrospective cohort of patients with aSAH. Fulfillment of the DCI criteria was a robust and independent risk factor for an unfavorable neurological outcome at discharge from hospital, as defined by GOS scores of 1 to 3. The median time from primary hemorrhage to occurrence of DCI was 97 h. Neurological deterioration was observed in most of the patients who fulfilled the DCI criteria (89.7%). Previously well-known independent risk factors for an unfavorable neurological outcome [20–23] such as the Hunt and Hess scale grade, the Fisher scale score, and increasing age, were also found in the current study.

In this study cohort, patients who met the 2010 consensus DCI criteria during the first 14 days after aSAH were prone to an unfavorable neurological outcome at discharge from hospital. Galea et al. [20] previously reported similar results from a large register-based study where DCI according to the 2010 consensus definition was an independent risk factor for poor neurological outcome at discharge from hospital. However, in contrast to the current study, they were unable to comprehensively examine the cases, and therefore, a detailed description of the diagnosis of DCI was missing. We extensively examined the cases for DCI inclusion and exclusion criteria from the ICU database, and in case of any lack of clarity regarding DCI, all investigators thoroughly evaluated the patient's history. Furthermore, we assessed the DCI criteria hourly from the ICU database, and therefore, the exact evolution of DCI was known.

The incidence of DCI in our cohort (37.1%) was high compared with the previous literature. In a systematic review that evaluated the association between radiological scales and the incidence of DCI, the incidence of DCI ranged from 11% to 57% in patients [24]. However, the most commonly reported incidence of DCI is approximately 30% [4,5]. Galea et al. [20] reported an incidence of 21.7% for DCI in their register-based study, which adhered to the 2010 consensus definition of DCI. A recent systematic review of outcome measures used in aSAH clinical research showed that there was substantial heterogeneity in the definition of DCI [25]. Only 40% of the studies described some form of clinical deterioration associated with DCI. Some of the studies that were included required a combination of clinical and radiological measures to fulfill DCI criteria, and others were purely clinical or radiological, and some did not provide a definition [25]. The relatively high incidence of DCI in the current study could reflect over-sensitivity of the 2010 consensus criteria.

Weir et al. [28] showed that the maximal angiographic vasospasm occurs 6 to 8 days after aSAH. That is significantly later than the fulfillment of DCI criteria in many patients in our study cohort, especially if the DCI diagnosis was based on or partly on the GCS score decline. Since the past literature has focused on the angiographic vasospasm it is possible that by adhering to the consensus 2010 DCI criteria the development of DCI can detected earlier than has been previously assumed.

Usually the assessment of new focal deficiencies in patients is simple, especially when focal deficiencies are clear (e.g. hemiparesis). However, if a patient is in a state of altered consciousness or is not cooperating, then assessment may be more complicated. Assessment of consciousness with the GCS score is prone to interrater variability [26] and the GCS score is unreliable with intubated patients [27]. Mild fluctuation of the GCS score is common after aSAH in the ICU environment (e.g., because of sleep deprivation and unexpected effects of analgo-sedative drugs). However, only 7.9% of the patients in our cohort fulfilled the DCI criteria solely on the basis of deterioration of the GCS score. Furthermore, the overall interrater agreement for the 2010 consensus definition of DCI was reported to be excellent when following explicit exclusion criteria [13], and this was also found in our study.

The 2010 consensus statement also recommends that neuroradiological imaging should be performed between 24 and 48 h after invasive

Table 3
Binary logistic regression for predicting an unfavorable neurological outcome.

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
DCI						
yes	2.65	1.69–4.22	< 0.001	3.23	1.90–5.60	< 0.001
no	1			1		
Age (years)	1.06	1.04–1.08	< 0.001	1.06	1.04–1.08	< 0.001
Sex						
Male	1.26	0.81–1.95	0.304	1.65	0.98–2.83	0.063
Female	1			1		
Hunt and Hess scale grade						
4–5	6.46	3.83–11.26	< 0.001	5.8	3.30–10.59	< 0.001
1–3	1			1		
Fisher scale score						
3–4	6.66	2.48–23.17	< 0.001	4.4	1.43–17.43	< 0.001
1–2	1			1		
Aneurysm location						
Anterior circulation	1.13	0.66–1.95	0.650	1.33	0.70–2.56	0.387
Posterior circulation	1			1		
Treatment modality						
Endovascular	1.14	0.75–1.75	0.544	1.21	0.72–2.05	0.476
Surgical	1			1		

Abbreviations: CI, confidence interval; DCI, delayed cerebral ischemia; OR, odds ratio.

treatment of the aneurysm to rule out possible iatrogenic brain lesions [12]. In our study, neuroradiological imaging was performed when decided as clinically necessary. When neuroradiological imaging is not performed systematically, it can complicate assessment of etiology of the infarction if it is found at a later date. Additionally, even when using the strict criteria for infarction, which is attributed to DCI, ascertainment of cases can be ambiguous [13]. It may also be debated whether the appearance of a small infarction on neuroradiological imaging without any clinical symptoms associated with it is significant. Overall, because most of the past literature is based on variable definitions of DCI, whether this increased incidence reflects only our study cohort or whether an increased incidence of DCI will be observed in other studies complying with the consensus criteria of DCI remains speculative.

As expected in our study, high Hunt and Hess scale grades and high Fisher scale scores were prognostic for an unfavorable neurological outcome. Surprisingly, Hunt and Hess scale grades and Fisher scale scores were not associated with fulfillment of the 2010 consensus DCI criteria. A recent systematic review showed that the Fisher scale, modified Fisher scale, and Hijdra sum scores were associated with DCI [24]. However, most of the studies evaluated in this review did not adhere to the 2010 consensus definition of DCI. Therefore, the definition of DCI affects how it is associated with scales reflecting the severity of early brain injury (i.e., Hunt and Hess and Fisher scales). The Fisher scale was developed in the 1980s and it was used to predict angiographic vasospasm on the basis of the amount of blood visualized in an initial head computed tomographic scan [19]. Because the 2010 consensus definition of DCI does not require angiographic vasospasm as a DCI criterion, this might explain a weaker association between the Fisher scale score and DCI. The lack of association between fulfillment of DCI criteria and the Hunt and Hess scale grade might be caused by more simple recognition of DCI criteria in patients whose neurological status is not comatose from the onset of aSAH.

This study has some limitations. First, this was a retrospective, single-center study. This limits the generalizability of the results but reduces bias of differences in interpretation of DCI criteria and selection of patients. Second, because of the retrospective nature of the study, we were unable to include some of the known risk factors for DCI (e.g., smoking) in logistic regression analysis. The retrospective nature of this study also made the assessment of infarction etiology uncertain. Third, because the neuroradiological imaging was done solely on the basis of clinical need, the assessment of the etiology of infarction can be complicated and case ascertainment can be open to interpretations. Finally, the neurological outcome was only assessed at discharge from hospital. We acknowledge that this hinders conclusions about the long-term neurological outcome of patients.

The multifactorial pathophysiology of DCI causes further brain injury and impairs neurological recovery of survivors of aSAH [4]. In practice, in the clinic and in research, detecting patients suffering from DCI is often challenging. Highly variable use of DCI definitions and terminology in the previous literature obscures well-defined conclusions of the incidence of DCI and its associations with other clinical variables, such as neurological outcome [12,14]. An explicit consensus recommendation for the definition of DCI exists, but it is underutilized [12,14]. In future research, use of a uniform terminology and definition of DCI (i.e., 2010 consensus criteria) is essential to further advance understanding of the pathophysiology, incidence, and effect of DCI on neurological outcome of this extremely complex phenomenon.

5. Conclusions

Fulfillment of the 2010 consensus DCI criteria was high in this study cohort and it was an independent predictor of unfavorable neurological outcome at discharge from hospital. This finding adds to the previous literature where DCI appears to be a major contributor affecting the functional ability of survivors of aSAH. By adhering to a uniform terminology and definition of DCI, improving understanding of this extremely complex phenomenon should be possible, as well as possibly improving patients' outcomes in the future.

Sources of funding

Research grants for this study were provided by the Finnish Society of Anesthesiology, The Finnish Medical Foundation, and a Government Grant (reference number: 9X020) for Health Care Research, Finland. The funding sources had no involvement in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration of Competing Interest

None.

Acknowledgments

We thank Alfred Sarno, MD, for assistance in development of the study design. We also thank Ellen Knapp, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/) for editing a draft of this

manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2020.117261.

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PUBLICATION II

Platelet count is not associated with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as defined by the 2010 consensus definition

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Journal of the neurological sciences, 2022, Vol.436, p.120227-120227
DOI: 10.1016/j.jns.2022.120227

Journal of the Neurological Sciences 436 (2022) 120227

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Platelet count is not associated with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as defined by the 2010 consensus definition

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ARTICLE INFO

Keywords:
Aneurysmal subarachnoid hemorrhage
Platelet
Delayed cerebral ischemia
Intensive care unit

ABSTRACT

Background: Although delayed cerebral ischemia (DCI) commonly complicates recovery in survivors of aneurysmal subarachnoid hemorrhage (aSAH), its pathophysiology is incompletely understood. Previous studies examining the association of DCI and platelet count have demonstrated contradictory results. This study aimed to investigate this association in a cohort of aSAH patients using the 2010 consensus definition of DCI.

Methods: We conducted a retrospective single-center observational study of consecutive adult aSAH patients admitted to the intensive care unit from January 2010 to December 2014. Platelet count and DCI evaluations were performed daily in the first 14 days after admission. DCI was defined according to the 2010 consensus criteria.

Results: A total of 340 patients were included for analysis. DCI incidence was 37.1%. Platelet count was not significantly associated with occurrence of DCI on any day. Mean platelet count was lowest on day 3 after aSAH and then increased to exceed the count at admission on day 6. Treatment modality and use of dual antiplatelet therapy were not associated with DCI.

Conclusions: Platelet count was not associated with DCI as defined by the 2010 consensus criteria. Future studies adhering to the 2010 consensus definition of DCI are needed to clarify the role of platelets and platelet function in DCI pathophysiology.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) remains a devastating disease. One-year mortality approaches 50%. [1] In those who survive, delayed cerebral ischemia (DCI) can result in poor outcomes. The mechanisms of DCI are incompletely understood. Although vasospasm of large cerebral arteries is one underlying mechanism, other factors are involved. [2,3] Post-mortem studies have shown that microthrombosis is a common finding in aSAH patients and that microclot burden is associated with DCI. [4,5] A recent review of the role of platelets in DCI pathophysiology concluded that platelets are involved at multiple stages. [6] Previous studies have used various definitions of DCI, which makes interstudy comparisons difficult. The 2010 consensus definition of DCI after aSAH was formulated to provide a clear and consistent definition to be used in future studies to enable valid interstudy comparisons. [7]

Findings regarding platelets and DCI in previous studies have been contradictory. In one study, platelet count in aSAH patients first decreased and then increased to exceed the count at admission. The same study found that platelet consumption was greater in patients with symptomatic vasospasm [8]. However, another study reported a platelet count increase in patients as they developed DCI. [9] Although procedural complications in aSAH patients are common and related to morbidity [10], the association of treatment modality with DCI

Abbreviations: DCI, delayed cerebral ischemia; aSAH, aneurysmal subarachnoid hemorrhage; GOS, Glasgow Outcome Scale; ADP, adenosine diphosphate.

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https://doi.org/10.1016/j.jns.2022.120227
Received 14 December 2021; Received in revised form 15 February 2022; Accepted 9 March 2022
Available online 15 March 2022

incidence is not known.

The present study evaluated absolute platelet count and change in platelet count during the first 14 days after aSAH and examined their association with DCI as defined by Vergouwen et al. [7] We also evaluated the effects of treatment modality and antiplatelet therapy on platelet count and their association with DCI.

2. Methods

2.1. Study design

The patients in this retrospective single-center observational cohort were included in our previous study of the predictive value for neurological outcome of the 2010 consensus definition of DCI after aSAH. [11] The local ethics committee of Pirkanmaa approved the study design (approval no. R115508S). The requirement for informed consent was waived because of the retrospective nature of the study.

In brief, adult patients with aSAH admitted to the intensive care unit (ICU) of Tampere University Hospital from January 2010 to December 2014 were eligible for inclusion. Tampere University Hospital is one of five tertiary referral centers in Finland and serves approximately one million inhabitants. All patients who require neurointensive care in its catchment area are treated there. All non-moribund aSAH patients admitted are initially treated in the ICU.

2.2. Selection of patients

Onset of aSAH symptoms was defined as the ictus. Time of ictus onset was obtained from the medical records. Patients with an unknown time of onset and those admitted >48 h after the ictus were excluded. We also excluded moribund patients with unsecured aneurysms and those admitted to the ICU solely because of organ donation. All patients received standardized aSAH care using our hospital protocol, which was created based on international multidisciplinary consensus guidelines. [12,13]

2.3. Blood sampling

Platelet count was performed at admission and daily thereafter while the patient remained in the ICU. After transfer from the ICU, it was performed according to clinical need. If more than one platelet count was obtained on any given day, the average was analyzed. When assessing the effect of circadian rhythm of platelets, only the platelet counts obtained in the morning were assessed.

2.4. Assessment of DCI

Three investigators (AK, AV, and ER) independently evaluated each patient for the development of DCI as defined by Vergouwen et al. [7] using patient data recorded between 48 h and 14 days from ictus onset. Data were obtained from the ICU database (Centricity Critical Care Clinisoft; GE Healthcare, Barrington, IL, USA) and the electronic medical records. In case of any doubt, all investigators thoroughly evaluated the patient's history and made a consensus decision. Detailed DCI criteria are described in our previously published paper [11] and in Supplementary table 1.

2.5. Assessment of other clinical factors

Other information was collected from the neurosurgical aneurysm database, including aneurysm location, treatment modality, Hunt and Hess scale grade, [14] Fisher scale grade, [15] and Glasgow Outcome Scale (GOS) score. [16] We also recorded the use of antiplatelet drugs in patients treated with stent-assisted coiling. All patients treated with stent-assisted coiling in our hospital receive aspirin 100 mg and an adenosine diphosphate (ADP) receptor inhibitor (clopidogrel, ticagrelor). Abciximab, a glycoprotein IIb/IIIa inhibitor, is used temporarily after stent placement until an ADP receptor inhibitor is initiated.

The Hunt and Hess scale was used to assess severity of early brain injury at hospital admission, which was dichotomized as mild (grades 1–3) and severe (grades 4–5). The Fisher scale was used to assess aSAH severity on the initial computed tomography, which was dichotomized as non-severe (grades 1–2) and severe (grades 3–4). The GOS was used to assess neurological outcome at discharge, which was dichotomized as favorable (scores 4–5) and unfavorable (scores 1–3).

The patients' medical history and medication prior to aSAH was not unambiguously retrievable from the neurosurgical database or electronical medical records.

2.6. Statistical methods

The continuous variables examined in this study (age, platelet count) were normally distributed and are presented as means with standard deviation. They were compared between groups using the *t*-test. The associations of categorical variables and DCI were evaluated using the Pearson chi-square test. Cox proportional hazards regression was used to examine the association of platelet count with DCI; daily platelet counts were used as time-dependent covariates and missing platelet count values were imputed with the last known platelet level. Analysis of variance was used to evaluate the association between platelet count and treatment modality. All statistical analyses were performed using R version 4.0.3 (The R Foundation, Vienna, Austria) and SPSS software version 27 (IBM Corp, Armonk, NY, USA).

3. Results

Four hundred thirty-nine aSAH patients were eligible for inclusion. After excluding 99 based on study criteria, 340 patients were analyzed. [11] Patient characteristics are shown in Table 1. Mean patient age was 56.4 ± 12.4 years. Most patients (60.6%) were women. Location of ruptured aneurysm was the anterior circulation in 80.9% of patients and the posterior circulation in 19.1%. One hundred eighty-one patients underwent endovascular coiling with or without stent assistance (53.5%) and 159 underwent surgical clipping (46.5%). Stent-assisted coiling was performed in 27 patients (7.9%).

One hundred twenty-six patients (37.1%) developed DCI as defined by the 2010 consensus criteria. Mean platelet count reached a minimum on day 3 after the ictus in both the DCI ($196 \pm 51.7 \times 10^9$/L) and no DCI ($196 \pm 50.4 \times 10^9$/L) groups and then increased to exceed the count at admission after day 6. On day 14, mean platelet count was slightly higher in the no DCI group, but the difference was not significant ($391 \pm 91.9 \times 10^9$/L vs. $362 \pm 115 \times 10^9$/L; $p = 0.2$). Platelet count did not significantly differ between groups on any given day in the first 14 days after ictus (Fig. 1). The time-dependent association of daily platelet count and DCI was assessed and no association was found (hazard ratio, 1.00; 95% confidence interval, 0.998–1.003). The circadian rhythm of platelets had no time-dependent association with DCI (hazard ratio, 1.001; 95% confidence interval, 0.998–1.003).

Treatment modality was not associated with DCI ($p = 0.977$). Mean platelet count on day 9 after the ictus significantly differed between the endovascular coiling without stent assistance ($273 \pm 83.5 \times 10^9$/L), stent-assisted coiling ($304 \pm 52.7 \times 10^9$/L), and surgical clipping ($308 \pm 80.6 \times 10^9$/L) groups ($p = 0.020$; Fig. 2). However, platelet count data were available in only 180 patients (52.9%) on day 9. The incidence of DCI did not significantly differ between patients treated with stent-assisted coiling (37.0%), coiling without stent assistance (37.7%), and surgical clipping (36.5%). Patients with severe aSAH had a significant decline in platelet count on days 1 and 2 after ictus ($p < 0.05$) that was not seen on other days (Fig. 3). Platelet count on days 1–6 after ictus significantly differed between patients who had a favorable neurological outcome and those who had an unfavorable outcome ($p < 0.05$, Fig. 4).

Table 1
Patient characteristics.

	DCI group $n = 126$		No DCI group $n = 214$		
	n	%	n	%	*p*-value
Mean age, years (SD)	55.7	(12.7)	56.8	(12.2)	0.47
Gender					
Male	47	37.0	87	40.7	0.62
Female	79	62.7	127	59.3	
Aneurysm location					
Anterior circulation	105	83.3	170	79.4	0.46
Posterior circulation	21	16.7	44	20.6	
Treatment modality					
Surgical clipping	58	46.0	101	47.2	0.98
Endovascular coiling	58	46.0	96	44.9	
Endovascular stent-assisted coiling	10	7.9	17	7.9	
Anti-platelet medication*					
Aspirin	10	100.0	17	100.0	0.68
ADP receptor inhibitors	10	100.0	17	100.0	
Glycoprotein IIb/IIIa inhibitors	8	80.0	12	70.6	
Hunt and Hess scale					
Grade 1–3	80	63.5	150	70.1	0.26
Grade 4–5	46	36.5	64	29.9	
Fisher scale					
Grade 1–2	6	4.8	20	9.3	0.19
Grade 3–4	120	95.2	194	90.7	
Glasgow Outcome Scale at discharge					
Score 1–3	84	66.7	92	43.0	<0.001
Score 4–5	42	33.3	122	57.0	

DCI, delayed cerebral ischemia; SD, standard deviation; ADP, adenosine diphosphate.
Partially previously published in Raatikainen E, Vahtera A, Kuitunen A, Junttila E, Huhtala H, Ronkainen A, et al. Prognostic value of the 2010 consensus definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. J Neurol Sci 2021;420:117261.
* only in stent-assisted coiling patients.

4. Discussion

This study evaluated the association of absolute platelet count and change in platelet count with DCI after aSAH as defined by the 2010 consensus criteria. [7] Neither was associated with DCI incidence. Moreover, neither treatment modality nor use of antiplatelet therapy was associated with DCI incidence. Patients with severe aSAH on initial computed tomography (Fisher grade 3–4) had significantly lower platelet count on days 1 and 2 after aSAH.

Contrary to previous speculation, in our patient cohort, platelet count was not associated with DCI after aSAH as defined by the 2010 consensus criteria. [8,9] Kasius et al. found that platelet count increased compared with baseline during the development of DCI in aSAH patients. [9] Hirashima et al. [8] and Schebesch et al. [17] performed similar studies that used a vasospasm-based definition of DCI in a Japanese and Caucasian population, respectively; however, both studies only included patients who underwent surgical aneurysm clipping. In contrast to Hirashima et al., Schebesch et al. found no association between platelet count and vasospasm or clinical outcome and postulated that genetic differences between Asians and Caucasians were responsible for the discrepancy. However, the different definitions of DCI across the above studies may also explain their different findings.

Previous studies have found that the hemostatic system shows significant circadian variation, with platelet counts typically increasing in the afternoon. [18] In our patient cohort there was no time-dependent association of the daily platelet count and DCI when considering the circadian rhythm. It seems that the platelet variability between subjects is greater than the variability within subjects.

In our study, treatment modality was not associated with DCI. Although patients treated with endovascular coiling without stent assistance had a significantly lower platelet count on day 9 after aSAH than those treated with stent-assisted coiling or surgical clipping, this did not have a clinical effect. In a large study that compared DCI incidence between patients treated with endovascular coiling and those treated with surgical clipping, the odds of DCI were 24% higher in the surgical group (95% CI, 1%–51%). However, DCI did not have a greater impact on poor outcome in the surgical group than the endovascular coiling group. [19]

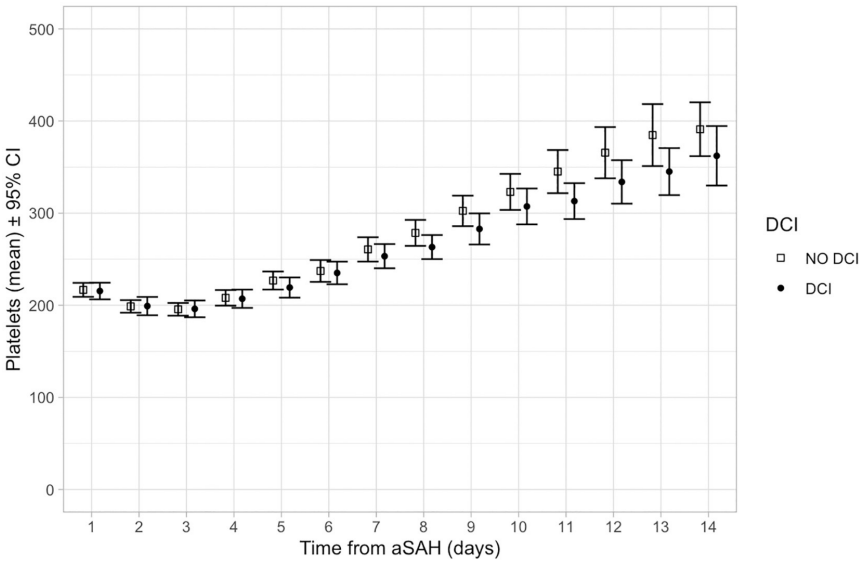

Fig. 1. Mean platelet count over time in patients with and without delayed cerebral ischemia.

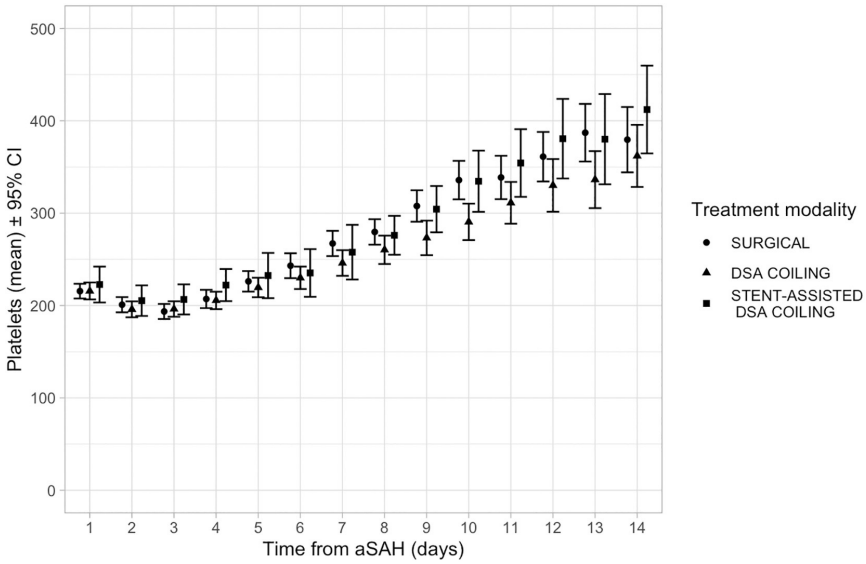

Fig. 2. Mean platelet count over time in patients grouped according to treatment modality.

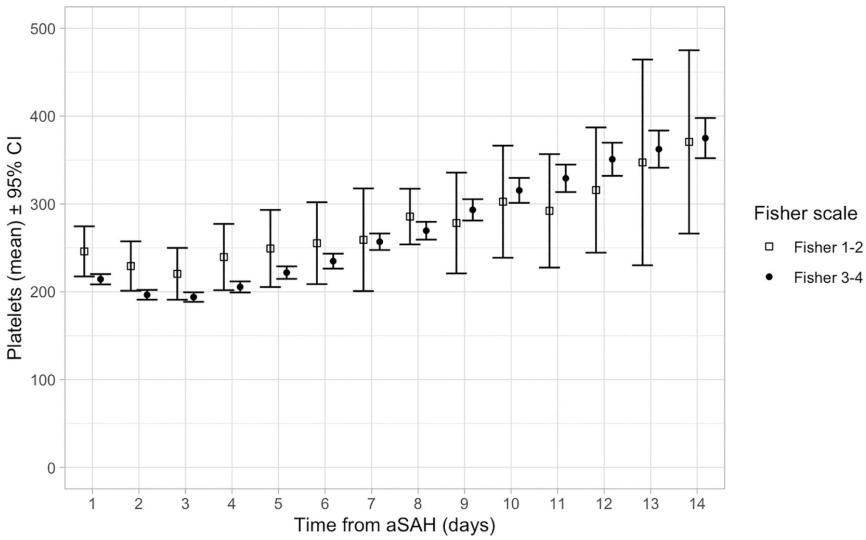

Fig. 3. Mean platelet count over time in patients grouped according to Fisher grade on initial computed tomography.

The use of antiplatelet therapy in stent-assisted coiling patients was not associated with reduced incidence of DCI in our patient cohort. Although preventing microclot formation using antiplatelet medications has been suggested to reduce the risk of DCI [6,20–24], studies have been conflicting, especially those evaluating dual antiplatelet therapy. A recent review of the role of platelets in DCI proposed several platelet-related therapeutic targets to prevent DCI and suggested two main reasons for the lack of clinical benefit from antiplatelet agents: 1) difficulty in predicting which patients develop DCI and 2) lack of understanding the mechanisms of DCI. [6] In a study of antiplatelet medications after aSAH, Sun et al. found that the incidence of DCI was lower in patients who received dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg daily) than in those who did not. [23] In another study, aspirin use was independently associated with reduced DCI risk. Dual antiplatelet therapy (aspirin and clopidogrel) was not but it was associated with increased risk of clinically relevant bleeding events. [19] Wallace et al. compared dual antiplatelet therapy (aspirin and clopidogrel/ticagrelor) with aspirin monotherapy and found no differences in incidence of DCI or good clinical outcome at 6 months; however, bleeding complications were more frequent in the dual antiplatelet

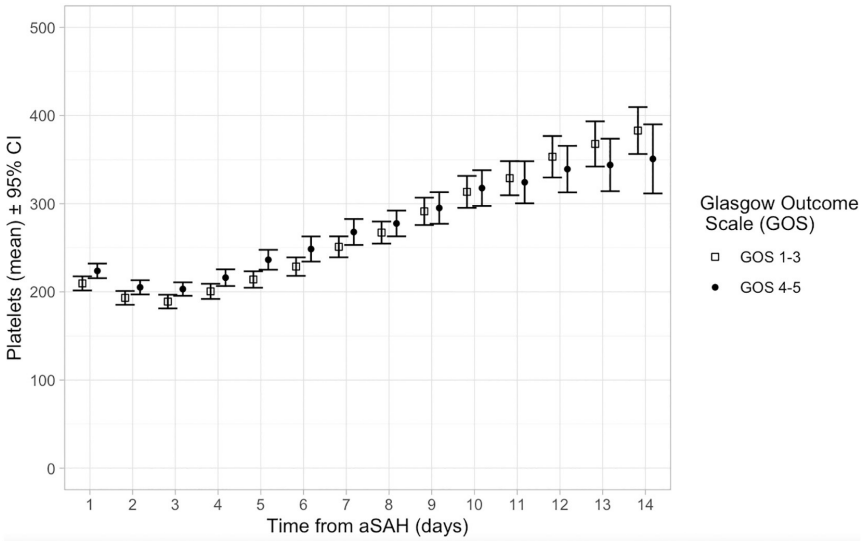

Fig. 4. Mean platelet count over time in patients grouped according to Glasgow Outcome Scale score.

therapy group. [25] Although these studies used different definitions of DCI, most were vasospasm-based.

In our study, the difference in platelet count was significant between patients with non-severe (Fisher grade 1–2) and severe (Fisher grade 3–4) aSAH on days 1 and 2 after, however the non-severe aSAH group consisted of only 26 patients. Nevertheless, previous studies have reported similar findings. Rzepliński et al. found that platelet count was lower in patients with Fisher grade 3–4 aSAH than those with Fisher grade 1–2 aSAH. [26] Similarly, in a thromboelastography and platelet mapping study, patients with severe aSAH (Hunt and Hess grade 4–5) had significantly higher levels of arachidonic acid and ADP inhibition compared with patients with non-severe aSAH. In addition, the degree of platelet dysfunction significantly correlated with Hunt and Hess and Fisher grades on admission. Furthermore, the study found that platelet dysfunction also played a role in rebleeding risk. [27]

4.1. Limitations

Our study has several limitations. As this was a retrospective study, platelet count data were not available for every patient on each day. Patients with better neurological status who did not require a long period of intensive care underwent laboratory testing less frequently. Therefore, information bias was present in the platelet count data. In addition, data regarding past medical history, previous use of antiplatelet drugs, bleeding events, and platelet transfusion were not available. Finally, platelet function testing was not performed, as it is not included in our hospital aSAH treatment protocol.

5. Conclusions

In this cohort of aSAH patients, we found no association between platelet count and DCI as defined by the 2010 consensus criteria. Dual antiplatelet therapy was not associated with DCI incidence. Future studies are warranted to clarify the role of platelets in DCI pathophysiology. These studies should define DCI according to the 2010 consensus criteria and examine platelet function testing in addition to platelet count.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2022.120227.

Sources of funding

Research grants for this study were provided by the Finnish Society of Anesthesiology, the Finnish Medical Foundation, and a Government Grant for Health Care Research, Finland (reference number: 9 X 020). The funding sources were not involved in study design, data collection and analysis, publishing decision making, or manuscript preparation.

Disclosures

None.

Acknowledgments

We thank Alfred Sarno, MD for assisting in study design development and Edanz (https://www.edanz.com/ac) for editing a draft of this manuscript.

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PUBLICATION III

Increased blood coagulation is associated with poor neurological outcome in aneurysmal subarachnoid hemorrhage

Raatikainen E., Kiiski, H., Kuitunen, A., Junttila, E., Huhtala, H., Kallonen, A., Ala-Peijari, M., Långsjö, J., Saukkonen, J., Valo, T., Kauppila, T., Raerinne, S., Frösen, J. & Vahtera, A.

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