Aus dem CharitéCentrum für Neurologie, Neurochirurgie und Psychiatrie
Klinik für Neurologie mit Experimenteller Neurologie
Charité Campus Benjamin Franklin
Direktor: Prof. Dr. Matthias Endres

Habilitationsschrift

Diagnostik, Therapie und prädiktive Bedeutung kardialer Pathologien bei akutem ischämischem Schlaganfall

Zur Erlangung der Lehrbefähigung
für das Fach Neurologie

Vorgelegt dem Fakultätsrat der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Dr. med. Simon Hellwig, M.Sc.

Eingereicht: Mai 2024
Dekan: Prof. Dr. med. Jochen Spranger

Für Sophie und unsere Kinder Anton, David und Jakob

Inhaltsverzeichnis

1. Abkürzungen

ACS	Akutes Koronarsyndrom
A-FABP	Adipozyten-Fettsäuren-bindendes Protein
AIS	Akuter ischämischer Schlaganfall
ASS	Acetylsalicylsäure
BNP	Brain natriuretic peptide
BSR	Berliner Schlaganfallregister
CAS	Carotid artery stenting
CE	Cardioembolism
CEA	Carotid endarterectomy
CISS	Chinese Ischemic Stroke Subclassification
CLP	Clopidogrel
CMR	Cardiac Magnetic Resonance Imaging
CRT	Cine real time
CSB	Centrum für Schlaganfallforschung Berlin
CSS	Causative Classification System
DALY	Disability-adjusted life year
DOAK	Direktes orales Antikoagulanz
EDMM	Enddiastolische Myokardmasse
ESRS	Essen Stroke Risk Score
ESUS	Embolic Stroke of Undetermined Source
GBD	Global Burden of Disease
HEBRAS	Heart and Brain Interfaces in Acute Ischemic Stroke
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard Ratio
hs-cTnI	High-sensitivity cardiac Troponin I
hs-cTnT	High-sensitivity cardiac Troponin T
ICB	Intrazerebrale Blutung
INR	International Normalized Ratio
IQR	Interquartile Range
KHK	Koronare Herzkrankheit
KI	Konfidenzintervall

LAA	Large-artery atherosclerosis
LGE	Late Gadolinium Enhancement
LOB	Limit of blank
MACE	Major Adverse Cardiovascular Events
MBL	Mannose-bindendes Lektin
MDCT	Multidetector-computed tomography
MR-proANP	Mid-regional pro-Atrial natriuretic peptide
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NOAK	Nicht-Vitamin K-abhängiges orales Antikoagulanz
NT-proBNP	N-terminales pro-Brain natriuretic peptide
OAK	Orale Antikoagulation
OR	Odds Ratio
pAVK	Periphere arterielle Verschlusskrankheit
PCT	Procalcitonin
PFO	Persistierendes Foramen Ovale
RMI	Recognized myocardial infarction
SAB	Subarachnoidalblutung
SAO	Small-artery occlusion
SPI-II	Stroke Prognosis Instrument II
SSFP	Steady-state free precession
TFH	Thrombozytenfunktionshemmung
TIA	Transitorische ischämische Attacke
TOE	Transösophageale Echokardiographie
TPFR	Time to peak filling rate
TTE	Transthorakale Echokardiographie
UMI	Unrecognized myocardial infarction
URL	Upper reference limit
VHF	Vorhofflimmern
VTC	Volume-Time-Curve
WHO	World Health Organization

2. Studienakronyme

ARCADIA	Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke
ATTICUS	Apixaban for Treatment of Embolic Stroke of Undetermined Source
CORONA-IS	Cardiomyocyte Injury Following Acute Ischemic Stroke
EAFT	European Atrial Fibrillation Trial
FIND-AF	Future Innovations in Novel Detection for Atrial Fibrillation
GARFIELD-AF	Global Anticoagulant Registry in the FIELD - Atrial Fibrillation
HEBRAS	Heart and Brain Interfaces in Acute Ischemic Stroke
INSPiRE-TMS	Intensified Secondary Prevention intending a Reduction of vascular re-events after TIA or Minor Stroke
LAAOS III	Left Atrial Appendage Occlusion Study III
NAVIGATE ESUS	New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source
NINDS	National Institute of Neurological Disorders and Stroke
OCEANIC-AF	Oral Factor Eleven A Inhibitor Asundexian as Novel Antithrombotic – Atrial Fibrillation Study
PEGASUS-TIMI 54	Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin – Thrombolysis in Myocardial Infarction 54
RESPECT ESUS	Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SPORTIF	Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation
TOAST	Trial of Org 10172 in Acute Stroke Treatment
WARCEF	Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction

3. Einleitung

3.1 Grundsätzliches und Historisches

Der Mensch verfügt wie alle Wirbeltiere über einen geschlossenen Blutkreislauf[1]. Eine intakte Zirkulation setzt dabei bestimmte Fließeigenschaften des Blutes im Sinne eines Gleichgewichts von gerinnungsfördernden und gerinnugshemmenden Faktoren voraus[2]. Erkrankungen als Folge einer Störung dieses Systems dürften dabei phylogenetisch so alt sein wie das System selbst[3]. Der Begriff der Apoplexie (altgriechisch *ἀπόπληκτος* – 1. vom Schlage gerührt, 2. betäubt, bestürzt, der Sinne beraubt) findet sich bereits bei den Hippokratikern im 5. Jahrhundert vor Christus[4]. Die Differenzierung zwischen einem Gefäßverschluss und einer Hämorrhagie als mögliche Ursachen eines Schlaganfalls findet sich erstmals bei dem Schweizer Arzt und Anatom Johann Jakob Wepfer 1658[5]. Der Virchow-Schüler Julius Cohnheim entwickelte 1872 ein experimentelles Modell, in welchem er durch Injektion von Wachskügelchen in Froschzungen sowohl ischämische als auch hämorrhagische Schlaganfälle erzeugen konnte[6].

3.2 Begriffsklärung und Definition

Sowohl in der wissenschaftlichen Literatur als auch in der klinischen Praxis wird der deutsche Begriff „Schlaganfall“ bzw. die englische Entsprechung „stroke“ uneinheitlich gebraucht[7]. Die „klassische“ Definition geht dabei auf die Weltgesundheitsorganisation (WHO) von 1970 zurück, die den Schlaganfall als „sich rasch entwickelnde klinische Zeichen fokaler oder globaler Störung der Hirnfunktion, die für mehr als 24 Stunden bestehen oder zum Tode führen, ohne anderen ersichtlichen Grund als eine vaskuläre Ursache“ beschreibt[8]. Aktuelle Definitionen bemühen sich, auch paraklinische bzw. apparative Erkenntnisse mit einfließen zu lassen: amerikanische Fachgesellschaften definieren einen Infarkt des zentralen Nervensystems als „Zelltod des Gehirns, des Rückenmarks oder der Retina infolge einer Minderdurchblutung, basierend auf neuropathologischen, bildgebenden und/oder klinischen Zeichen permanenter Schädigung“[7]. Der Begriff „Schlaganfall“ umfasst dabei im weiteren Sinne neben dem ischämischen Schlaganfall infolge eines Gefäßverschlusses auch den hämorrhagischen Schlaganfall im Sinne einer intrazerebralen Blutung (ICB) oder Subarachnoidalblutung (SAB)[9].

Soweit Empfehlungen zur Nomenklatur in Deutschland vorliegen, sollte vom Gebrauch veralteter Begriffe aus dem allgemeinen Sprachgebrauch wie „Hirninfarkt“, „Apoplex“

oder „zerebraler Insult“ abgesehen werden[10]. Im Folgenden soll der Begriff „ischämischer Schlaganfall“ spezifisch für zerebrale Ischämien stehen, die durch Minderdurchblutung zerebraler oder präzerebraler Arterien verursacht sind. Soweit intrazerebrale Blutungen eine Rolle spielen, werden diese gesondert als solche benannt.

3.3 Epidemiologie des Schlaganfalls

Der Schlaganfall ist eine Erkrankung von weltweiter Bedeutung: gemäß dem aktuellen Bericht (2019) des *Global Burden of Disease* (GBD) Projektes bleiben Schlaganfälle nach der ischämischen Herzkrankheit die zweithäufigste Todesursache als auch die zweithäufigste Ursache von Behinderung (im Sinne verlorener Krankheits-adjustierter Lebensjahre [*disability-adjusted life years*, DALY]) bei Erwachsenen[11]. Im Jahr 2019 traten weltweit geschätzt 12,2 Millionen Schlaganfälle auf bei einer globalen Prävalenz von ca. 101 Millionen stattgehabter Ereignisse[12]. Statistisch gesehen wird jede vierte Person über 25 Jahre in ihrem Leben einen Schlaganfall erleiden[12]. Während die Schlaganfallraten insbesondere in Ländern mit niedrigem Einkommen (gem. WHO-Definition) steigen, bleibt die Erkrankung auch in Ländern mit hohem Einkommen von großer Bedeutung, da trotz fallender Inzidenzen aufgrund des demographischen Wandels die absolute Rate an Schlaganfällen gleichbleibt oder sogar ansteigt[13, 14]. In diesem Kontext wurde 2022 die globale ökonomische Belastung durch Schlaganfälle auf über 721 Milliarden US-Dollar geschätzt[12].

Auch in Deutschland spielt der Schlaganfall in der Gesundheitsversorgung eine herausragende Rolle. Daten aus dem Jahr 2008 berichten über mehr als 262.000 Neuerkrankungen pro Jahr, wobei ca. 196.000 erstmaligen und ca. 66.000 erneuten Schlaganfällen zuzurechnen sind[15]. Daten aus der Gesundheitsberichterstattung des Bundes extrapolierten, das Ende 2010 ca. 1,76 Millionen Erwachsene in Deutschland einen Schlaganfall erlitten hatten[16]. Aktuelle Daten des Robert-Koch-Instituts aus den Jahren 2019/2020 berichten eine 12-Monats-Prävalenz des Schlaganfalls oder chronischer Beschwerden in Folge eines Schlaganfalls von 2,1% bei Frauen und 2,3% bei Männern der erwachsenen Gesamtbevölkerung, wobei ein erheblicher Unterschied in Abhängigkeit des Alters besteht (<0,6% in der Altersgruppe unter 44 Jahren bis 5,5% bei Menschen im Alter von min. 80 Jahren)[17]. Eine Analyse von Daten des statistischen Bundesamtes (DESTATIS) für das Jahr 2017 errechnete eine Sterberate von 7,2% bei annähernd 228.000 registrierten Schlaganfällen[18]. In einer Untersuchung von Krankenkassendaten aus Niedersachsen fand sich eine Mortalität nach erstmaligem

Schlaganfall in den Jahren 2010 und 2011 von 6,8% nach 30 Tagen, 9,4% nach 90 Tagen, 17,0% nach einem Jahr und 45% nach 5 Jahren[19]. Auch für das deutsche Gesundheitssystem bedeutet dies eine relevante ökonomische Belastung, eine Auswertung aus dem Jahr 2005 taxierte die durchschnittlichen direkten Kosten für das Gesundheitssystem in den ersten drei Monaten nach erstmaligem Schlaganfall auf annährend 16.000 EUR[20]. Mehrere in dieser Habilitationsschrift vorgelegte Arbeiten untersuchten Patientinnen und Patienten, die an der Charité bzw. in Berliner Krankenhäusern behandelt wurden. Für das Land Berlin gibt das Berliner Schlaganfallregister (BSR) in seiner Auswertung für das Jahr 2022 8.282 ischämische Schlaganfälle, 2.659 transitorische ischämische Attacken (TIA) und 612 intrazerebrale Blutungen für die teilnehmenden Kliniken (n=18) an[21].

3.4 Behandlung des akuten Schlaganfalls und frühe Sekundärprävention

Die Behandlung akuter zerebraler Ischämien hat als Teilbereich der Neurologie in den vergangenen ca. dreißig Jahren zunehmend an Bedeutung gewonnen: mit der Verfügbarkeit der i.v. Thrombolysetherapie, der Etablierung zertifizierter Stroke Units sowie der Möglichkeit interventioneller Thrombektomien stehen mittlerweile wirksame und sichere Instrumente zur Akutbehandlung des Schlaganfalls zur Verfügung[22-24]. Neben der Akutbehandlung ist ein möglichst früher Beginn einer adäquaten Sekundärprophylaxe von hoher Bedeutung für die Verhinderung erneuter Ereignisse: so wird geschätzt, dass hierdurch die Rezidivrate nach erstmaligem Schlaganfall oder TIA um bis zu 25% reduziert werden kann[25]. Entscheidend für die bestmögliche Sekundärprävention ist die Identifikation der mutmaßlichen Schlaganfallursache (→ *3.5 Schlaganfallätiologien*). Es liegen umfangreiche nationale und internationale Leitlinien zu diesem Thema vor[26, 27]. Soweit medikamentöse Strategien betroffen sind, ist die Auswahl der antithrombotischen Therapie sowie ggf. die Behandlung pharmakologisch potentiell modifizierbarer kardio-vaskulärer Risikofaktoren wie Hyperlipoproteinämie, Hyperglykämie und Hypertonie bedeutsam[26]. Hinsichtlich der antithrombotischen Medikation sollte in der Regel eine dauerhafte Thrombozytenfunktionshemmung mit z.B. Acetylsalicylsäure (ASS) oder Clopidogrel erfolgen[26]. Neuere Studien haben gezeigt, dass bei Patientinnen und Patienten mit einem leichten Schlaganfall oder Hochrisiko-TIA die frühe und zeitlich begrenzte (für 21 bzw. 30 Tage) Gabe einer dualen Thrombozytenfunktionshemmung das Rezidivrisiko signifikant senkt[26, 28].

Patientinnen und Patienten mit bekanntem Vorhofflimmern (VHF) sollten eine orale Antikoagulation (OAK) erhalten, sofern keine Kontraindikationen vorliegen[29]. Bis 2010 standen in Deutschland nur Vitamin K-Antagonisten (Phenprocoumon, Marcumar®, Falithrom®) zur Verfügung. Zwischen 2011 und 2015 wurden die sog. nicht-Vitamin K-abhängigen oralen Antikoagulanzien (NOAK) zugelassen: die Faktor Xa-Antagonisten Apixaban (Eliquis®), Rivaroxaban (Xarelto®) und Edoxaban (Lixiana®) sowie der direkte Thrombin-Inhibitor (Faktor IIa) Dabigatran (Pradaxa®). Alternativ wird auch das Akronym DOAK (direkte orale Antikoagulanzien) verwendet. Grundlage für die Indikationsstellung für eine OAK bei Patient*innen mit Vorhofflimmern ist das Risikoassessment mittels CHA_2DS_2-VASc Score[30]. Die Einflussfaktoren werden in Tabelle 1 dargestellt:

Tabelle 1 – Der CHA_2DS_2-VASc Score (adaptiert nach Joglar et al.[30])

	Risikofaktor		**Punkte**
C	Congestive heart failure	Herzinsuffizienz	1
H	Hypertension	Arterielle Hypertonie (≥ 140/90 mmHg oder unter Medikation)	1
A_2	Age ≥75 years	Alter ≥75 Jahre	2
D	Diabetes	Diabetes mellitus	1
S_2	Stroke	Vorausgegangener Schlaganfall, TIA oder sonstige Thromboembolie	2
V	Vascular disease	Vaskuläre Erkrankung (pAVK, Myokardinfarkt oder Aortenplaque)	1
A	Age 65-74 years	Alter 65-74 Jahre	1
Sc	Sex category (female)	Weibliches Geschlecht	1

Der Score reicht von 0 bis 9 Punkten und ist mit einer (errechneten) 1-Jahres-Rate für Schlaganfall oder systemische Thromboembolie von 0.0 (bei einem Score = 0) bis 15.2 (Score = 9) verbunden[31]. Kardiologische Leitlinien empfehlen eine OAK in Abhängigkeit des CHA_2DS_2-VASc Scores und des Geschlechts (wobei das Geschlecht bereits in den Score einfließt) wie folgt: ein niedriges Schlaganfallrisiko ohne Indiktion zur OAK wird Männern mit einem Score von 0 und Frauen mit einem Score von 0 oder 1 zugeordnet. Bei einem Score von 1 (Männer) oder 2 (Frauen) wird eine „Kann"-Indikation

abgeleitet („OAK sollte erwogen werden“), eine eindeutige Indikation zur OAK besteht also ab einem CHA_2DS_2-VASc Score von 2 (Männer) bzw. 3 (Frauen)[32, 33]. Deutsche, europäische und amerikanische Leitlinien zur Sekundärprävention bei Schlaganfallpatient*innen mit VHF empfehlen eine OAK ohne Bezugnahme auf den CHA_2DS_2-VASc Score, da ein stattgehabter Schlaganfall oder TIA hier bereits mit zwei Punkten und weibliches Geschlecht mit einem Punkt eingeht[26, 27, 34].

Neben Empfehlungen zur Lebensstiländerung wie Nikotinkarenz, Ausgewogenheit in der Ernährung und ausreichender körperlicher Aktivität sind individuelle Situationen zu berücksichtigen, die mit bestimmten Therapieoptionen assoziiert sind[35]. Ergibt die Diagnostik eine mindestens 50%ige ipsilaterale Karotisstenose, sollte eine operative Thrombendarteriektomie (*carotid endarterectomy*, CEA) diskutiert werden[36]. Alternativ steht auch das Verfahren einer Stentversorgung (*carotid artery stenting*, CAS) zur Verfügung[36]. Lange unklar blieb die therapeutische Konsequenz aus der Feststellung eines persistierenden Foramen Ovale (PFO), welches sich als i.d.R. hämodynamisch irrelevantes Relikt der fetalen Zirkulation bei mindestens 25% der Allgemeinbevölkerung nachweisen lässt[37]. Bei Patientinnen und Patienten mit kryptogenem Schlaganfall (→ *3.5 Schlaganfallätiologien*) ist die Rate an detektierten PFOs jedoch ungefähr doppelt so hoch[38]. Dabei scheint die kausale Bedeutung bzw. das attributale Risiko eines detektierten PFOs für den Schlaganfall mit dem Alter der Patientinnen und Patienten abzunehmen[37]. Aktuelle Leitlinien empfehlen daher einen interventionellen PFO-Verschluss nur für Patientinnen und Patienten zwischen 16 und 60 Jahren mit kryptogenem Schlaganfall und mindestens moderat ausgeprägtem Shunt-Volumen[39, 40]. An dieser Stelle kann nicht auf alle speziellen diagnostischen und therapeutischen Empfehlungen nach Schlaganfall oder TIA wie z.B. bei Dissektion oder Vaskulitis eingegangen werden und es sei auf die Empfehlungen der jeweiligen Leitlinien verwiesen.

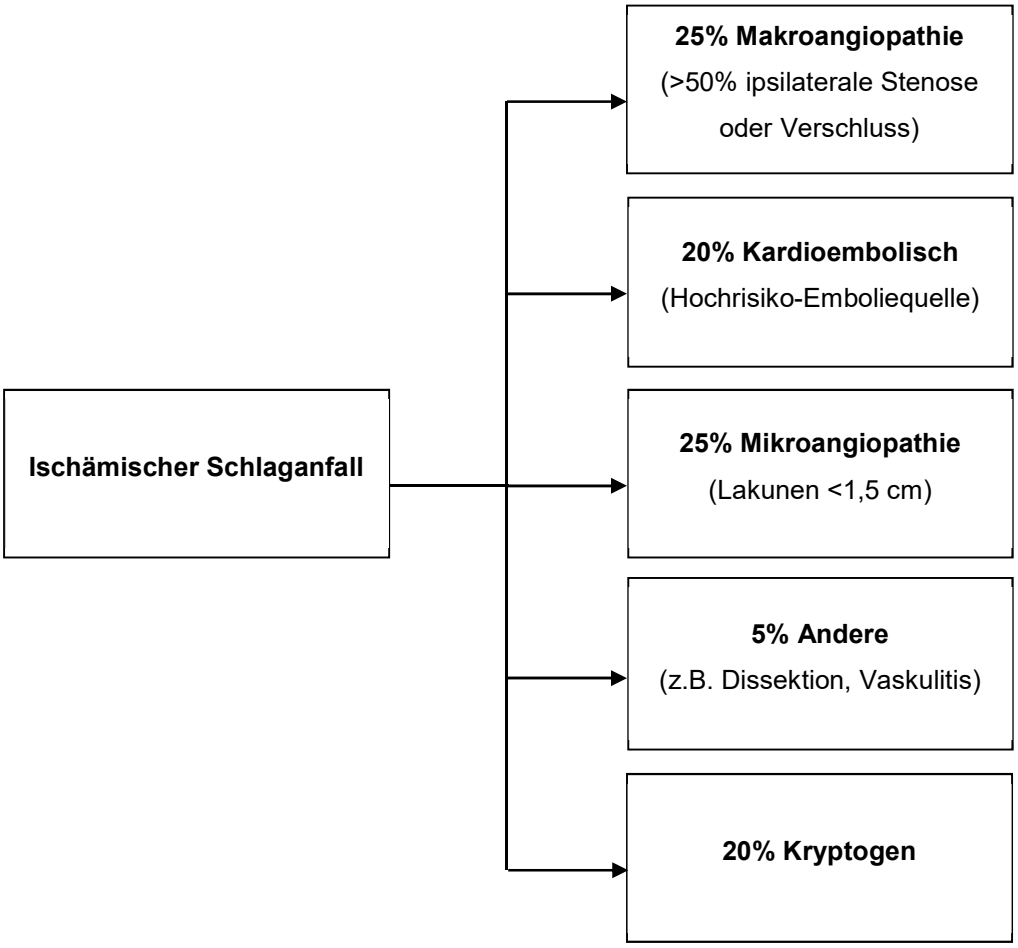
3.5 Schlaganfallätiologien

Wie bereits erwähnt, ist eine standardisierte und möglichst vollständige diagnostische Abklärung nach einem Schlaganfall unerlässlich hinsichtlich der Festlegung bzgl. der mutmaßlichen Schlaganfallursache und mithin für die Entscheidung über die bestmögliche Sekundärprävention. Zur Klassifikation der Schlaganfallätiologie wurden verschiedene Schemata vorgeschlagen wie das Causative Classification System (CSS, 2007), das ASCO(D)-Schema (2009/2013) oder die Chinese Ischemic Stroke Subclassification (CISS, 2011)[41]. Das sowohl klinisch als auch wissenschaftlich am weitesten

verbreitete Schema bleibt jedoch die sog. TOAST Klassifikation (Trial of Org 10172 in Acute Stroke Treatment) aus dem Jahre 1993[42]. Die TOAST Klassifikation unterteilt in fünf ätiologische Kategorien: 1. „*Large-artery atherosclerosis*“ (LAA; im deutschen Sprachraum häufig als „makroangiopathisch“ oder „arterio-arteriell embolisch“ bezeichnet oder unzulässig verkürzend nur für >50%ige Karotisstenosen verwendet). Diese Kategorie erfordert eine >50%ige Stenose oder Verschluss dem Schlaganfall vorgeschalteter präzerebraler oder zerebraler Arterien mutmaßlich arteriosklerotischer Ursache. 2. „*Cardioembolism*“ (CE): als kardio-embolisch werden Schlaganfälle bezeichnet, bei denen zumindest eine kardiale Emboliequelle nachgewiesen werden kann (in Abwesenheit einer LAA). Die TOAST-Klassifikation unterscheidet hierbei weiter zwischen „high-risk“ und „medium-risk“ Emboliequellen und nachfolgend auch zwischen einer wahrscheinlichen („probable“) und einer möglichen („possible“) kardioembolischen Schlaganfallgenese (→ *3.6 Bedeutung kardialer Pathologien*). 3. „*Small-artery occlusion*“ (SAO; im Deutschen häufig als mikroangiopathisch oder „lakunärer Schlaganfall“ bezeichnet) – diese Schlaganfallentität bezieht sich auf subkortikale Infarkte mit einer längsten Ausdehnung von max. 1,5 cm in der Bildgebung (CT oder MRT) in Abwesenheit einer LAA und/oder CE. Klinisch typisch sind lakunäre Syndrome ohne Zeichen einer kortikalen Beteiligung[43]. 4. „*Other*“: diese Gruppe umfasst alle selteneren, aber wohldefinierten Schlaganfallätiologien, die nicht 1.-3. zuzuordnen sind, wie z.B. Dissektionen, Vaskulitiden oder Gerinnungsstörungen. 5. „*Undetermined*“ (häufig auch als „kryptogen“ bezeichnet): in diese Kategorie fallen drei sehr heterogene Konzepte, die eigentlich wiederum voneinander getrennt betrachtet werden müssen: a) Nachweis von mehr als einer Ätiologie gem. 1.-4. (also z.B. gleichzeitiger Nachweis einer ipsilateralen Karotisstenose und von Vorhofflimmern); b) fehlende Zuordnung zu 1.-4. bei unvollständiger diagnostischer Abklärung (es wurde z.B. keine extrakranielle Gefäßdarstellung durchgeführt) und c) keine Zuordnung zu 1.-4. trotz umfangreicher Diagnostik (*kryptogen* im engeren Sinne, z.B. Nachweis eines kortikalen Infarktes ohne Nachweis einer ipsilateralen Karotisstenose oder sonstiger Emboliequelle). Obwohl die TOAST-Klassifikation explizit zum Einsatz in klinischen Studien entwickelt wurde (und nicht primär für den klinischen Alltag) und der Nutzen hinsichtlich der Therapie und Prävention von Schlaganfällen wiederholt in Frage gestellt wurde, bleibt sie doch bis heute der gängige Standard[41, 44]. Abbildung 1 zeigt die prozentuale Verteilung der TOAST-Kategorien in nordamerikanischen und europäischen

Studien (adaptiert nach[45]). Insgesamt ist die Datenlage uneinheitlich, und einzelne Studien deuten darauf hin, dass der Anteil kardio-embolischer Schlaganfälle noch deutlich höher liegen könnte[46].

Abbildung 1 – Prozentuale Verteilung der TOAST-Kategorien in nordamerikanischen und europäischen Studien (adaptiert nach Hart et al. 2014[45])



Im Jahr 2014 wurde erstmals das ESUS-Konzept vorgestellt (*Embolic Stroke of Undetermined Source*)[45]. Grundlage war die Annahme, dass ein relevanter Anteil der als kryptogen klassifizierten Schlaganfälle mutmaßlich thromboembolischer Genese sei[45]. Als Voraussetzung wurde ein embolisches (also nicht-lakunäres) Infarktmuster in der Bildgebung benannt (kortikale Infarkte bzw. subkortikale Infarkte mit einem Mindestdurchmesser von ≥1,5 cm [CT] bzw. ≥2,0 cm [diffusionsgewichtete Sequenz im MRT])[45]. Weiterhin mussten alternative Ursachen wie eine korrespondierende ≥50%

intra- oder extrakranielle Gefäßstenose, Vorhofflimmern (≥24 Stunden EKG-Monitoring), sonstige kardiale Hochrisiko-Emboliequellen (mittels TTE), oder andere spezifische Schlaganfallursachen ausgeschlossen sein[45]. Ein systematisches Review mit Meta-Analyse aus dem Jahr 2017 schätzte den Anteil an ESUS in Bezug auf die Gesamtheit aller Schlaganfälle auf 17% (Range: 9%-25%)[47]. Auf Grundlage des ESUS-Konzepts wurde in mehreren großen randomisierten Studien (NAVIGATE ESUS, RESPECT ESUS) eine Sekundärprophylaxe mittels NOAK im Vergleich zu ASS bei Patient*innen untersucht, die jedoch keinen Vorteil hinsichtlich erneuter Schlaganfälle bei gleichzeitig erhöhten Blutungsraten zeigen konnten[48, 49]. Auch in der ARCADIA und der ATTICUS Studie, die Apixaban mit ASS bei ESUS-Patient*innen mit Zeichen der atrialen Kardiopathie (ARCADIA) bzw. zumindest einem prädiktiven Faktor für Vorhofflimmern oder Nachweis eines PFO (ATTICUS) hinsichtlich des Auftretens neuer bildgebend nachgewiesener Ischämien nach einem Jahr verglichen, konnte hier keinen Vorteil für die Therapie mit einem NOAK belegen[50, 51]. Es wurde spekuliert, dass okkultes Vorhofflimmern ein selteneres Phänomen bei ESUS Patient*innen sein könnte als erwartet, und dass das ESUS Konzept nicht spezifisch für kardiale Emboliequellen sei[52].

3.6 Bedeutung kardialer Pathologien

Kardiale Pathologien spielen eine herausragende Rolle in der Genese des ischämischen Schlaganfalls[53]. In der Literatur wird ca. jeder fünfte ischämische Schlaganfall auf eine kardiale Embolie zurückgeführt (Abbildung 1)[54]. Gleichzeitig sind Patientinnen und Patienten, die eine kardiale zerebrale Embolie erleiden, im Durchschnitt schwerer betroffen als bei Schlaganfällen anderer Ursache[55]. Das häufigste pathologische Substrat einer kardialen Embolie ist dabei das Vorhofflimmern[56]. Das Auftreten von Vorhofflimmern weist einen klaren Altersbezug auf mit einer Prävalenz von <0,1% bei Erwachsenen unter 55 Jahren bis hin zu >10% in der Altersgruppe >80 Jahre[57]. Ähnliches gilt für weitere kardiale Erkrankungen, die mit einem ischämischen Schlaganfall in Verbindung stehen können, wie z.B. den Myokardinfarkt, das Vorliegen einer Herzinsuffizienz oder degenerative Veränderungen der Herzklappen[58]. In Anbetracht einer alternden Bevölkerung zumindest in Ländern mit hohem Einkommen muss von einer weiteren Zunahme sowohl der Prävalenz kardialer Erkrankungen als auch einer weiteren Zunahme durch kardiale Embolien verursachter Schlaganfälle ausgegangen werden (Modelle aus Großbritannien gehen von einer Verdreifachung der Rate kardio-

embolischer Schlaganfälle bis zum Jahr 2050 aus)[59]. Eine Vielzahl weiterer kardialer Pathologien ist ursächlich mit der Genese zerebraler Embolien in Verbindung gebracht worden[53]. Bei der Mehrheit der genannten Pathologien besteht jedoch Unklarheit bezüglich einer spezifischen therapeutischen Konsequenz[29]. Ausnahmen sind hier im Wesentlichen das Vorliegen von Vorhofflimmern (ggf. mit Indikation zur OAK in Abhängigkeit vom CHA_2DS_2-VASc Score), der strukturelle Nachweis einer infektiösen Endokarditis oder Nachweis eines PFO in relevanter Risikokonstellation (gem. ROPE bzw. PASCAL-Score) bei Patientinnen und Patienten ≤60 Jahren[39, 40]. Hinsichtlich der Detektion eines intraventrikulären Thrombus konnte bisher gezeigt werden, dass eine OAK in ca. 70% der Fälle zu einer Rückbildung des Thrombus führt[60]. Dass bei Patientinnen und Patienten mit einem intraventrikulären Thrombus durch eine Antikoagulation Schlaganfälle verhindert würden, ist nicht bewiesen[61].

Auch der akute Myokardinfarkt ist als kardialer Risikofaktor mit dem Auftreten von Schlaganfällen assoziiert, insbesondere im Kontext von konkomitantem Vorhofflimmern[62, 63]. Dabei ist das Schlaganfallrisiko insbesondere in den ersten fünf Tagen nach Myokardinfarkt erhöht[64]. Gleichzeitig haben 10-15% aller Schlaganfallpatient*innen in der Vergangenheit einen Myokardinfarkt erlitten[65, 66]. Eine Folge der myokardialen Minderdurchblutung können Wandbewegungsstörungen bzw. hypo- oder akinetische Segmente und mithin eine relevante Pumpfunktionsstörung sein[67]. Verschiedene Studien konnten zeigen, dass ein Nachweis akinetischer Segmente bzw. eine reduzierte linksventrikuläre Ejektionsfraktion (LVEF) eine intrakardiale Thrombusformierung begünstigt[68]. Eine Analyse der SCD-HeFT Studie fand eine jährliche Thromboembolierate von 1.7% bei Patient*innen ohne bekanntes VHF und antiarrhythmische Therapie[69]. Einschlusskriterium für die SCD-HeFT Studie bzgl. der systolischen Herzfunktion war eine LVEF ≤35%[70]. Insbesondere die Gruppe mit einer LVEF ≤20% zeigte eine erhöhte Rate thrombembolischer Ereignisse, während sich die Gruppen 21-29% und 30-35% nicht signifikant unterschieden[69]. In der WARCEF Studie konnte trotz einer signifikanten Reduktion der Rate an ischämischen Schlaganfällen kein Vorteil für eine OAK mit Warfarin gegenüber ASS bei Patienten mit einer LVEF ≤35% ohne bekanntes Vorhofflimmern gezeigt werden, da gleichzeitig die Rate großer Blutungen erhöht war[71]. Eine post-hoc Analyse der WARCEF-Studie konnte eine LVEF <15% als unabhängigen Risikofaktor für das Auftreten von ischämischen Schlaganfällen idenzifizieren[72]. Es ist weiterhin unklar, ob eine OAK bei Schlaganfallpatient*innen mit reduzierter

LVEF ohne nachgewiesenes VHF oder intrakardialen Thrombus in bestimmten Situationen von Vorteil gegenüber einer Thrombozytenfunktionshemmung sein kann[72]. Für das ESUS Konzept wurde eine LVEF <30% als Hochrisiko-Emboliequelle definiert[45]. Eine Subgruppenanalyse der NAVIGATE ESUS Studie konnte bei ESUS-Patienten mit reduzierter linksventrikulärer Dysfunktion einen Vorteil einer OAK mit Rivaroxaban gegenüber ASS hinsichtlich des Auftretens von Rezidivschlaganfällen oder systemischen Embolien zeigen[73]. Eine linksventrikuläre Dysfunktion war hierbei definiert als das Vorliegen einer regionalen Wandbewegungsstörung und/oder einer moderat bis schwer eingeschränkten Kontraktilität des linken Ventrikels, wobei diese wiederum durch eine LVEF <40% definiert war[73]. Die aktuellen Leitlinien sprechen sich nicht generell für eine OAK bei Schlaganfallpatient*innen mit eingeschränkter Pumpfunktion aus: gemäß den deutschen Leitlinien kann „bei Nachweis einer Herzinsuffizienz mit reduzierter Ejektionsfraktion (LVEF ≤35%) bei Patienten mit ischämischem Schlaganfall oder TIA im Sinusrhythmus eine Therapie mit OAK anstelle einer Thrombozytenfunktionshemmung erwogen werden“[61].

3.7 Kardiale Diagnostik nach ischämischem Schlaganfall

Eine kardiale Diagnostik ist elementarer Teil der diagnostischen Abklärung nach einem ischämischen Schlaganfall[29]. Im Kern besteht hierbei jedoch nur Konsens, allen Schlaganfallpatientinnen und -patienten ein EKG-Monitoring über die Dauer von mindestens 24 Stunden im Rahmen der Stroke Unit Behandlung zukommen zu lassen[29]. Bereits über die Indikation und Auswahl einer Echokardiographie herrscht Uneinigkeit: die deutschen Leitlinien empfehlen eine Echokardiographie, wenn die Schlaganfallätiologie durch die übrige Diagnostik nicht geklärt werden konnte[29]. Andererseits wird die transthorakale Echokardiographie (TTE) indirekt regelhaft empfohlen, da sie unter dem Begriff „Routinediagnostik“ mit aufgeführt wird[29]. Während die TTE eine nicht-invasive, ggf. bettseitige Option zur Beurteilung der Pumpfunktion und Klappenmorphologie darstellt, ist die transösophageale Echokardiographie (TOE) hinsichtlich der Mehrzahl für eine potentielle Schlaganfallätiologie relevanten Fragestellungen der TTE überlegen[74]. Dabei muss jedoch berücksichtigt werden, dass es sich bei der TOE um ein semi-invasives Verfahren handelt, dass potentiell relevante Komplikationen birgt, in der Regel eine Sedierung erforderlich macht und einen höheren personellen und apparativen Aufwand im Vergleich zum TTE bedeutet[74]. Eine deutschlandweite Analyse von Audit-Daten aus der Stroke Unit Zertifizierung erbrachte dabei, dass nur zwei Drittel aller

Stroke Unit-Patient*innen eine TTE und nur ca. jede*r fünfte ein TOE erhält, wobei die TTE-Rate mit der Größe des Zentrums (Zahl der behandelten Patient*innen) abnahm[75]. Die ätiologische Schlaganfallklassifikation nach TOAST (→ *3.5 Schlaganfallätiologien*) berücksichtigt Befunde der Echokardiographie, ohne jedoch explizite Angaben zu machen, welche diagnostischen Maßnahmen eine „vollständige Evaluation" eigentlich ausmachen[42]. Das ESUS-Konzept hingegen fordert explizit eine „präkordiale [d.h. transthorakale] Echokardiographie" zum Ausschluss einer kardialen Emboliequelle[45].

Die kardiale Schnittbildgebung mittels Kardio-CT oder Kardio-MRT (*cardiovascular MRI*, CMR) ist zuletzt mehr in den Fokus als diagnostische Alternative bzw. Ergänzung bei Patientinnen und Patienten mit Schlaganfall geraten[76]. Als Alternative zur Echokardiographie steht einerseits das EKG-getriggerte Multidetektor-CT zur Verfügung (*multidetector computed tomography*, MDCT)[77]. Offensichtliche Vorteile sind hier eine verkürzte Untersuchungszeit, Unabhängigkeit von einem notwendigen Schallfenster und eine verbesserte räumliche Auflösung[78]. Studien, die den Einsatz der kardialen CT im Kontext des ischämischen Schlaganfalls untersuchten, fanden einen relevanten Anteil kardialer Pathologien[79, 80]. Potentielle Nachteile der kardialen CT stellen der unzureichende Weichteilkontrast dar, der eine myokardiale Gewebedifferenzieung limitiert, die dem Verfahren inhärente Exposition zu ionisierenden Strahlen sowie ggf. die Gabe iodhaltiger, potentiell thyreo- und nephrotoxischer Kontrastmittel[81].

Insbesondere die CMR bei 3,0 Tesla bietet eine hervorragende Gewebskontrastierung einschließlich Cine-Bildgebung, MR Koronarangiographie, Perfusionsmessung, Kontrastmittelspätanreicherung und Darstellung der Gefäßwände[82]. State-of-the-art Sequenzen wie T1 und T2 Mapping versprechen eine noch weitergehende Gewebedifferenzierung hinsichtlich diffuser Fibrosierung und/oder Ödembildung[83, 84]. Einzelne Studien haben den Einsatz der CMR bei Schlaganfallpatient*innen untersucht und fanden diese praktikabel und sicher bei ausgewählten Patientinnen und Patienten in einem Studiensetting[85-87]. Auch zur Bestimmung funktioneller Parameter wie der LVEF gilt die CMR als Goldstandard[88]. Ob eine erweiterte kardiale Bildgebung mittels MDCT oder CMR einen diagnostischen oder gar therapeutisch relevanten Mehrwert bietet, ist unklar: einzig die deutschen Leitlinien erwähnen die Option zur komplementären Durchführung einer erweiterten kardialen Bildgebung dahingehend, dass „eine zusätzliche kardiale CT/MRT in der Akutsituation oder Frühphase entscheidende diagnostische Vorteile hinsichtlich der Schlaganfallätiologie bieten kann"[29].

3.8 Prognoseabschätzung

Die Identifizierung und adäquate Versorgung von Schlaganfallpatient*innen mit besonders hohem Risiko für Rezidiv- und Folgeereignisse bleibt eine große Herausforderung[89]. Aktuelle Modelle zur individuellen Risikovorhersage basieren i.d.R. auf den bekannten kardio-vaskulären Risikofaktoren und liefern unzureichende Ergebnisse[90, 91]. Verschiedene Prognosescores wurden zur Einschätzung des kurz- und langfristigen Risikos für das Auftreten von Rezidivschlaganfällen und/oder schwerwiegenden kardio-vaskulären Ereignissen vorgeschlagen[92]. Obwohl ursprünglich für die Triage nach TIA entwickelt, ist der $ABCD^2$ Score das klinisch am weitesten verbreitete Werkzeug zur Prognoseabschätzung für das Auftreten von Rezidivschlaganfällen auch nach ischämischen Schlaganfall[93, 94]. Verschiedene Modifikationen des $ABCD^2$ Scores unter Hinzunahme weiterer Informationen (z.B. bildgebende Befunde i.S. eines Infarktnachweises in der DWI-Sequenz [$ABCD^2$I Score] oder einer überdies vorliegenden ≥50% ipsilateralen Karotisstenose [$ABCD^3$-I Score]) wurden vorgeschlagen und validiert[95, 96]. Für die Langzeitprognose scheinen insbesondere der Essen Stroke Risk Score (ESRS) und das Stroke Prognosis Instrument II (SPI-II) nützlich zu sein[92]. Das Schlaganfallrisiko im Kontext von Vorhofflimmern wird mit dem bereits erwähnten CHA_2DS_2-VASc Score eingeschätzt (→ *3.4 Behandlung des akuten Schlaganfalls und frühe Sekundärprävention*).

Für die Beurteilung des Schlaganfallschweregrads hat sich sowohl für die wissenschaftliche Analyse als auch im klinischen Alltag der NIHSS (*National Institutes of Health Stroke Scale*) Score etabliert[97]. In seiner heutigen Form wurde er ursprünglich für die NINDS Studie 1994 konzipiert[98]. Der NIHSS erfasst insgesamt 11 Domänen aus den Bereichen Bewusstsein, Orientierung, Okulomotorik, Gesichtsfeld, Motorik, Koordination, Sensibilität, Sprache/Sprechen sowie Aufmerksamkeit[98]. Die mögliche Punktzahl liegt zwischen 0 und 42, wobei eine höhere Punktzahl einer Zunahme des Schlaganfallschweregrads entspricht[98]. Zur Erfassung des funktionellen Zustands nach Schlaganfall wird im Rahmen von klinischen Studien üblicherweise der modified Rankin Scale (mRS) Score verwendet[99]. Der Score entspricht dabei einer ordinalen Skala mit diskreten Werten zwischen 0 und 6 Punkten, wobei ein höherer Punktwert eine größere funktionelle Abhängigkeit bedeutet[100]. Null Punkte entsprechen völliger Beschwerdefreiheit und 5 Punkte vollständiger Abhängigkeit; 6 Punkte werden für Versterben vergeben[101].

In Ergänzung zu einer Risikoabschätzung auf Grundlage „klassischer“ Risikofaktoren wurde eine Vielzahl blut-basierter Biomarker hinsichtlich einer Prognoserelevanz nach Schlaganfall analysiert[102]. Gleichzeitig besteht eine Diskrepanz zwischen der Anzahl publizierter Studien und der Umsetzung in klinisch relevante und anwendbare Prognoseinstrumente[102]. Eine Ursache hierfür sind sich methodologische und statistische Schwächen vieler Studien sowie fehlende Standards für das Berichten von Biomarker-basierten Studien[102]. Unter >250 analysierten Biomarkern insbes. natriuretische Peptide, Stressmarker (Copeptin und Cortisol), Inflammationsmarker (Procalcitonin und Mannose-bindendes Protein [MBP]) sowie Marker der Atherogenese (Adipozyten-Fettsäure-bindendes Protein [AFABP]) mit schlechtem Outcome nach Schlaganfall assoziiert[102]. So wurde z.B. ein Risikoscore für ein schlechtes Outcome drei Monate nach Schlaganfall basierend auf Alter, NIHSS und Rekanalisationstherapie unter Hinzunahme von Copeptin (der *CoRisk Score*) vorgeschlagen[103]. Unter den natriuretischen Peptiden konnte auch für das Vorläuferprotein des atrialen natriuretischen Peptids (Midregional pro-ANP [MR-proANP]) ein Zusammenhang mit schlechtem Outcome nach Schlaganfall, Mortalität nach drei Monaten sowie der Detektion einer kardioembolischen Schlaganfallursache bzw. VHF nachgewiesen werden[104, 105].

3.9 Ziele der Arbeit

In dieser kumulativen Habilitationsschrift werden eigene Publikationen, die sich im Kern mit der Diagnostik, Therapie und prädiktiven Bedeutung kardialer Pathologien für den akuten ischämischen Schlaganfall befasst haben, vorgestellt und diskutiert.

Übergeordnetes Ziel war es einerseits, mit Hilfe der MRT des Herzens eine möglichst umfassende kardiale Phänotypisierung bei Patientinnen und Patienten mit akutem Schlaganfall zu erreichen und mithin zum besseren pathophysiologischen Verständnis kardialer Pathologien im Kontext der vaskulären Diagnose „ischämischer Schlaganfall“ beizutragen. Anderseits sollte die prädiktive Bedeutung von kardialem Troponin für das Auftreten schwerwiegender kardialer Folgeereignisse nach ischämischem Schlaganfall untersucht werden. Demgegenüber steht eine Analyse der therapeutischen Versorgungsrealität bei Indikation für eine orale Antikoagulation vor und nach Einführung der sog. „neuen“, nicht Vitamin-K abhängigen oralen Antikoagulanzien (NOAKs). Eine weitere Arbeit befasst sich mit den Ursachen, Sekundärprävention und Behandlungsergebnissen bei Patientinnen und Patienten mit sog. „Durchbruchschlaganfall“, also einem Schlaganfall im Kontext des Vorhofflimmerns unter bestehender Antikoagulation. Die abschließend dargestellte Arbeit untersuchte die Fragestellung, ob eine bestehende Therapie mit einem NOAK einen Einfluss auf den Schlaganfallschweregrad im Falle eines ischämischen Schlaganfalls trotz OAK hat.

Im Folgenden werden die einzelnen Arbeiten genauer beschrieben und die jeweilige Originalpublikation vorgelegt.

4. Eigene Arbeiten

*4.1 Eine intensivierte diagnostische Aufarbeitung erhöht die Rate pathologischer Befunde bei Patient*innen mit akutem ischämischem Schlaganfall: Ergebnisse der prospektiven HEBRAS Studie.*

Hellwig S., Krause T., Scheitz J. F., Herm J., Grittner U., Jauert N., Fiebach J. B., Kasner M., Döhner W., Endres M., Wachter R., Elgeti T., Nolte C. H., Haeusler K. G.: Enhanced diagnostic workup increases pathological findings in patients with acute ischaemic stroke: results of the prospective HEBRAS study. *Stroke Vasc Neurol.* 2024 Apr 30;9(2):145-152. DOI: 10.1136/svn-2022-002179

Die HEBRAS Studie (*Heart and Brain Interfaces in Acute Ischemic Stroke*) war eine prospektive, monozentrische Studie des Centrums für Schlaganfallforschung der Charité - Universitätsmedizin Berlin (CSB)[106]. Primäre Hypothese war, dass ein Ansatz mit intensivierter diagnostischer Aufarbeitung in der Akutphase nach einem Schlaganfall (einschließlich kardiovaskulärer MRT, MR-Angiographie des Aortenbogens sowie eines additiven, bis zu 10-tägigen Langzeit-EKGs) mit einer erhöhten Detektionsrate prädefinierter pathologischer Befunde assoziiert ist[106]. Dies ist bedeutsam vor dem Hintergrund, dass bei einem relevanten Anteil von Schlaganfallpatient*innen nach Abschluss der Routine-Diagnostik keine definitive Schlaganfallursache eruiert werden kann (→ *3.5 Schlaganfallätiologien*)[107]. Ein erweiterter diagnostischer Ansatz könnte als dazu beitragen, die Rate als „kryptogen“ klassifizierter Schlaganfälle zu reduzieren und somit möglicherweise auch einen Einfluss auf die Sekundärprävention nach Schlaganfall haben[106].

In Vorarbeiten konnte gezeigt werden, dass der Einsatz der CMR bei einer ausgewählten Population von Schlaganfallpatient*innen sicher und durchführbar ist[87]. In der HEBRAS Studie standen insgesamt 356 Patient*innen für die primäre Analyse zur Verfügung, wobei in 292 Fällen (82.0%) eine kardiovaskuläre MRT durchgeführt werden konnte[108]. Alle Patient*innen erhielten das additive, studienspezifische Langzeit-EKG mit einer durchschnittlichen Aufzeichnungsdauer von 162 Stunden (IQR 98-210 Stunden)[108]. Die Detektionsrate der präspezifizierten pathologischen Befunde konnte durch den intensivierten diagnostischen Ansatz mehr als verdreifacht werden (16,1% vs. 5,3%), wobei die Rate an erstmalig detektiertem Vorhofflimmern verdoppelt wurde

(4.5% vs. 2.0%)[108]. Entsprechend reduzierte sich die Rate der als „kryptogen“ klassifizierten Schlaganfälle um 7% (38,5% vs. 45,5%), wobei darauf hingewiesen werden muss, dass konkurrierende Ursachen nicht als „kryptogen“ klassifiziert wurden (→ *3.5 Schlaganfallätiologien*)[108]. Zu bemerken bleibt, dass im Wesentlichen die Detektion von Vorhofflimmern zu einer Änderung der Sekundärprävention führte, sonstige therapierelevante Befunde blieben selten (intraventrikulärer Thrombus bei drei Patient*innen)[108]. Die Rate an Echokardiographien war vergleichsweise niedrig (da eine solche nicht als studienspezifische Maßnahme, sondern ggf. im Rahmen der Routinediagnostik stattfand): eine TTE wurde bei 127 Patient*innen (35.7%) und eine TOE bei 195 Patient*innen (54,8%) durchgeführt[108]. Die CMR fand eine reduzierte LVEF (per Studienprotokoll definiert als <45%) bei 40 Patienten (11.2%) und eine LVEF <30% (entsprechend der ESUS Definition) bei 8 Patienten (2.2%)[108]. In diesem Kontext zeigte unlängst eine post-hoc Analyse der NAVIGATE ESUS Studie einen Vorteil einer OAK mit Rivaroxaban bei ESUS Patient*innen mit gestörter linksventrikulärer Funktion zeigen (Definition siehe → *3.6 Bedeutung kardialer Pathologien*)[73]. Ob sich dies auch in einem prospektiven, randomisierten Studiendesign replizieren lässt, muss in Folgestudien adressiert werden.

SVN Stroke & Vascular Neurology

Enhanced diagnostic workup increases pathological findings in patients with acute ischaemic stroke: results of the prospective HEBRAS study

Simon Hellwig ,[1,2,3] Thomas Krause,[4] Jan F Scheitz ,[1,2,3,5] Juliane Herm ,[1,2] Ulrike Grittner ,[6] Nadja Jauert,[2,5,7,8] Jochen B Fiebach ,[2] Mario Kasner,[9] Wolfram Doehner ,[2,5,7,8] Matthias Endres ,[1,2,3,5,10] Rolf Wachter ,[11] Thomas Elgeti ,[12] Christian H Nolte ,[1,2,3,5,10] Karl Georg Haeusler [13]

To cite: Hellwig S, Krause T, Scheitz JF, *et al*. Enhanced diagnostic workup increases pathological findings in patients with acute ischaemic stroke: results of the prospective HEBRAS study. *Stroke & Vascular Neurology* 2024;**9**: e002179. doi:10.1136/svn-2022-002179

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/svn-2022-002179).

CHN and KGH contributed equally.

Received 17 November 2022
Accepted 5 June 2023
Published Online First 23 June 2023

For numbered affiliations see end of article.

Correspondence to
Karl Georg Haeusler, Department of Neurology, University Hospital Würzburg, Josef-Schneider-Straße 11, 97080 Würzburg, Germany; haeusler_k@ukw.de

ABSTRACT

Background Stroke aetiology remains cryptogenic in a relevant proportion of patients with acute ischaemic stroke (AIS). We assessed whether enhanced diagnostic workup after AIS yields a higher rate of prespecified pathological findings compared with routine diagnostic care in-hospital.

Methods Hospitalised patients with AIS were prospectively enrolled in the investigator-initiated observational HEart and BRain Interfaces in Acute Ischaemic Stroke (HEBRAS) study at the Charité, Berlin, Germany. Patients with AIS without known atrial fibrillation (AF) underwent cardiovascular MR imaging (CMR), MR-angiography of the aortic arch and prolonged Holter-ECG monitoring on top of routine diagnostic care.

Results Among 356 patients with AIS (mean age 66 years, 37.6% female), enhanced workup yielded a higher rate of prespecified pathological findings compared with routine care (17.7% vs 5.3%; p<0.001). Consequently, fewer patients were classified as cryptogenic after enhanced diagnostic workup (38.5% vs 45.5%, p<0.001). Routine care included echocardiography in 228 (64.0%) patients. CMR was successfully performed in 292 (82.0%) patients and revealed more often a prespecified pathological finding compared with routine echocardiography (16.1% vs 5.3%). Furthermore, study-related ECG monitoring (median duration 162 hours (IQR 98–210)) detected AF in 16 (4.5%) patients, while routine monitoring (median duration 51 hours (IQR 34–74)) detected AF in seven (2.0%) patients.

Conclusions Enhanced diagnostic workup revealed a higher rate of prespecified pathological findings in patients with AIS compared with routine diagnostic care and significantly reduced the proportion of patients with cryptogenic stroke.

Trial registration number NCT02142413.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Routine diagnostic care in-hospital does not allow a definite conclusion on stoke aetiology in a relevant proportion of patients with acute ischaemic stroke. Cardiovascular MRI and prolonged Holter-ECG are not part of clinical routine, but might be useful to improve aetiological classification after stroke.

WHAT THIS STUDY ADDS

⇒ In this prospective observational trial, enhanced cardiac workup led to a more than threefold increase in pathological findings and significantly reduced the rate of cryptogenic strokes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More accurate assessment of stroke aetiology may improve secondary prevention strategies in the future and thus help to reduce cardiovascular disease burden.

INTRODUCTION

The efficacy of secondary prevention after acute ischaemic stroke (AIS) depends on accurate and early determination of stroke aetiology.[1] Despite its well-known shortcomings, the long-established TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria remain the most widely used aetiological classification system in clinical routine.[2 3] Dating back to 1993, the classification is essentially based on then-available diagnostic means, mainly cerebral CT and ultrasound of the brain-supplying arteries.[2] Since then, additional diagnostic techniques have evolved, and the concept of embolic stroke of undetermined source (ESUS) was introduced to facilitate clinical research in the field of cryptogenic strokes with presumably (cardio)embolic origin.[4] Yet, to date, there is no universal consensus regarding the recommended diagnostic procedures and the extent of cardiovascular evaluation to determine stroke aetiology,[5 6] even in healthcare systems with standardised nationwide stroke unit systems.[7 8] For example, a recent investigation has found transesophageal echocardiography (TEE) to yield a higher number of treatment-relevant findings compared with transthoracic echocardiography (TTE)

in patients with undetermined cause of stroke, most often due to detection of patent foramen ovale (PFO).[9] However, TEE is a semi-invasive procedure and is typically provided only to a small proportion of patients with AIS.[10 11] With adequate assessment of the left atrium and the aortic arch being necessary to rule out high-risk sources of cardioembolism,[6] cardiovascular MR imaging (CMR) has been found feasible in selected patients with AIS and has become a complimentary diagnostic method to the clinical gold standard echocardiography.[12–14] With regard to the detection of arrhythmias, prolonged ECG monitoring has been found to increase the rate of patients diagnosed with atrial fibrillation (AF) after AIS.[5 15] However, there is no randomised controlled trial demonstrating a benefit of prolonged ECG monitoring in secondary stroke prevention.[16 17]

In the prospective HEart and BRain Interfaces in Acute Ischaemic Stroke (HEBRAS) study, we aimed to investigate whether an enhanced approach for diagnostic workup after AIS, consisting of CMR, contrast-enhanced MR-angiography of the aortic arch, and prolonged Holter-ECG (for up to 10 days) (1) increases the rate of pathological findings relevant for stroke aetiology compared with routine diagnostic care and (2) leads to a significant reduction in the proportion of patients with cryptogenic stroke aetiology.[18]

METHODS

Study design

The design of the study including primary and secondary outcomes, and a definition of cardiac pathologies regarded relevant for stroke aetiology were published before completing recruitment.[18] Adult patients admitted to the Campus Benjamin Franklin of the Charité with imaging-proven AIS and without a history of AF or AF detection prior to study enrolment were eligible to participate after providing written informed consent. Enhanced diagnostic workup consisted of additional CMR (including cardiac MRI and contrast-enhanced MR-angiography of the aortic arch) and an additional Holter-ECG for up to 10 days (starting immediately after enrolment in-hospital and including up to 5 days after hospital discharge). CMR examinations were assessed centrally by radiologists, being aware of patients' sex, age and the participation in the HEBRAS study. Echocardiography was performed as part of the clinical routine by indication of the treating neurologists and was conducted and assessed by cardiologists regularly unaware of CMR results. The study protocol with a detailed description of all inclusion and exclusion criteria, MRI (3 Tesla MR scanner TIM TRIO, Siemens, Erlangen, Germany) and MRI parameters, study ECG (CardioMem®4000, GETEMED AG, Teltow, Germany), core lab analysis (German Centre for Cardiovascular Research (DZHK), Partner Site Göttingen, Germany) and study follow-up (conduced at three and twelve months after the index stroke) was published before.[18] A summary of respective information can be found in the online supplemental file.

Study outcomes

The primary outcome measure of the HEBRAS study was the rate of pathological findings relevant to stroke aetiology in patients with AIS obtained by enhanced diagnostic workup in comparison to findings obtained by routine diagnostic care in this cohort of patients.[18] The primary hypothesis was that the detection rate of pathological findings can be increased by undergoing enhanced diagnostic workup. The key secondary outcome of HEBRAS was the potential benefit of prolonged continuous ECG-monitoring in patients with AIS by assessing the proportion of patients with first detected paroxysmal AF by prolonged Holter-monitoring in-hospital and for up to 5 days after discharge. For primary and secondary analyses, results of routine diagnostic care and results of enhanced diagnostic care were evaluated in the same cohort of patients.

Definition of stroke aetiology

Stroke aetiology was determined according to TOAST and ESUS criteria.[2 4] Stroke subtype classification was performed by two investigators (SH, CHN). The following cardioaortic sources of embolism were prespecified as relevant based on the original publications for TOAST and ESUS criteria[2 4]: paroxysmal, persistent or permanent AF, sick-sinus-syndrome, bacterial or non-bacterial endocarditis, left-sided intracardiac thrombus or tumour, prosthetic heart valve, higher-grade mitral valve stenosis, left ventricular akinetic segment(s), aortic plaque of ≥4 mm or left ventricular ejection fraction (LVEF) <45% according to TTE or CMR (see online supplemental file for details of LVEF assessment). Myocardial segmentation and nomenclature followed the recommendations of the American Heart Association.[19]

Sample size calculation and statistical analysis

A sample size of 475 patients was initially assumed to provide a power of 79% to detect a difference in the number of strokes classified as cryptogenic (from 30% after routine diagnostic care to 25% after enhanced diagnostic workup with an assumed 13% of discordant pairs and an expected drop-out rate of about 20%) using a McNemar's Test and a two-sided significance level of α=0.05.[18] The prespecified interim analysis after the inclusion of 264 patients led to a readjustment of the sample size (368 patients).

The analysis of the primary hypothesis was tested in all HEBRAS patients ('whole cohort'), following the 'intention to diagnose' principle. Furthermore, we tested the study hypothesis following a 'per-protocol' approach in the subgroup of patients who underwent all diagnostic procedures to be qualified as ESUS patients ('ESUS cohort'). This required brain imaging (CT or MRI), Holter-ECG >20 hours (stroke unit and/or Holter-ECG monitoring), imaging of brain-supplying arteries and

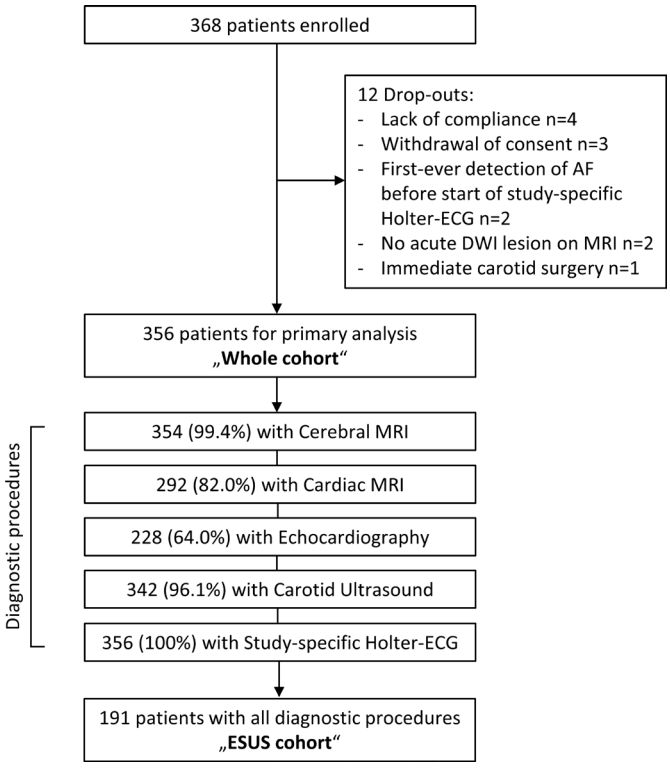


Figure 1 Study flow chart. AF, atrial fibrillation; DWI, diffusion-weighted imaging; ESUS, embolic stroke of undetermined source.

echocardiography (TTE and/or TEE) in routine diagnostic care as well as enhanced diagnostic workup (including study-specific Holter-ECG and CMR).[20 21] A sensitivity analysis was carried out defining an LVEF <30% (instead of <45%) as a relevant pathological finding.

Results are reported as frequencies and percentages for categorical variables. In the case of continuous variables, mean and SD are reported for sufficiently normally distributed data or median and limits of IQR for quantitatively skewed variables. In the case of categorical variables and independent samples, Pearson's χ^2 test was used, whereas the Mann-Whitney U test was implemented as a rank-sum test for ordinal variables. McNemar's test was used for the comparison of paired samples with dichotomised variables. Data were analysed using SPSS statistics V.27 (IBM). To visualise changes in aetiological stroke classification based on routine diagnostic care and enhanced diagnostic workup, respectively, we created a Sankey diagram using the web-based tool SankeyMATIC.

RESULTS

Between May 2014 and February 2017, 368 patients with AIS provided written informed consent for participation in the HEBRAS study. Excluding 12 drop-outs (3.3%), 356 patients were included in the primary analysis ('whole cohort', figure 1). Mean age was 66 years (SD 12, range 24–91) and 134 (37.6%) patients were of female sex. Median National Institutes of Health Stroke Scale score on admission was two points (IQR 1–4). Median mRS on admission was two (IQR 1–3). Intravenous thrombolysis was administered in 66 (18.5%) patients and mechanical thrombectomy was performed in three (0.8%) patients. A detailed description of baseline characteristics can be found in table 1.

Table 1 Baseline characteristics of all 356 patients with AIS included in the HEBRAS study ('whole cohort') and the subgroup of 191 patients undergoing brain imaging, stroke unit or Holter-ECG monitoring >24 hours, imaging of extracranial and intracranial brain-supplying arteries and echocardiography (TTE and/or TEE) according to routine diagnostic care as well as completed enhanced diagnostic workup ('ESUS cohort)

	Whole cohort (n=356)	ESUS cohort (n=191)
Female sex	134 (37.6)	68 (35.6)
Age (years)	66 (±12)	63 (±12)
Length of in-hospital stay (days)	5 (4–6)	5 (4–6)
NIHSS on admission	2 (1–4)	2 (0–3)
mRS on admission	2 (1–3)	2 (1–3)
Barthel Index on admission	100 (75–100)	100 (80–100)
Intravenous thrombolysis	66 (18.5)	35 (18.3)
Diabetes mellitus	65 (18.3)	35 (18.3)
Arterial hypertension	212 (59.6)	98 (51.3)
High blood lipids	125 (35.1)	69 (36.1)
Current tobacco use	96 (27.0)	49 (25.7)
Previous ischaemic stroke or TIA	58 (16.3)	26 (13.6)
Coronary artery disease	42 (11.8)	26 (13.6)
Prior myocardial infarction	31 (8.7)	16 (8.4)
Chronic heart failure	7 (2.0)	2 (1.0)
Oral anticoagulation on admission*	6 (1.7)	2 (1.1)
Antiplatelet(s) on admission	114 (32.0)	59 (30.9)
Acetylsalicylic acid	97 (27.2)	50 (26.2)
Clopidogrel	11 (3.1)	6 (3.1)
Dual antiplatelets†	6 (1.7)	3 (1.6)
Beta blocker on admission	100 (28.1)	48 (25.1)
ACE inhibitor on admission	64 (18.0)	28 (14.7)
Angiotensin II receptor antagonist on admission	73 (20.5)	38 (19.9)
Calcium channel blocker on admission	65 (18.3)	32 (16.8)
Statin on admission	98 (27.5)	52 (27.2)

Data are given as mean (±SD), median (IQR) or n (%).
*Reasons for OAC on admission: known left ventricular aneurysm (phenprocoumon); known intraventricular cardiac thrombus (phenprocoumon); prior myocardial infarction with apical akinesia (phenprocoumon); recent deep venous thrombosis (rivaroxaban), recent pulmonary embolism (rivaroxaban n=1; phenprocoumon n=1).
†ASA+clopidogrel n=4, ASA+ticagrelor n=1, ASA+dipyridamol n=1.
ESUS, embolic stroke of undetermined source; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; TEE, transesophageal echocardiography; TIA, transient ischaemic attack; TTE, transthoracic echocardiography.

Routine diagnostic care in-hospital

In total, 354 (99.4%) of 356 patients underwent brain MRI and had an acute DWI lesion corresponding to

AIS-related clinical deficits. In the remaining two patients, ischaemic stroke was proven by brain CT. A 12-lead ECG was performed in the emergency department or immediately on admission to the stroke unit in 353 (99.2%) patients. Overall, 352 (98.9%) patients were admitted to the stroke unit and underwent monitor-based ECG recording of 52 hours (IQR 35–74). Four patients not admitted to the stroke unit received 24-hour Holter-ECG monitoring according to clinical routine. Taken together, the median duration of ECG monitoring during routine diagnostic care was 51 hours (IQR 34–74). In total, 355 (99.7%) patients received imaging of the extracranial brain-supplying arteries (using duplex sonography in 344 (96.6%), MR-angiography in 90 (25.3%) and CT-angiography in 29 (8.1%) patients). Imaging of the intracranial brain-supplying arteries was performed in all MRI examinations as part of the routine protocol. All patients also received transcranial duplex sonography. Echocardiography was performed in 228 (64.0%) patients, including 127 (35.7%) receiving TTE, 195 (54.8%) receiving TEE and 94 (26.4%) patients receiving both. A comparison of baseline characteristics between study patients who underwent echocardiography and those who did not can be found in the online supplemental material and in online supplemental table 1. Taken together, 228 (64.0%) patients underwent diagnostic workup including echocardiography, brain imaging, ECG monitoring for at least 24 hours and imaging of brain-supplying arteries.

Results of routine diagnostic care in-hospital

Routine diagnostic care in-hospital led to the detection of 103 pathological findings (a priori defined as relevant for stroke aetiology) in 96 (27.0%) of 356 patients. Echocardiography detected 13 relevant pathological findings in 12 (3.4%) patients. In detail, TTE detected at least one akinetic left ventricular segment in 5 (1.4%) of 356 patients, and an LVEF <45% in 2 (0.6%) patients. TEE detected an aortic plaque >4 mm in 5 (1.4%) patients and a type-A aortic dissection in 1 (0.3%) patient. Moreover, although not defined as a relevant pathological finding at the time the study was designed, a PFO was detected in 41 (11.5%) patients, an atrial septal defect in 2 (0.6%) patients and an atrial septal aneurysm in 1 (0.3%) patient. Routine imaging of the brain supplying arteries showed ≥50% ipsilateral arterial stenosis or occlusion in 83 (23.3%) patients. Routine cardiac monitoring revealed a first-ever episode of AF in seven (2.0%) patients.

Stroke aetiology according to routine diagnostic care in-hospital

Aetiology of AIS was categorised as 'large-artery atherosclerosis' in 70 (19.7%) of 356 patients, as 'cardioembolic' in 15 (4.2%) patients, as 'small-artery occlusion' in 85 (23.9%) patients and 10 (2.8%) patients were found to have another determined aetiology according to routine diagnostic care. The remaining 176 (49.4%) patients were classified as 'cryptogenic' at hospital discharge ('stroke of undetermined aetiology').[2] Of those, 14 (3.9%) patients were found to have competing aetiologies, leaving 162 (45.5%) patients with cryptogenic stroke.[2] As 45 of these 162 patients did not receive echocardiography in clinical routine, 117 (32.9%) patients fulfilled the ESUS criteria. A detailed description of the subcategories can be found in the online supplemental file.

Feasibility of enhanced diagnostic workup

In total, 292 patients (82.0%) underwent CMR, of which 6 examinations had to be terminated prematurely according to the patients' will. Individual reasons not to undergo CMR are described in the online supplemental material. Likewise, baseline characteristics of those patients who received CMR and those who did not are presented in online supplemental table 2. Contrast agent was administered in 247 (69.4%) CMR examinations. In total, 239 (67.1%) of 356 patients completed CMR including MR-angiography of the aortic arch. Median examination time for the complete CMR protocol (including contrast-enhanced sequences) was 41 min (IQR 35–48). Median time from stroke onset or time last seen well to CMR was 82.5 hours (IQR 58–112) and median time from admission to CMR was 67 hours (IQR 44–92).

Study-specific Holter-ECG was performed in-hospital in all 356 patients for up to 5 days (median duration 72.5 hours (IQR 47–116)), and in 241 (67.7%) patients after hospital discharge starting in-hospital (median duration 120 hours (IQR 96–120)). The total duration of study-specific Holter-monitoring was 162 hours (IQR 98–210). Median time from stroke onset or last seen well to start of Holter-ECG monitoring was 51 hours (IQR 32–75), and median time from admission to Holter-ECG monitoring was 30 hours (IQR 20–52). In total, 182 (51.1%) of 356 patients completed CMR including MR-angiography of the aortic arch and underwent Holter-ECG monitoring in-hospital and after hospital discharge.

Results of enhanced diagnostic workup

Enhanced diagnostic workup led to the detection of 73 pathological findings in 67 (18.8%) of 356 study participants. CMR detected 60 pathological findings in 47 (13.2%) patients. In detail, at least 1 akinetic left ventricular segment was detected in 14 (3.9%) patients, an LVEF <45% in 40 (11.2%) patients, an intraventricular thrombus in 3 (0.8%) patients, a dilated cardiomyopathy in 2 (0.6%) patients and an intracardiac tumour (intraventricular lipoma) in 1 (0.3%) patient. With regard to the sensitivity analysis implementing an LVEF <30% as a high-risk cardioembolic source, an LVEF <30% was present in 8 (2.2%) patients. Study-specific contrast-enhanced extracranial MR-angiography of the brain supplying arteries including the aortic arch detected a severe aortic plaque ≥4 mm in 1 (0.3%) patient (who was not examined by TEE). Routine echocardiography was performed in 27 of those 47 patients with prespecified pathological findings in CMR, revealing an akinetic left ventricular segment in 5 patients, an LVEF <45% in 2

patients, a severe aortic plaque ≥4 mm in 5 patients and a type-A aortic dissection in 1 patient.

The study-specific Holter-ECG detected a first episode of AF in 16 (4.5%) patients, 6 of which were also detected during routine diagnostic care. Taken together, enhanced diagnostic workup led to a detection of relevant pathological findings in an additional 35 (9.8%) patients compared with routine diagnostic care alone.

Primary and secondary outcomes of the HEBRAS study

Verifying the primary hypothesis, the rate of prespecified pathological findings relevant to classification of stroke aetiology was increased after enhanced diagnostic workup compared with routine diagnostic care in the whole cohort (103 findings (28.1%) in routine diagnostic care vs 161 findings (45.2%) according to enhanced workup). In total, a first episode of AF was detected in 16 patients by study-specific Holter-ECG vs 7 patients according to routine diagnostic care (4.5% vs 2.0%; p=0.01). Out of those seven patients with AF according to routine diagnostic care, one was not detected by study-specific Holter-ECG. On the other hand, study-specific Holter-ECG detected paroxysmal AF in 10 patients without AF detection according to routine diagnostic care. This corresponds to a proportion of 10 (2.8%) out of 356 patients with first detected paroxysmal AF by study-specific Holter-ECG.

Stroke aetiology according to routine diagnostic care and enhanced workup

Enhanced diagnostic workup led to a change in aetiological classification in 48 (13.5%) of all study patients (see figure 2 and online supplemental file for details). The proportion of patients categorised as cryptogenic at hospital discharge was significantly reduced by enhanced diagnostic workup (38.5% vs 45.5% according to routine diagnostic care, p<0.001). This observation remained significant in the ESUS cohort (42.9% vs 50.8% according to routine diagnostic care, p<0.001). A sensitivity analysis using LVEF <30% as a pathological finding (instead of <45%) resulted in a 4.5% reduction of the proportion of patients classified as 'cryptogenic' in the whole cohort by enhanced diagnostic workup (41.0% vs 45.5% according to routine diagnostic care, p<0.001) and in a 5.3% reduction of the proportion of patients classified as 'cryptogenic' in the ESUS cohort (45.5% vs 50.8% according to routine diagnostic care, p=0.001).

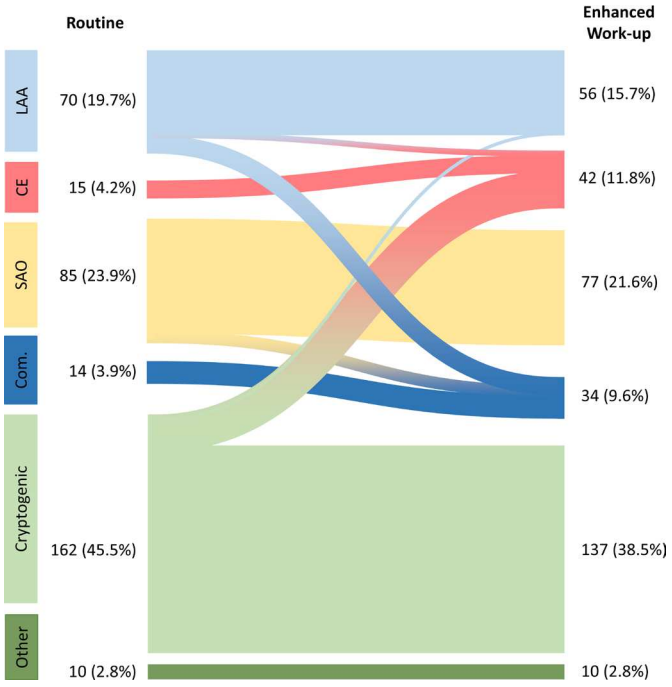


Figure 2 Aetiological classification in 356 patients with AIS considering routine diagnostic findings ('routine') and considering enhanced diagnostic workup ('enhanced workup'); including cardiac MRI, MR-angiography of the aortic arch and study-specific Holter ECG for up to ten days. AIS, acute ischaemic stroke; CE, cardioembolism; Com., competing aetiology; LAA, large-artery atherosclerosis; SAO, small-artery occlusion.

DISCUSSION

The primary finding of the prospective, observational HEBRAS study is that enhanced diagnostic workup significantly improves the detection of pathological findings after AIS, proving the prespecified study hypothesis. Taken together, application of CMR and prolonged Holter-monitoring (in-hospital and up to 5 days after discharge vs routine monitoring in-hospital) increased the rate of prespecified pathological findings relevant to stroke aetiology by 17%. Subsequently, enhanced diagnostic workup led to a significant decrease of patients with AIS diagnosed with cryptogenic stroke according to TOAST criteria at hospital discharge.

In HEBRAS, CMR could be performed in 82% of the included patients who had a stroke, which is well in line with previously reported rates.[14] CMR was able to detect more cardiac pathologies such as intracardiac thrombi or tumours, and revealed a higher rate of akinetic myocardial segments compared with routine diagnostic care. However, we cannot draw definite conclusions on implications for improved secondary stroke prevention. Future trials are needed to investigate a possible therapeutic relevance of an enhanced diagnostic approach. Moreover, assessing LVEF by CMR analysis found a significantly higher rate of reduced LVEF both according to the definition of the study protocol (LVEF <45%) and to define ESUS (<30%).[18] Indeed, a reduced LVEF was the most frequent pathological finding using CMR (online supplemental table 3). It has been shown that both the presence of akinetic myocardial segments as well as reduced LVEF promotes intracardiac thrombus formation.[22] However, there is no clear recommendation on the therapeutic consequences of these conditions in the absence of thrombus or AF.[23] This might change in the future, as a subgroup analysis of the NAVIGATE ESUS trial found rivaroxaban to be superior to acetylsalicylic acid in reducing the risk of recurrent stroke or

systemic embolism.[24] Nevertheless, identification of an akinetic myocardial segment and/or reduced LVEF may already have therapeutic consequences in terms of additional diagnostics (ie, coronary angiography) or change of medication.[25] From our perspective, the HEBRAS findings support the notion to consider advanced cardiac imaging like CMR in selected patients with stroke or TIA due to presumed cardioembolism and no identifiable cardioembolic source after routine diagnostic care.

In our analysis, the detection rate of a first AF episode in patients with AIS was more than doubled by the study-specific prolonged Holter-ECG monitoring. In detail, the study-specific Holter-ECG led to an absolute increase in AF detection after stroke of 2.5%. This is in line with the randomised MonDAFIS trial, which demonstrated an absolute increase in AF detection of 1.8% by prolonged Holter-monitoring in-hospital compared with routine monitoring.[16] Notably, all first episodes of AF were detected by the study-specific Holter-ECG during the in-hospital stay. Therefore, one might argue that the more thorough the search for AF is performed in-hospital, the less likely might be an additional diagnostic benefit of out-of-hospital rhythm monitoring after AIS.

From a pathophysiological perspective, early assessment and better understanding of stroke aetiology may improve secondary stroke prevention and thereby help to reduce the rate of stroke recurrence. Overall, exclusive findings of HEBRAS would have warranted changes in antithrombotic medication (ie, indication for oral anticoagulation (OAC)) in accordance with current guidelines in 13 (3.7%) patients (due to detection of AF or intracardiac thrombi) and an intensified LDL target in one patient (due to a severe aortic plaque). Regarding AF, we are unable to answer the question whether AF first detected after the index stroke was causal for the index stroke, was present but unnoticed before the stroke or was induced by the index stroke itself.[5 26 27] Whether or not enhanced diagnostic workup would translate into improved secondary stroke prevention and subsequent reduction of stroke recurrence was not an aim of the HEBRAS study,[18] and deserves further investigation in a large prospective multicentre trial.

Of note, the proportion of patients with AIS classified as 'competing aetiology' increased following the enhanced workup in the HEBRAS study, as an additional stroke aetiology was identified in patients who had a stroke already diagnosed with a definite aetiology following routine diagnostic care. It has been repeatedly pointed out that the original TOAST classification comprises three very heterogeneous groups of patients with cryptogenic stroke, namely those with incomplete diagnostics, those with more than one identified cause of stroke and those with no identified cause despite complete investigation.[2 28] Therefore, we differentiated between cryptogenic strokes with competing aetiology and cryptogenic strokes without an identified cause.

The following limitations have to be addressed and might mitigate the validity of our results. First, our findings cannot be generalised to all patients with AIS, as patients unable to provide informed consent or patients with previously detected AF were excluded. This indicates a selection bias and might have resulted in the inclusion of younger, less severely affected patients who had a stroke. In addition, 18% of all study participants did not receive CMR. Second, with a median time of 30 hours from hospital admission to the start of the study-specific Holter-ECG, there is a chance that we might have missed the diagnosis of AF in some patients. Third, not all study patients underwent TTE and/or TEE and we cannot exclude a respective selection bias. However, this reflects routine diagnostic care in clinical practice, even in developed countries with a nationwide stroke unit system like Germany.[7 8 29] Notably, neither stroke unit certification requirements according to the German nor the European Stroke Organisation include specific recommendations on the use of echocardiography.[30 31] Fourth, one might argue that the chosen LVEF threshold (<45% or even <30%) defining a high-risk cardioembolic source is debatable in the absence of a cardiac thrombus.[32] Based on a risk model including history of ischaemic stroke, a recent meta-analysis including >20 000 heart failure patients with reduced LVEF and sinus rhythm identified a subgroup of patients with a similar stroke risk to AF patients without OAC.[33] Nevertheless, there are no randomised controlled trials demonstrating a benefit of OAC in this population. The same holds true for left ventricular akinetic segments, despite the fact that this finding goes along with a higher chance of thrombus formation.[34] However, the recently updated German guidelines on secondary stroke prevention recommend to consider OAC instead of antiplatelet therapy in patients who had an ischaemic stroke with an LVEF <35% and sinus rhythm.[35] The relevance of an interatrial septal abnormality for secondary stroke prevention was low at the time the HEBRAS study was designed, as randomised controlled trials (like CLOSURE I, PC trial and RESPECT PFO) did not demonstrate a significant reduction of stroke recurrence in PFO patients and otherwise cryptogenic stroke.[36] According to current guidelines, PFO closure should be considered in patients 18–60 years who do not have another identifiable cause of stroke after comprehensive workup. Therefore, TTE is essential in these patients.[37] Fifth, besides feasibility, timing and cost-effectiveness are major considerations for CMR.[12 14] Prolonged non-invasive ambulatory ECG monitoring for 14 as well as 30 days after cryptogenic stroke was estimated to be highly cost-effective based on data from the EMBRACE trial.[38] However, as a cost–benefit analysis was not aim of the HEBRAS study, it is very difficult to draw definitive conclusions on that matter. To the best of our knowledge, no such analysis has been performed on the use of CMR in patients who had a stroke. CMR may be cost-effective in patients with AIS undergoing brain MRI and CMR immediately afterwards, subsequently shortening the in-hospital stay after AIS. Additionally, CMR might be reasonable in a subset of patients with AIS with a high presumed risk of cardioembolic stroke or (undetected) coronary heart disease.

CONCLUSION

Enhanced diagnostic workup including CMR and prolonged Holter-ECG monitoring resulted in a significant increase of pathological findings compared with routine diagnostic care in a specialised stroke centre. Enhanced diagnostic workup significantly reduced the proportion of patients with AIS categorised as cryptogenic stroke or ESUS. Whether enhanced diagnostic workup after AIS may lead to a reduction of cardiovascular endpoints by improving secondary stroke prevention has to be addressed in future studies.

Author affiliations
[1]Department of Neurology with Experimental Neurology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
[2]Center for Stroke Research Berlin, Berlin, Germany
[3]Berlin Institute of Health at Charité –Universitätsmedizin Berlin, BIH Biomedical Innovation Academy, Berlin, Germany
[4]Department of Neurology, Jüdisches Krankenhaus Berlin, Berlin, Germany
[5]German Center for Cardiovascular Diseases (DZHK), Partner Site Berlin, Berlin, Germany
[6]Institute of Biometry and Clinical Epidemiology, Charité - Universitätsmedizin Berlin, Berlin, Germany
[7]BIH Center for Regenerative Therapies (BCRT), Berlin Institute of Health at Charité –Universitätsmedizin Berlin, Berlin, Germany
[8]Department of Cardiology, Charité - Universitätsmedizin Berlin, Berlin, Germany
[9]Department of Cardiology, Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin, Berlin, Germany
[10]German Center for Neurodegenerative Diseases (DZNE), Partner Site Berlin, Berlin, Germany
[11]Department of Cardiology, University Hospital Leipzig, Leipzig, Germany
[12]Department of Radiology, Charité - Universitätsmedizin Berlin, Berlin, Germany
[13]Department of Neurology, University Hospital Würzburg, Würzburg, Germany

Acknowledgements SH is participant in the BIH Charité Clinician Scientist Program funded by the Charité—Universitätsmedizin Berlin, and the Berlin Institute of Health at Charité (BIH). We thank Kristin Simon (former CSB, now BIH) and Tatjana Wittenberg (CSB) for their outstanding support in conducting the study. In addition, we thank Michael Scherf (GETEMED AG, Teltow, Germany) for providing technical support and study ECGs.

Contributors CHN and KGH contributed to the design of the study. TK, JH and SH contributed to data acquisition. CHN, KGH, SH and UG performed statistical analysis. CHN, KGH and SH prepared the figures, wrote the first draft of the manuscript and drafted the manuscript. TE performed imaging analysis of CMR. JF performed imaging analysis of brain MRI. NJ, WD, MK and RW were involved in analysis of ECG and Echocardiography. JF and ME contributed major intellectual content and drafted the manuscript. All authors read, drafted and approved the manuscript. KGH accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This study was supported by the German Ministry of Education and Research (grant G.2.17, Center for Stroke Research Berlin), by the DZHK (German Center for Cardiovascular Research) (grant B14-035_SE) and by the GETEMED AG, Teltow, Germany by supplying ECG recorders.

Competing interests RW received grants from Deutsches Zentrum für Herz-/Kreislaufforschung, Deutsche Forschungsgemeinschaft, European Union, Bundesministerium für Bildung und Forschung, Medtronic and Boehringer Ingelheim as well as personal fees from Astra, Bayer, Boehringer Ingelheim, CVRx, Daiichi, BMS, Medtronic, Novartis, Pfizer, Pharmacosmos and Servier, all outside the submitted work. ME received funding from DFG under Germany's Excellence Strategy—EXC-2049—390688087, BMBF, DZNE, DZHK, EU, Corona Foundation, and Fondation Leducq. ME reports grants from Bayer and fees paid to the Charité from AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Amgen, GSK, Sanofi, Covidien, Novartis, Pfizer, all outside the submitted work. CHN received research grants from German Ministry of Research and Education, German Center for Neurodegenerative Diseases, German Center for cardiovascular Research, and speaker and/or consultation fees from Alexion, Abbott, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer Pharma and Daiichi Sankyo. KGH reports a study grant by Bayer, lecture fees/advisory board fees from Abbott, Amarin, Alexion, AstraZeneca, Bayer, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol-Myers-Squibb, Daiichi Sankyo, Edwards Lifesciences, Medtronic, Pfizer, Portola, Sun Pharma and W. L. Gore & Associates. All other authors declare no conflicts of interest.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study was approved by the Ethics Committee of the Charité—Universitätsmedizin Berlin (EA1/045/14). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Individual participant data that underlie the results reported in this article will be available to researchers who provide a methodologically sound proposal beginning at 12 months and ending 5 years after publication. Proposals should be directed to the corresponding author.

ORCID iDs
Simon Hellwig http://orcid.org/0000-0002-6925-4768
Jan F Scheitz http://orcid.org/0000-0001-5835-4627
Juliane Herm http://orcid.org/0000-0001-6873-2812
Ulrike Grittner http://orcid.org/0000-0003-2595-0224
Jochen B Fiebach http://orcid.org/0000-0002-7936-6958
Wolfram Doehner http://orcid.org/0000-0001-7598-708X
Matthias Endres http://orcid.org/0000-0001-6520-3720
Rolf Wachter http://orcid.org/0000-0003-2231-2200
Thomas Elgeti http://orcid.org/0000-0002-7155-6044
Christian H Nolte http://orcid.org/0000-0001-5577-1775
Karl Georg Haeusler http://orcid.org/0000-0002-6389-5054

REFERENCES

1 Powers WJ, Rabinstein AA, Ackerson T, *et al*. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019;50:e344–418.
2 Adams Jr. HP, Bendixen BH, Kappelle LJ, *et al*. Classification of subtype of acute ischemic stroke. definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35–41.
3 Landau WM, Nassief A. Editorial comment--time to burn the TOAST. *Stroke* 2005;36:902–4.
4 Hart RG, Diener H-C, Coutts SB, *et al*. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13:429–38.
5 Schnabel RB, Haeusler KG, Healey JS, *et al*. Searching for atrial fibrillation poststroke: a white paper of the AF-SCREEN International Collaboration. *Circulation* 2019;140:1834–50.
6 Schnabel RB, Camen S, Knebel F, *et al*. Expert opinion paper on cardiac imaging after ischemic stroke. *Clin Res Cardiol* 2021;110:938–58.
7 Giruparajah M, Bosch J, Vanassche T, *et al*. Global survey of the diagnostic evaluation and management of cryptogenic ischemic stroke. *Int J Stroke* 2015;10:1031–6.
8 Rizos T, Quilitzsch A, Busse O, *et al*. Diagnostic work-up for detection of paroxysmal atrial fibrillation after acute ischemic

stroke: cross-sectional survey on German stroke units. *Stroke* 2015;46:1693–5.
9 Thomalla G, Upneja M, Camen S, *et al*. Treatment-relevant findings in transesophageal echocardiography after stroke: a prospective multicenter cohort study. *Stroke* 2022;53:177–84.
10 Douen A, Pageau N, Medic S. Usefulness of cardiovascular investigations in stroke management: clinical relevance and economic implications. *Stroke* 2007;38:1956–8.
11 Herm J, Konieczny M, Jungehulsing GJ, *et al*. Should transesophageal echocardiography be performed in acute stroke patients with atrial fibrillation? *J Clin Neurosci* 2013;20:554–9.
12 Haeusler KG, Wollboldt C, Bentheim LZ, *et al*. Feasibility and diagnostic value of cardiovascular magnetic resonance imaging after acute ischemic stroke of undetermined origin. *Stroke* 2017;48:1241–7.
13 Hellwig S, Grittner U, Elgeti M, *et al*. Evaluation of left ventricular function in patients with acute ischaemic stroke using cine cardiovascular magnetic resonance imaging. *ESC Heart Fail* 2020;7:2572–80.
14 Meinel TR, Eggimann A, Brignoli K, *et al*. Cardiovascular MRI compared to echocardiography to identify Cardioaortic sources of ischemic stroke: a systematic review and meta-analysis. *Front Neurol* 2021;12:699838.
15 Haeusler KG, Tütüncü S, Schnabel RB. Detection of atrial fibrillation in cryptogenic stroke. *Curr Neurol Neurosci Rep* 2018;18:66.
16 Haeusler KG, Kirchhof P, Kunze C, *et al*. Systematic monitoring for detection of atrial fibrillation in patients with acute ischaemic stroke (MonDAFIS): a randomised, open-label, Multicentre study. *Lancet Neurol* 2021;20:426–36.
17 Tsivgoulis G, Triantafyllou S, Palaiodimou L, *et al*. Prolonged cardiac monitoring and stroke recurrence: a meta-analysis. *Neurology* 2022;98:e1942–52.
18 Haeusler KG, Grittner U, Fiebach JB, *et al*. HEart and BRain interfaces in Acute ischemic Stroke (HEBRAS)--rationale and design of a prospective oberservational cohort study. *BMC Neurol* 2015;15:213.
19 Cerqueira MD, Weissman NJ, Dilsizian V, *et al*. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105:539–42.
20 Hart RG, Connolly SJ, Mundl H. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;379:987.
21 Diener H-C, Sacco RL, Easton JD, *et al*. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;380:1906–17.
22 Levine GN, McEvoy JW, Fang JC, *et al*. Management of patients at risk for and with left ventricular thrombus: a scientific statement from the American Heart Association. *Circulation* 2022;146:e205–23.
23 Pullicino PM, Qian M, Sacco RL, *et al*. Recurrent stroke in the warfarin versus aspirin in reduced cardiac ejection fraction (WARCEF) trial. *Cerebrovasc Dis* 2014;38:176–81.
24 Merkler AE, Pearce LA, Kasner SE, *et al*. Left ventricular dysfunction among patients with Embolic stroke of undetermined source and the effect of rivaroxaban vs aspirin: a subgroup analysis of the NAVIGATE ESUS randomized clinical trial. *JAMA Neurol* 2021;78:1454–60.
25 Heidenreich PA, Bozkurt B, Aguilar D, *et al*. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e895–1032.
26 Sposato LA, Chaturvedi S, Hsieh C-Y, *et al*. Atrial fibrillation detected after stroke and transient ischemic attack: a novel clinical concept challenging current views. *Stroke* 2022;53:e94–103.
27 Scheitz JF, Sposato LA, Schulz-Menger J, *et al*. Stroke-heart syndrome: recent advances and challenges. *J Am Heart Assoc* 2022;11:e026528.
28 Diener H-C, Easton JD, Hart RG, *et al*. Review and update of the concept of embolic stroke of undetermined source. *Nat Rev Neurol* 2022;18:455–65.
29 Rizos T, Jenetzky E, Nabavi DG, *et al*. Echocardiography in acute stroke patients: a nationwide analysis in departments with certified stroke units in Germany. *Neurol Res Pract* 2023;5:3.
30 Nabavi DG, Koennecke H-C, Ossenbrink M, *et al*. Certification criteria for stroke units in Germany: update 2018. *Nervenarzt* 2019;90:335–42.
31 Waje-Andreassen U, Nabavi DG, Engelter ST, *et al*. European Stroke Organisation certification of stroke units and stroke centres. *Eur Stroke J* 2018;3:220–6.
32 Saric M, Armour AC, Arnaout MS, *et al*. Guidelines for the use of echocardiography in the evaluation of a cardiac source of embolism. *J Am Soc Echocardiogr* 2016;29:1–42.
33 Kondo T, Abdul-Rahim AH, Talebi A, *et al*. Predicting stroke in heart failure and reduced ejection fraction without atrial fibrillation. *Eur Heart J* 2022;43:4469–79.
34 Weinsaft JW, Kim HW, Shah DJ, *et al*. Detection of left ventricular thrombus by delayed-enhancement cardiovascular magnetic resonance prevalence and markers in patients with systolic dysfunction. *J Am Coll Cardiol* 2008;52:148–57.
35 Olma MC, Röther J, Grau A, *et al*. Secondary prevention ischemic stroke and transient ischemic attack - Part 2, Sk2-Guideline. In: German Neurological Society (DGN) and German Stroke Society (DSG). 2022.
36 Mir H, Siemieniuk RAC, Ge L, *et al*. Patent foramen ovale closure, antiplatelet therapy or anticoagulation in patients with patent foramen ovale and cryptogenic stroke: a systematic review and network meta-analysis incorporating complementary external evidence. *BMJ Open* 2018;8:e023761.
37 Messé SR, Gronseth GS, Kent DM, *et al*. Practice advisory update summary: patent foramen ovale and secondary stroke prevention: report of the guideline subcommittee of the American Academy of Neurology. *Neurology* 2020;94:876–85.
38 Yong JHE, Thavorn K, Hoch JS, *et al*. Potential cost-effectiveness of ambulatory cardiac rhythm monitoring after cryptogenic stroke. *Stroke* 2016;47:2380–5.

4.2 Kardiales Troponin und schwerwiegende vaskuläre Ereignisse nach leichtem Schlaganfall oder TIA

Hellwig S., Ihl T., Ganeshan R., Laumeier I., Ahmadi M., Steinicke M., Weber J. E., Endres M., Audebert H. J., Scheitz J. F.: Cardiac troponin and recurrent major vascular events after minor stroke or TIA. *Ann Neurol.* 2021 Dec;90(6):901-912. DOI: 10.1002/ana.26225.

Wie bereits erwähnt, ist ein Hauptanliegen dieser Habilitationsschrift die Identifizierung von Schlaganfallpatient*innen mit einem besonders hohen Risiko für mögliche vaskuläre Rezidiv- oder Folgeereignisse (→ *3.9 Ziele der Arbeit*). Die Bestimmung kardialer Troponine (cTn) ist ein etablierter Bestandteil in der Diagnostik des akuten Koronarsyndroms (ACS) bzw. Myokardinfarkts[109]. Die Assays der 5. Generation (*high-sensitivity cardiac Troponin T*, hs-cTnT) erlauben dabei eine Differenzierung bis zu einem Limit of blank (LOB) von 3 ng/l bei einem oberen Referenzlimit (upper reference limit [URL]) von 14 ng/l, korrespondierend zur 99. Perzentile einer gesunden Referenzpopulation[110]. In Vorarbeiten konnte bereits überzeugend dargelegt werden, dass sich 1.) erhöhte Troponin-Werte (d.h. >URL) häufig (bei >50% aller Patient*innen) im Rahmen eines akuten Schlaganfalls finden und dass 2.) erhöhte Troponin-Werte sowohl in der Allgemeinbevölkerung als auch in einem Kollektiv von Patientinnen und Patienten mit Vorhofflimmern mit einem erhöhten Risiko für thrombembolische bzw. schwerwiegende kardio-vaskuläre Ereignisse verbunden sind[111-114].

In dieser Analyse wurde der Zusammenhang zwischen hs-cTnT und dem Auftreten von schwerwiegenden kardiovaskulären Ereignissen (*major adverse cardiovascular events*, MACE) über einen durchschnittlichen Nachverfolgungszeitraum von 3,2 Jahren untersucht[115]. Studienpopulation war eine Subgruppe (n=889) von Patient*innen mit leichtem Schlaganfall („*minor stroke*“) oder TIA und konsekutiv bestimmtem hs-cTnT bei Aufnahme als Teil der prospektiven, multizentrischen INSPiRE-TMS Studie[116]. Es fand sich eine robuste Assoziation eines erhöhten Troponin-Werts mit dem Auftreten von MACE (9,3% pro Jahr bei erhöhtem hs-cTnT vs. 4,4% pro Jahr bei normalem hs-cTnT, adjustierte Hazard Ratio 1,63 [95% KI 1,13–2,35])[115].

In einem zweiten Schritt wurde die Frage adressiert, ob sich Unterschiede bzgl. dieses Zusammenhangs in Abhängigkeit einer Risikostratifizierung basierend auf traditionellen klinischen Risikofaktoren ergaben, in diesem Fall basierend auf dem $ABCD^2$ Score

(→ *3.8 Prognoseabschätzung*). In großen, registerbasierten Studien war ein $ABCD^2$ Score von ≥6 mit einem mehr als verdoppelten Schlaganfallrisiko nach leichtem Schlaganfall oder TIA verbunden[93]. In der vorliegenden Analyse zeigten interessanterweise diejenigen Patient*innen, die gemäß dem $ABCD^2$ Score eigentlich als Niedrigrisikogruppe eingestuft wurden (d.h. $ABCD^2$ <6) eine vergleichbar hohe Ereignisrate wie die Hochrisikogruppe (d.h. $ABCD^2$ ≥6), wenn das Troponin bei Aufnahme erhöht war[115].

In der INSPiRE-TMS Studie wurden die Studienteilnehmer*innen 1:1 in einen Interventionsarm und eine Kontrollgruppe randomisiert[116]. Teilnehmer*innen im Interventionsarm nahmen an einem Nachsorgeprogramm zur intensivierten Sekundärprävention über zwei Jahre teil, Teilnehmer*innen in der Kontrollgruppe erhielten Routineversorgung[116]. Hinsichtlich des primären Endpunktes (Auftreten von MACE) zeigte sich kein signifikanter Unterschied zwischen den beiden Gruppen (Ereignisrate 15,8% in der Interventionsgruppe vs. 16,8% in der Kontrollgruppe, Hazard Ratio 0,92 [95% KI 0,75-1,14])[116]. In der Subgruppenanalyse von Patient*innen mit erhöhtem Troponin bei Aufnahme fand sich zwar eine numerisch geringere Ereignisrate in der Interventionsgruppe im Vergleich zur Kontrollgruppe, es ergab sich jedoch kein statistisch belastbarer Unterschied (Ereignisrate pro 1000 Patientenjahre: 86 in der Interventionsgruppe vs. 100 in der Kontrollgruppe, log-rank $p = 0.59$)[115].

Diese Analyse unterstreicht die potentielle Bedeutung des blutbasierten Biomarkers Troponin für die individuelle vaskuläre Risikoabschätzung nach ischämischem Schlaganfall oder TIA[115]. Ob eine Risikostratifizierung unter Berücksichtigung von Troponin nützlich ist, um eine Hochrisikogruppe zu identifizieren, die möglicherweise von einer intensivierten medikamentösen Sekundärprävention oder einer erweiterten (kardialen) Diagnostik profitiert, muss in zukünftigen Studien adressiert werden[115].

Cardiac Troponin and Recurrent Major Vascular Events after Minor Stroke or Transient Ischemic Attack

Simon Hellwig, MD, MSc,[1,2] Thomas Ihl, MD,[1] Ramanan Ganeshan, MD,[1] Inga Laumeier, MD,[1] Michael Ahmadi, MD,[1,3] Maureen Steinicke, MD,[1] Joachim E. Weber, MD,[1,2,3] Matthias Endres, MD,[1,2,3,4,5,6] Heinrich J. Audebert, MD,[1,2†] and Jan F. Scheitz, MD[1,2,3,6†]

Objective: This study was undertaken to investigate whether high-sensitivity cardiac troponin T (hs-cTnT) is associated with major adverse cardiovascular events (MACE) in patients with minor stroke or transient ischemic attack (TIA), and whether this association differs after risk stratification based on the Age, Blood Pressure, Clinical Features, Duration of Symptoms, Diabetes ($ABCD^2$) score.

Methods: INSPiRE-TMS was a randomized controlled trial allocating patients with minor stroke or TIA to an intensified support program or conventional care. In this post hoc analysis, participants were categorized using hs-cTnT levels (5th generation; Roche Diagnostics, Manheim, Germany; 99th percentile upper reference limit [URL] = 14ng/l). Vascular risk was stratified using the $ABCD^2$ score (lower risk = 0–5 vs higher risk = 6–7). Cox proportional hazard regression was performed using covariate adjustment and propensity score matching (PSM) for the association between hs-cTnT and MACE (stroke/nonfatal coronary event/vascular death).

Results: Among 889 patients (mean age = 70 years, 37% female), MACE occurred in 153 patients (17.2%) during a mean follow-up of 3.2 years. hs-cTnT was associated with MACE (9.3%/yr, >URL vs 4.4%/yr, ≤URL, adjusted hazard ratio [HR] = 1.63 [95% confidence interval (CI) = 1.13–2.35], adjusted HR [Q_4 vs Q_1] = 2.57 [95% CI = 1.35–4.97], adjusted HR [log-transformed] = 2.31 [95% CI = 1.37–3.89]). This association remained after PSM (adjusted HR = 1.76 [95% CI = 1.14–2.72]). There was a significant interaction between hs-cTnT and $ABCD^2$ category for MACE occurrence ($p_{interaction} = 0.04$). In the lower risk category, MACE rate was 9.5%/yr in patients with hs-cTnT > URL, which was higher than in those ≤URL (3.8%/yr) and similar to the overall rate in the higher risk category.

Interpretation: hs-cTnT levels are associated with incident MACE within 3 years after minor stroke or TIA and may help to identify high-risk individuals otherwise deemed at lower risk based on the $ABCD^2$ score. If confirmed in independent validation studies, this might warrant intensified secondary prevention measures and cardiac diagnostics in stroke patients with elevated hs-cTnT.

ANN NEUROL 2021;90:901–912

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26225

Received Apr 7, 2021, and in revised form Sep 8, 2021. Accepted for publication Sep 19, 2021.

Address correspondence to Dr Hellwig, Klinik für Neurologie mit Experimenteller Neurologie, Charité–Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany. E-mail: simon.hellwig@charite.de

†H.J.A. and J.F.S. contributed equally.

From the [1]Department of Neurology, Charité–Universitätsmedizin Berlin, Berlin, Germany; [2]Center for Stroke Research Berlin, Charité–Universitätsmedizin Berlin, Berlin, Germany; [3]Berlin Institute of Health, Berlin, Germany; [4]Excellence Cluster NeuroCure, Charité–Universitätsmedizin Berlin, Berlin, Germany; [5]German Center for Neurodegenerative Diseases, partner site Berlin, Berlin, Germany; and [6]German Center for Cardiovascular Research, partner site Berlin, Berlin, Germany

Additional supporting information can be found in the online version of this article.

Patients with acute ischemic stroke or transient ischemic attack (TIA) have a high risk of recurrent vascular events.[1] Several clinical prediction schemes such as the Age, Blood Pressure, Clinical Features, Duration of Symptoms, Diabetes ($ABCD^2$) score have been proposed to guide clinical triage of patients.[2] Although initially conceived for early triage purposes after TIA, it has been suggested that higher $ABCD^2$ scores are also associated with an increased risk of recurrent vascular events after ischemic stroke.[1] However, individual stratification of future vascular risk after cerebrovascular events is still limited and the individual risk may vary substantially.[2,3] It is increasingly recognized that blood-based biomarkers may be useful to provide an individual risk estimate beyond conventional risk factors by capturing biologically relevant pathways.[4,5] Recent observations highlight the potential role of high-sensitivity cardiac troponin (hs-cTn) levels for this purpose.[6,7] Myocardial injury with high-sensitivity cardiac troponin T (hs-cTnT) elevation above the assay-specific 99th percentile upper reference limit (URL) is common after stroke and associated with poor long-term outcome.[8] Higher hs-cTn levels are associated with an increased risk of thromboembolic and major adverse cardiovascular events (MACE) in the general population as well as in patients with atrial fibrillation.[9,10] However, this association is less well established in patients with recent ischemic stroke or TIA.[7,11]

Usually, antithrombotic treatment and risk factor control are considered indicated in all patients after stroke, but it remains unknown whether certain patients benefit from intensified secondary prevention measures.[12,13] The recently completed INSPiRE-TMS trial (INtensified Secondary Prevention intending a Reduction of recurrent Events after Transient ischaemic attack and Minor Stroke) demonstrated a significant improvement in risk factor control in patients randomized to a multicomponent secondary prevention support program in comparison to conventional care. Yet this did not transform into a significant reduction of subsequent MACE in these patients.[14] However, subgroup analyses suggested that patients with a higher risk $ABCD^2$score may benefit from the study intervention.[14]

By using data from INSPiRE-TMS, we aimed to investigate (1) whether presence of myocardial injury (hs-cTnT levels above URL) is associated with recurrent MACE in patients with minor stroke or TIA, (2) whether this association is maintained in patients deemed at lower or higher vascular risk based on the $ABCD^2$ score, and (3) whether the effect of the multicomponent support program tested in INSPiRE-TMS is modified by levels of hs-cTnT.

Patients and Methods

Study Population

INSPiRE-TMS was a prospective open-label, multicenter, blinded endpoint, and event-driven international randomized controlled trial that recruited 2,098 patients from August 2011 to October 2017. The protocol for the study received prior approval by the institutional review board (ethics committee) of the Charité–Universitätsmedizin Berlin (EA2/084/11) and was registered online (NCT01586702). Informed consent was obtained from each subject. The details of the protocol and final results of the trial have been published elsewhere.[14,15] In brief, patients aged 18 years or older with nondisabling stroke (ie, modified Rankin Scale (mRS) <3, indicating functional independency) or TIA and at least one modifiable risk factor (ie, arterial hypertension, diabetes, atrial fibrillation, or smoking) within 2 weeks from the index event were eligible to participate. Patients with symptom duration <24 hours but with an ischemic lesion on cerebral imaging were diagnosed as minor stroke patients. The $ABCD^2$ score ranges from 0 to 7 points and assesses age (<60 years = 0 points, ≥60 years = 1 point), blood pressure upon admission (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg = 0 points, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg = 1 point), clinical symptoms (unilateral weakness = 2 points, isolated speech disturbance = 1 point, other symptoms = 0 points), duration of symptoms (<10 minutes = 0 points, 10–59 minutes = 1 point, ≥60 minutes = 2 points), and history of diabetes (no = 0 points, yes = 1 point), with a higher score indicating a higher risk of subsequent stroke.[2] An $ABCD^2$ score ≥6 is considered to indicate a higher risk of recurrent ischemic stroke and MACE.[16] Further refinements to the score have been suggested, such as the $ABCD^3I$ score with addition of a preceding TIA within 7 days before the index TIA (present = 2 points), an ipsilateral >50% stenosis of the carotid artery (present = 2 points), and a possible stroke correlate on brain imaging (present = 2 points).[17] With a range from 0 to 13 points, we used a cutoff at ≥8 points to differentiate between high-risk and low-risk patients as suggested by the literature.[18]

Study participants were randomized in a 1:1 fashion to receive either a multicomponent support program in addition to conventional care or conventional care alone. The support program consisted of 8 outpatient visits at 3, 6, and 12 weeks, then 6, 9, 12, 18, and 24 months after randomization, aiming to improve adherence to secondary prevention targets. Using feedback and motivational interviewing strategies, comprehensive and repeated information on the pathophysiology of the individual's

risk for recurrent vascular events and potential for vascular risk reduction was provided, including changes in lifestyle and adherence to medication. For this biomarker subgroup analysis, we considered patients enrolled at the Charité Campus Benjamin Franklin recruitment site, because measurement of hs-cTnT levels is part of clinical routine upon hospital admission at this center. We did not include patients suffering from intracerebral hemorrhage because of different pathophysiology.

Study Outcomes

The primary outcome of interest was the time to first occurrence of MACE, defined as a composite of vascular events including stroke, nonfatal coronary events (ie, unstable angina pectoris, ST-elevation and non–ST-elevation myocardial infarction), and vascular death. The secondary outcome of interest was time to the first occurrence of stroke, acute coronary syndrome, or vascular death. Stroke was defined as an acute (focal) neurological syndrome caused by a blood supply disorder in the brain with the presence of an ischemic lesion in the corresponding territory on brain imaging, or clinical evidence of an imaging-negative ischemic lesion with symptom duration longer than 24 hours. Nonfatal coronary events were defined as (1) typical clinical symptoms (eg, chest pain, cardiac failure) together with typical electrocardiogram (ECG) abnormalities, (2) typical clinical symptoms with elevation of troponin >2 × the URL, (3) nonspecific symptoms with elevation of troponin >2 × the URL together with typical ECG findings, or (4) so-called silent myocardial infarction as diagnosed on follow-up ECG by comparison with baseline ECG combined with corresponding results in echocardiography or coronary angiography. Vascular death was defined as death within 30 days of stroke, death within 7 days of a nonfatal coronary event, death caused by noncerebral hemorrhage or necrosis following peripheral artery occlusion or pulmonary embolism, or death within 24 hours of a previous good and stable condition and without other identifiable cause. Outcomes were assessed at annual follow-ups, and the endpoint committee adjudicated all possible primary and secondary outcomes using prespecified criteria unaware of treatment allocation.

Biomarker Sampling

As recommended by current guidelines, measurement of hs-cTnT upon hospital admission was performed according to a standardized operating procedure during routine clinical care at the study center Charité Campus Benjamin Franklin.[19,20] hs-cTnT levels were measured using a high-sensitivity electrochemiluminescence immunoassay (Roche Elecsys 2010 5th-generation assay; Roche Diagnostics, Mannheim, Germany) with a URL of 14ng/l corresponding to the 99th percentile of a healthy reference population, a limit of blank set at 3ng/l, and a limit of detection of 5ng/l. The assay properties have been described previously.[21]

Statistical Analysis

Study participants were dichotomized according to the 99th percentile URL of baseline hs-cTnT levels: >14 ng/l (above 99th percentile URL, ie, "elevated") or ≤14 ng/l (reference).[21,22] This cutoff was chosen because it is the established cutoff to define myocardial injury and represented the highest quartile in our cohort.[22] In addition, participants were categorized according to quartiles of hs-cTnT (see sensitivity analyses below). Due to the laboratory reporting system, hs-cTnT values <13 ng/l were not specified until March 2013. Therefore, constitution of hs-cTnT quartiles and log transformation was only possible for participants enrolled after March 18, 2013.

Results are reported as absolute and relative frequencies for categorical variables. In the case of continuous variables, mean and standard deviation (SD) are reported for sufficiently normally distributed data (|skewness|<1) or median and limits of interquartile range (IQR) for variables with skewed distribution or ordinal variables. Continuous variables were compared using a *t*-test or Mann–Whitney *U* test, as appropriate. Categorical variables were compared using Pearson chi-squared test. Unadjusted and adjusted Cox proportional hazards regression analyses were used to explore the association of hs-cTnT levels with the respective outcomes by obtaining hazard ratios (HRs) with their 95% confidence intervals (CIs). The regression models included potential confounders determined a priori based on literature review with known influence on vascular events and/or hs-cTnT levels (age, sex, type of index event [stroke vs TIA], arterial hypertension, diabetes, atrial fibrillation, history of smoking, history of stroke or TIA, coronary artery disease and/or history of myocardial infarction, congestive heart failure, impaired renal function, and treatment arm [intensified secondary prevention program vs conventional care]). Sensitivity analyses were performed by (1) entering hs-cTnT levels as a log-transformed continuous variable (because of skewedness) into the model, (2) categorizing hs-cTnT levels into quartiles and comparing the highest to the lowest quartile, and (3) excluding subgroups of patients considered to have probable hs-cTnT levels above URL (ie, history of myocardial infarction, impaired kidney function, and atrial fibrillation). In case of analyses based on the $ABCD^2$ score, factors already included in the score (age, blood pressure, and diabetes) were not included separately in the adjusted model. If patients had >1 outcome

event, the time leading up to the first event was used for the regression analyses.

To further account for selection bias, we performed propensity score matching (PSM) in a 1:1 fashion without replacement ("optimal matching") to balance baseline characteristics between patients with hs-cTnT below or above URL.[23,24] We used a caliper (ie, the maximum distance that two cases can be apart from each other based on their estimated propensity scores) of 0.2 to prevent matches with very dissimilar estimated propensity scores.[25] Variables used for PSM were age, sex, event type (stroke or TIA), hypertension, diabetes, atrial fibrillation, smoking, prior stroke or TIA, coronary artery disease and/or prior myocardial infarction, congestive heart failure, and renal failure. In the case of missing data, we first tested the data to be missing completely at random using Little's MCAR test. Missing data among covariates used in the model were then imputed using the Expectation–Maximization algorithm. Across all chosen variables for PSM, 1.1% of data were missing. In detail, missing data of individual covariates were prior stroke or TIA (n = 33, 3.7%), coronary artery disease (n = 26, 2.9%), prior myocardial infarction (n = 11, 1.2%), congestive heart failure (n = 36, 4.0%), and renal failure (n = 16, 1.8%). Covariate balance was assessed with standardized mean differences (SMDs). Postmatching SMD <0.1 indicated a good covariate balance between groups.[24,26] After PSM, Cox proportional hazard models were repeated to determine the association between hs-cTnT and recurrent vascular events, also adjusting for the propensity score.[27] PSM was performed using the STATS R35 extension plug-in for SPSS to implement R version 3.5.0 and the PSMATCHING3 custom dialog.[28] Kaplan–Meier plots for dichotomous hs-cTnT and intervention groups were

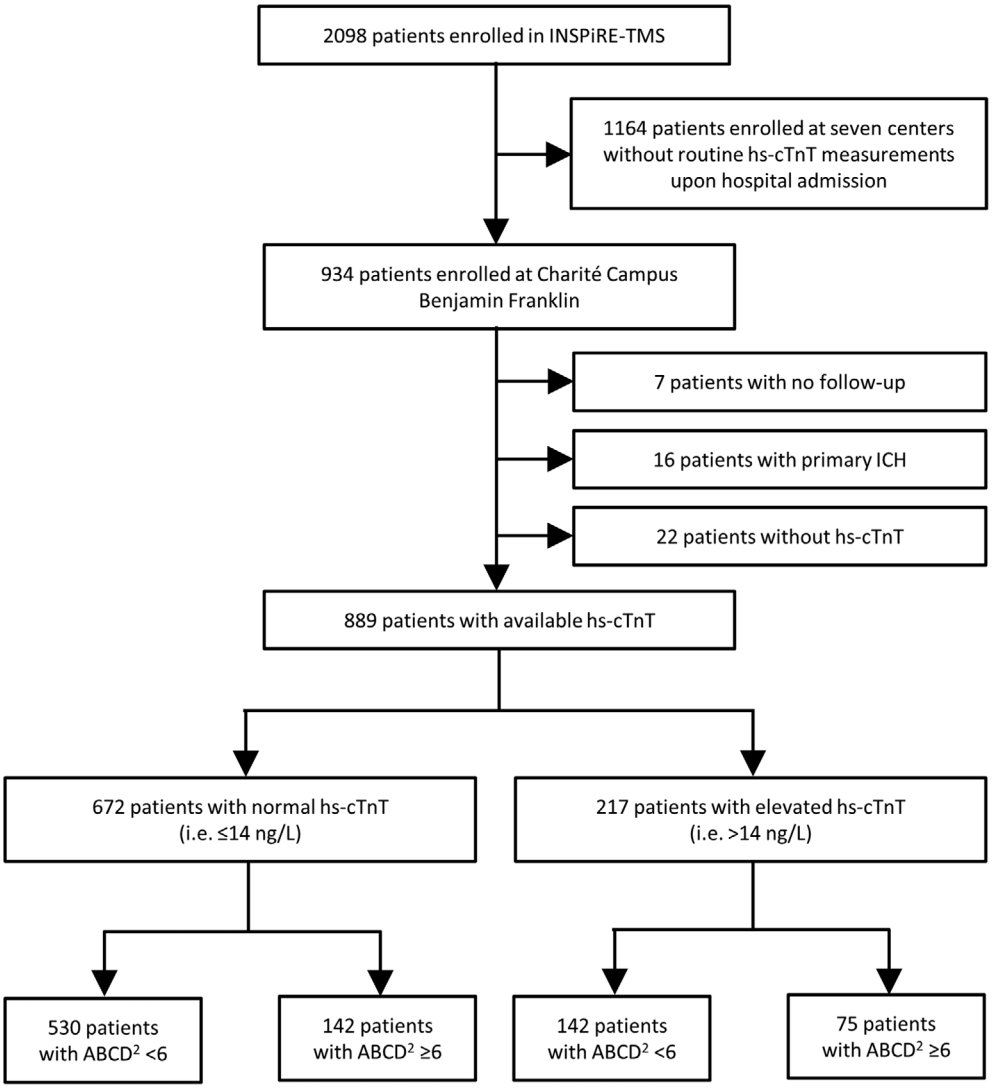


FIGURE 1: Study flowchart. ABCD² (Age, Blood Pressure, Clinical Features, Duration of Symptoms, Diabetes) indicates vascular risk. hs-cTnT = high-sensitivity cardiac troponin T; ICH = intracerebral hemorrhage.

TABLE. Baseline Characteristics[a]

Characteristic	hs-cTnT ≤ URL, n = 672		hs-cTnT > URL, n = 217	
	Control, n = 335	Intervention, n = 337	Control, n = 111	Intervention, n = 106
Age, yr	69.3 (9.4)	67.0 (10.2)	73.5 (9.1)	74.4 (8.8)
Sex				
Female	131 (39.1%)	136 (40.4%)	29 (26.1%)	30 (28.3%)
Modifiable risk factors				
Arterial hypertension	305 (91.0%)	289 (85.8%)	103 (92.8%)	97 (91.5%)
Diabetes	76 (22.7%)	64 (19.0%)	39 (35.1%)	44 (41.5%)
Atrial fibrillation	50 (14.9%)	51 (15.1%)	33 (29.7%)	27 (25.5%)
Current tobacco use	67 (20.0%)	60 (17.8%)	11 (9.9%)	18 (17.0%)
History (before index event)				
Stroke	56 (16.7%)	51 (15.1%)	21 (18.9%)	14 (13.2%)
Transient ischemic attack	19 (5.7%)	20 (5.9%)	9 (8.1%)	6 (5.7%)
Myocardial infarction	33 (9.9%)	14 (4.2%)	14 (12.6%)	15 (14.2%)
Peripheral artery disease	11 (3.3%)	13 (3.9%)	15 (13.5%)	6 (5.7%)
Risk factor measurements at baseline				
RR systolic, mmHg	132.9 (25.4)	132.8 (25.0)	137.1 (24.9)	139.0 (22.6)
RR diastolic, mmHg	76.7 (14.5)	77.5 (14.4)	76.4 (13.5)	76.1 (13.0)
HbA1c, mmol/mol	5.9 (0.8)	5.9 (1.0)	6.4 (1.4)	6.3 (1.1)
LDL, mg/dl	125.9 (40.3)	127.9 (41.6)	111.1 (41.8)	115.0 (37.2)
Index event				
Ischemic stroke	176 (52.5%)	176 (52.2%)	74 (66.7%)	71 (67.0%)
Transient ischemic attack	159 (47.5%)	161 (47.8%)	37 (33.3%)	35 (33.0%)
TOAST classification				
Large vessel	32 (9.6%)	36 (10.7%)	13 (11.7%)	15 (14.2%)
Small vessel	35 (10.4%)	23 (6.8%)	7 (6.3%)	9 (8.5%)
Cardioembolic	48 (14.3%)	48 (14.2%)	32 (28.8%)	32 (30.2%)
Other determined	3 (0.9%)	1 (0.3%)	1 (0.9%)	—
Undetermined	217 (64.8%)	229 (68.0%)	58 (52.3%)	50 (47.2%)
Competing mechanisms	27 (8.1%)	24 (7.1%)	6 (5.4%)	6 (5.7%)
Complete investigation	77 (23.0%)	98 (29.1%)	20 (18.0%)	17 (16.0%)
Incomplete investigation	113 (33.7%)	107 (31.8%)	32 (28.8%)	27 (25.5%)
Event to inclusion, days	3.4 (2.5)	3.5 (2.7)	3.9 (2.8)	3.5 (2.4)
NIHSS at hospital admission	1 (0–2)	1 (0–2)	1 (0–3)	1 (0–3)
MOCA	24.9 (3.1)	25.0 (2.9)	23.4 (3.7)	23.1 (4.1)
Physical activity, days/wk	1.2 (1.8)	1.1 (1.6)	0.7 (1.4)	0.9 (1.6)

[a]Data are mean (standard deviation), n (%), or median (interquartile range).

HbA1c = glycated hemoglobin; hs-cTnT = high-sensitivity cardiac troponin T; LDL = low-density lipoprotein; MOCA = Montreal Cognitive Assessment; NIHSS = National Institutes of Health Stroke Scale (indicating stroke severity); RR = blood pressure (method of Riva-Rocci); TOAST = Trial of ORG 10172 in Acute Stroke Treatment (indicating stroke etiology); URL = 99th percentile upper reference limit (14ng/l).

used to determine the cumulative survival and event rate of the subgroups at specified times. To assess a possible association of hs-cTnT levels with the occurrence of MACE after minor stroke or TIA in addition to established risk prediction schemes (ie, $ABCD^2$ score), we dichotomized the cohort based on previously published findings with a cutoff at 6 points or more on the $ABCD^2$ score.[16] To evaluate whether the effect of the intensified support program tested in INSPiRE-TMS on the occurrence of the primary outcome event differed according to hs-cTnT levels, patients were categorized into 4 strata based on hs-cTnT (above vs below URL) and INSPiRE-TMS intervention group (support program vs conventional care). Patients with hs-cTnT below URL and randomized to conventional care were defined as reference (stratum with background risk). Data were analyzed using SPSS statistics 27 (IBM, Armonk, NY) and R version 3.5.0.

Results

From August 2011 to October 2017, 934 patients were enrolled in INSPiRE-TMS at the Charité Campus Benjamin Franklin recruitment site. Seven patients (0.8%) who were lost to follow-up and 16 (1.7%) patients with primary intracerebral hemorrhage were excluded from the analysis. Mean time from onset to study inclusion was 3.5 days (SD = 2.5 days) and did not differ between the conventional care and the intensified support program group (3.5 days [SD = 2.6 days] vs 3.5 days [SD = 2.7 days]). hs-cTnT levels were available in 889 (95.2%) patients (mean age = 70 years [SD = 10, range = 32–92], 37% female). A study flowchart is shown in Figure 1. Compared with the entire INSPiRE-TMS cohort, our population differed in some baseline characteristics, being 2 years older and less frequently smokers, with a slightly higher proportion of patients with TIA as the entry event and a slightly higher proportion of patients with undetermined stroke etiology, mainly due to incomplete workup (Supplementary Table S1). The index event upon study entry was ischemic stroke in 497 (55.9%) and TIA in 392 (44.1%) patients. In total, 443 (49.8%) patients were randomized to the support program and 446 (50.2%) received conventional care. hs-cTnT was obtained within 48 hours after onset of neurological deficits in 80% and within 96 hours in 93.5% of all cases (median = 0 days, IQR = 0–1 days, range = 0–12 days). In total, 217 patients (24.4%) had hs-cTnT above URL (ie, >14 ng/l). Specification of hs-cTnT values <13 ng/l was available for 668 patients (75.1%; median = 9 ng/l, IQR = 6–15 ng/l) and above the limit of detection in 76.2%. The range of hs-cTnT quartiles was 0–5 ng/l (Q_1), 6–8 ng/l (Q_2), 9–14 ng/l (Q_3), and >14 ng/l (Q_4).

Baseline characteristics of the entire cohort, separated by hs-cTnT levels and intervention group, are shown in the Table. In general, patients with hs-cTnT above URL were older, more likely to have a medical history of vascular risk factors, and more likely to have suffered an ischemic stroke (vs TIA) as entry event compared to patients with hs-cTnT levels below URL. Systolic blood pressure and glycated hemoglobin levels were higher, whereas low-density lipoprotein cholesterol levels were lower among patients with an initial hs-cTnT above URL. After PSM, the aforementioned baseline characteristics were well balanced between the two groups.

hs-cTnT and Recurrent Vascular Events

During a mean follow-up of 3.2 years (SD = 1.66, range = 0–6.9), there were 153 patients with the primary outcome of MACE (17.2%; 102 stroke, 31 nonfatal coronary event, 20 vascular death). Rate of MACE was higher in patients with hs-cTnT above URL compared to those below (93 per 1,000 person-years vs 44 per 1,000 person-years, unadjusted HR = 2.04 [95% CI = 1.46–2.84], adjusted HR = 1.63 [95% CI = 1.13–2.35]; Fig 2). After PSM, adjusted HR was 1.76 (95% CI = 1.14–2.72). This association was also present in patients without prior myocardial infarction (n = 802, adjusted HR = 1.57 [95% CI = 1.04–2.36]), without impaired renal function (n = 819, adjusted HR = 1.52 [95% CI = 1.03–2.24]), and without atrial fibrillation (n = 728, adjusted HR = 1.74 [95% CI = 1.16–2.60]). When hs-cTnT

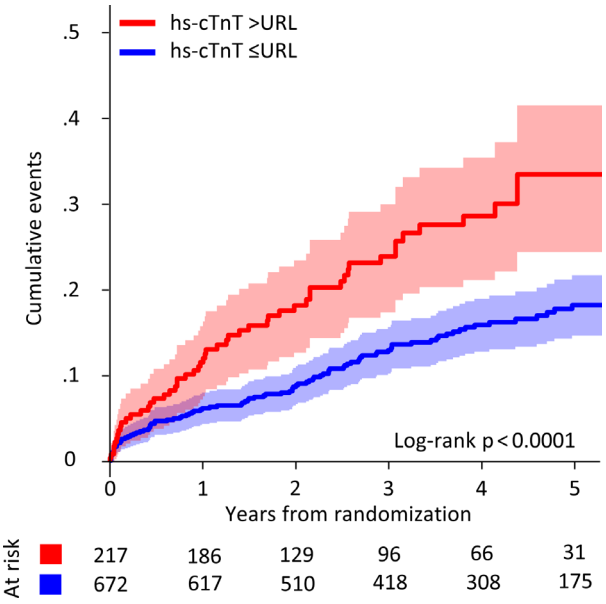


FIGURE 2: Kaplan–Meier plots for the primary outcome (major adverse cardiovascular events) by high-sensitivity cardiac troponin T (hs-cTnT) level (> vs ≤99th percentile upper reference limit [14ng/l; URL]) in the entire cohort.

levels were entered as a log-transformed continuous variable, adjusted HR was 2.31 (95% CI = 1.37–3.89 per log unit; n = 668). Finally, comparing the highest versus the lowest quartile of hs-cTnT values, event rates were 99 per 1,000 person years in Q_4 versus 31 per 1,000 person-years in Q_1 (adjusted HR = 2.59 [95% = CI 1.35–4.97, n = 668]). Figure 3 shows individual unadjusted and adjusted HRs for the composite endpoint MACE and individual vascular events.

Regarding individual vascular events, recurrent stroke occurred in 33 patients with hs-cTnT above URL and in 69 of patients with hs-cTnT below URL (15.2% vs 10.3%; unadjusted HR = 1.73 [95% CI = 1.15–2.61], adjusted HR = 1.49 [95% CI = 0.96–2.33]). A nonfatal coronary event occurred in 12 patients with hs-cTnT above URL and in 19 patients with hs-cTnT below URL (5.5% vs 2.8%; unadjusted HR = 2.53 [95% CI = 1.28–5.02], adjusted HR = 1.79 [95% CI = 0.84–3.81]). Vascular death occurred in 9 patients with hs-cTnT above URL and in 11 patients with hs-cTnT below URL (4.1% vs 1.6%; unadjusted HR = 4.07 [95% CI = 2.05–8.08], adjusted HR = 2.79 [95% CI = 1.28–6.05]; Supplementary Table S2).

hs-cTnT and Risk Stratification for Future Cardiovascular Events

Within the entire cohort, 672 patients (75.6%) had a low estimated vascular risk based on an $ABCD^2$ score of ≤5, and 217 patients (24.4%) had a high estimated vascular risk based on an $ABCD^2$ score of ≥6 after the index event. The rate of MACE was numerically higher in patients with an $ABCD^2$ score of ≥6 compared to those with an $ABCD^2$ score of ≤5 (74 per 1,000 person-years vs 48 per 1,000 person-years, unadjusted HR = 1.53 [95% CI = 1.09–2.16], adjusted HR = 1.38 [95% CI = 0.96–1.97]; Fig 4A).

There was a significant interaction between hs-cTnT levels and $ABCD^2$ risk category for the occurrence of MACE ($p_{interaction} = 0.04$). In the group of patients deemed to be at lower vascular risk (ie, $ABCD^2$ <6), hs-cTnT above URL was associated with the occurrence of MACE (95 per 1,000 person-years vs 38 per 1,000 person-years, adjusted HR = 1.83 [95% CI = 1.17–2.86]), whereas in the group of patients deemed to be at higher risk ($ABCD^2$score ≥6), rate of MACE was similar in patients with hs-cTnT above and below URL (89 per 1,000 person-years vs 67 per 1,000 person-years, adjusted HR = 1.27 [95% CI = 0.65–2.47]; Fig 5A).

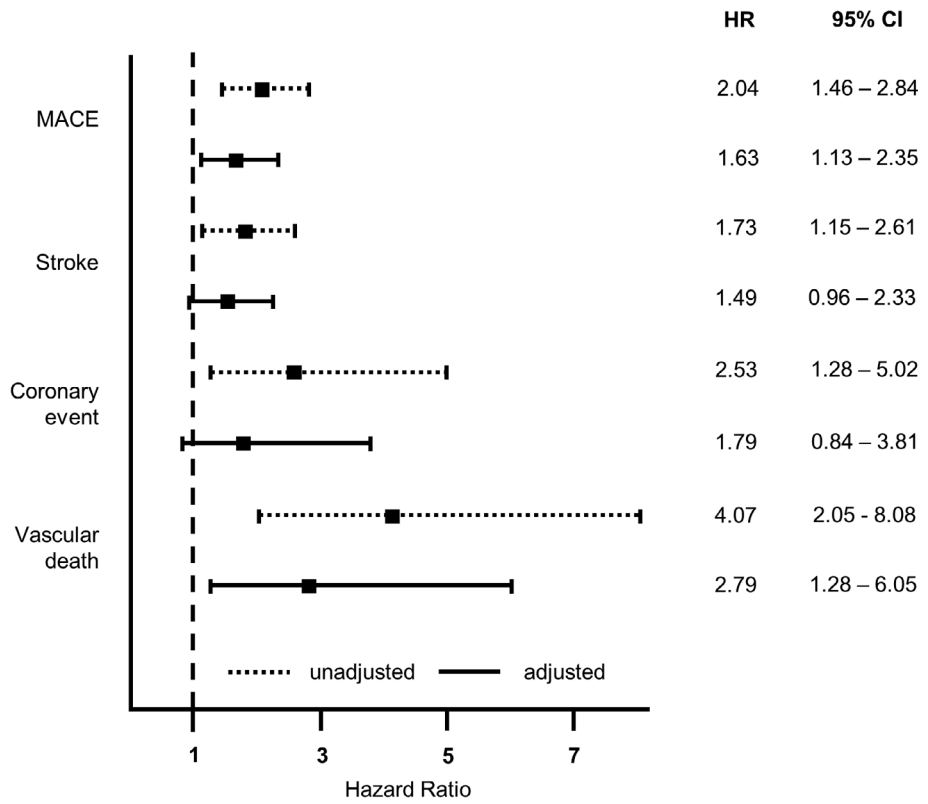


FIGURE 3: Forest plot depicting unadjusted and adjusted hazard ratios (HRs) for the primary outcome (major adverse cardiovascular events [MACE]) as well as secondary outcome measures (stroke, nonfatal coronary event, vascular death) in patients with high-sensitivity cardiac troponin T above the 99th percentile upper reference limit compared to those below. CI = confidence interval.

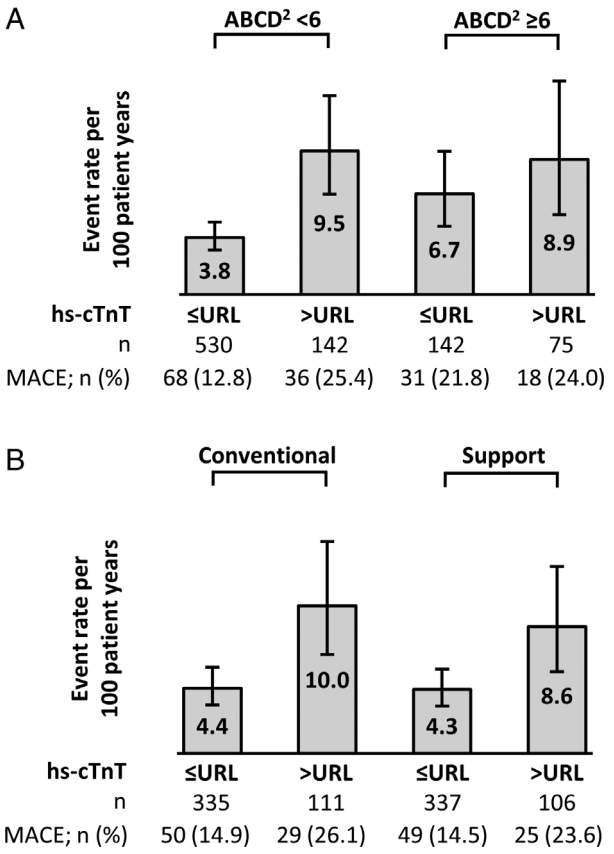


FIGURE 4: Event rates per 100 patient-years, according to Age, Blood Pressure, Clinical Features, Duration of Symptoms, Diabetes (ABCD²; indicates vascular risk) category (lower risk vs higher risk; A) and intervention group (conventional care vs support program; B). "Conventional" indicates conventional care group. "Support" indicates support program group. hs-cTnT = high-sensitivity cardiac troponin T; MACE = major adverse cardiovascular events; URL = 99th percentile upper reference limit.

With respect to the ABCD³I score, 704 patients (79.2%) had a score of ≤7 (ie, lower risk group) and 185 patients (20.8%) had a score of ≥8 (ie, higher risk group). As with the ABCD² score, hs-cTnT above URL was associated with a higher rate of MACE in the lower risk group (adjusted HR = 1.67 [95% CI = 1.08–2.57]). In the higher risk group, there was no statistically significant difference in the rate of MACE between those with hs-cTnT above and below URL (adjusted HR = 1.57 [95% CI = 0.79–3.13]; see Fig 5B).

hs-cTnT and Intensified Support Program

Randomization to the intensified support program was not associated with reduced rate of MACE (adjusted HR = 0.99 [95% CI = 0.72–1.36]). Event rates were higher in patients with hs-cTnT above URL, both in the group of patients randomized to conventional care (100 per 1,000 person-years vs 42 per 1,000 person-years) and in those randomized to the intensified support program (86 per 1,000 person-years vs 43 per 1,000 person-years; see Fig 4B). Patients presenting with hs-cTnT above URL who were randomized to conventional care had the highest risk of the primary outcome (adjusted HR = 1.79 [95% CI = 1.11–2.87]) compared with patients with hs-cTnT below URL and conventional care (Fig 6). There was no statistically significant difference with regard to the occurrence of MACE in patients with hs-cTnT above URL and participation in the support program compared with those receiving conventional care (100 per 1,000 patient years vs 86 per 1,000 patient years, log-rank $p = 0.589$).

Discussion

In this post hoc analysis of INSPiRE-TMS, a randomized controlled trial with blinded endpoint assessment, we report 3 major findings regarding the potential utility of hs-cTnT testing in ischemic stroke and TIA. First, presence of myocardial injury as indicated by hs-cTnT levels above URL was independently associated with the occurrence of MACE within 3 years after minor ischemic stroke or high-risk TIA. This association remained robust after PSM, in sensitivity analyses excluding patient subgroups with higher probability of vascular events and higher probability of hs-cTnT elevation, and was more pronounced when the highest hs-cTnT quartile was compared with the lowest. Second, in patients presumed to be at lower risk for recurrent MACE based on their ABCD² score, annual event rates were more than 2× higher in patients with hs-cTnT above URL than in those below. In this group with lower ABCD² score and hs-cTnT above URL, the annual MACE rate was similar to the rate observed in the higher risk ABCD² category, irrespective of hs-cTnT levels. This held true also for categorization based on the ABCD³I score. Third, participation in the support program had no significant impact on the risk of MACE, irrespective of the hs-cTnT status.

Our findings add to the growing evidence supporting an association between hs-cTn levels and increased risk of cardiovascular events and extend previous observations to the population of patients with minor ischemic stroke or TIA.[7,9] Elevation of hs-cTn has been linked to cardiovascular events in both the general population and different patient populations.[6,9] In patients with cerebrovascular disease, such an association is less clear. It is well established that hs-cTnT levels after stroke are associated with increased mortality.[19] However, a recent meta-analysis concluded that there are insufficient data regarding the question of whether hs-cTn is associated with recurrence of ischemic stroke in stroke patients.[7] So far, a small subgroup analysis of the Find-AF trial suggested a

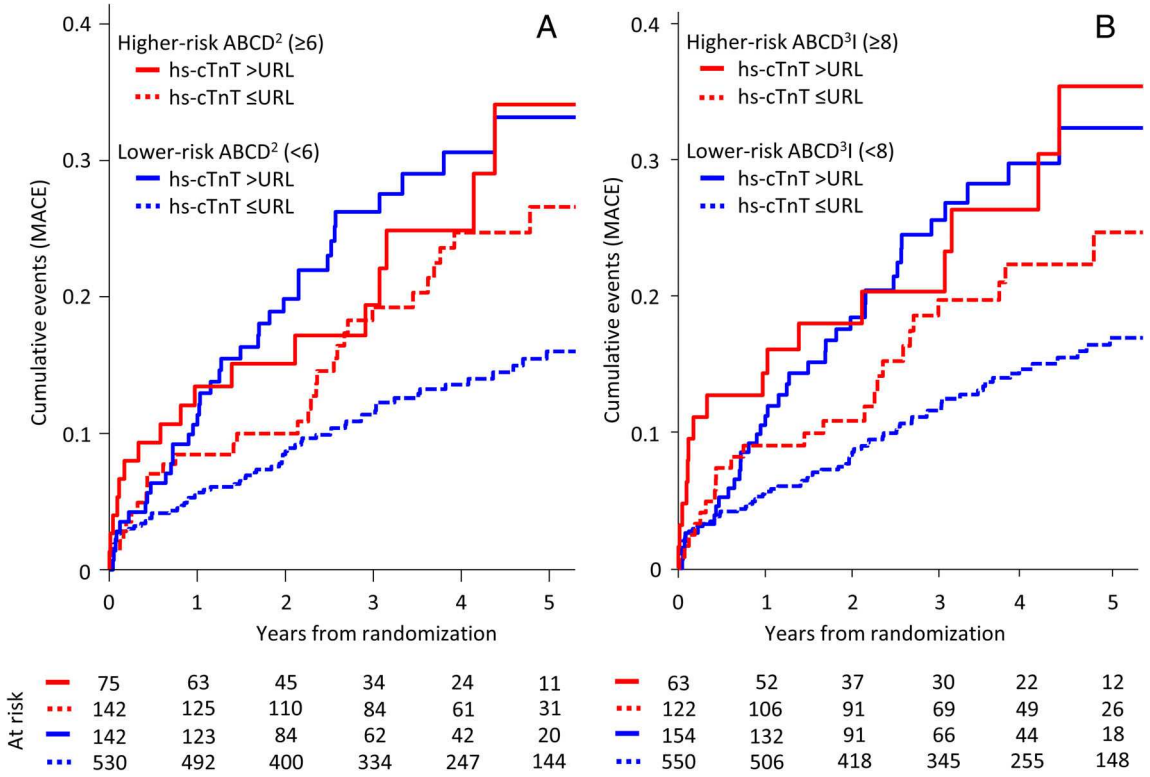


FIGURE 5: Reclassification of cardiovascular risk as assessed with the Age, Blood Pressure, Clinical Features, Duration of Symptoms, Diabetes ($ABCD^2$) score (A) and the $ABCD^3I$ score (B) with addition of high-sensitivity cardiac troponin T (hs-cTnT) levels (> vs ≤99th percentile upper reference limit [14ng/l; URL]). $ABCD^2$/$ABCD^3I$ indicate cardiovascular risk group. MACE = major adverse cardiovascular events.

possible association between hs-cTnT levels above URL and vascular events (n = 23) during a 1-year follow-up.[29] In a cohort of patients with recent embolic stroke of undetermined source enrolled in the NAVIGATE ESUS trial, hs-cTnT above URL was associated with a higher crude rate of MACE within approximately 1 year after the event, albeit not being statistically significant.[11] A possible explanation for the stronger association observed in our cohort than in previous studies might be the longer duration of follow-up and higher number of outcome events.

Individual stratification of vascular risk after minor stroke or TIA is challenging and usually based on presence or absence of traditional vascular risk factors. The $ABCD^2$ score has been proposed and validated to identify patients who have an increased risk of vascular events. Although initially conceived for early triage purposes after TIA, it has been suggested that higher $ABCD^2$ scores are also associated with increased longer term stroke risk within 5 years after TIA or minor stroke, although the specificity of the $ABCD^2$ score was only moderate in previous studies.[1–3] One long-discussed limitation of the $ABCD^2$ score is that a relevant proportion of patients diagnosed with TIA may not actually have suffered a cerebrovascular event, but rather a mimic (migraine with aura, carpal tunnel syndrome, etc). INSPiRE-TMS only included patients without hints of an alternative diagnosis (eg, subsequent headache, sensory march). In our study, we confirmed a 1.5-fold increase in the annual MACE rate in patients estimated to be at higher risk according to the $ABCD^2$ score, with event rates of approximately 7%/yr. These numbers are well in line with those observed in the recently published TIA registry.[1] In contrast, annual event rates in patients with presumably lower risk based on the $ABCD^2$ score were markedly different after stratification for hs-cTnT. Patients deemed to be at lower risk but with elevated hs-cTnT had similar annual event rates as patients with presumed higher risk based on the $ABCD^2$ score. This suggests that hs-cTnT levels may help to identify a subgroup of high-risk individuals with a relevant risk of MACE after stroke or TIA who are not captured by the $ABCD^2$ score alone. This could be of relevance, as current guidelines recommend triage of patients with TIA on the basis of the risk estimated by the $ABCD^2$ score alone.[20] There is evidence that biomarker-based risk models including hs-cTnT may be superior to traditional risk factor–based models.[4,10,30,31] Recently, a subgroup analysis of the PEGASUS-TIMI54 trial observed that addition of hs-cTn levels to guideline-derived risk groups resulted

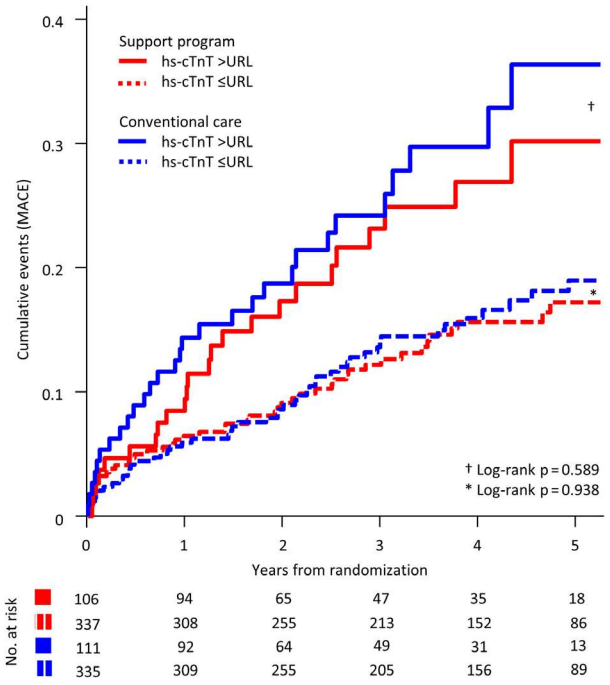


FIGURE 6: Kaplan–Meier plots for the primary end point (major adverse cardiovascular events [MACE]) according to treatment allocation in INSPiRE-TMS (ie, participation in the intensified secondary prevention support program vs conventional care) and subclassification according to high-sensitivity cardiac troponin T (hs-cTnT) levels. URL = 99th percentile upper reference limit (14ng/l).

in substantial reclassification of vascular risk.[32] If confirmed and validated in other cohorts, our findings may have implications for the design of future trials and informing clinical practice with regard to triage purposes of patients with minor stroke or TIA. As a potential consequence, intensified secondary prevention measures and advanced cardiac workup should be considered in stroke patients with elevated hs-cTnT. A relevant proportion of patients with ischemic stroke or TIA remain without a definitive cause of stroke after routine clinical workup.[33] Routine measurement of hs-cTnT in patients with acute ischemic stroke or TIA might help to identify individuals who should receive echocardiography at high priority, especially because there appears to be an association between elevated troponin and cardioembolic stroke etiology.[34,35]

Previous studies suggested that hs-cTn levels may identify individuals who benefit from intensified secondary prevention measures.[36,37] For instance, the absolute and relative benefit of statin treatment was markedly higher in individuals with high versus low hs-cTn levels in the PROVE-IT trial and LIPID study.[36,37] Therefore, we hypothesized that there might be an effect of the intensified secondary prevention support program tested in the INSPiRE-TMS trial on patients with hs-cTnT above URL. In our analyses, there was no clear evidence of a benefit of the intensified support program in patients with hs-cTnT above URL. This is in line with the overall INSPiRE-TMS trial results, which showed no statistically significant impact of the intensified support program on the occurrence of MACE, although significantly more patients achieved the predefined secondary prevention targets.[14] A possible explanation might be that the absolute difference of risk factor control in the groups was smaller than anticipated and control of modifiable risk factors was already at a high standard in the conventional care group. Moreover, numbers and overall event rates in our stratified analyses were too low to finally reject our hypothesis. Of note, INSPiRE-TMS observed a signal toward a benefit of the support program in patients with a higher $ABCD^2$ score.[14] This suggests that certain high-risk groups may benefit from more aggressive stroke prevention. Our findings encourage further investigation regarding the effect of more rigorous risk factor control in stroke patients with elevated hs-cTnT.

Per study protocol of the INSPiRE-TMS trial, our analyses included patients with minor, nondisabling stroke or TIA. Therefore, the results may not be generalizable to the population of more severely affected stroke patients. This may have reduced our power to detect relevant differences, as hs-cTn elevation above URL is associated with higher stroke severity, severity of vascular risk factors, and cardioembolic stroke etiology, and the risk of recurrent vascular events is higher in patients suffering major ischemic stroke. Second, our analysis was restricted to trial participants enrolled at the coordinating trial center only, because other centers did not routinely measure hs-cTnT in all patients admitted with suspected stroke or TIA. Due to these limitations, the overall number of events in this study was too low to allow for in-depth risk prediction analyses (eg, reclassification improvement of risk scores), especially in the analyses of combined exposures. hs-cTnT was measured in the acute phase after stroke, and transient hs-cTnT elevation as a stroke-associated phenomenon cannot be excluded.[8] Time from symptom onset to measurement of hs-cTnT was only documented in days and not in hours. Because hs-cTnT levels might have changed over time, this could have an impact on possible cutoff values for the prediction of MACE. Thus, we cannot draw definite conclusions on the ideal time point and relevance of serial hs-cTnT measurements for risk stratification. Although this affects the biological interpretation of hs-cTnT, it does not negate our observation that the effect of elevated hs-cTnT is different per treatment group. There is evidence that hs-cTnT levels rise during the first few days after stroke and might be lower in the postacute phase.[8,11] Therefore, it remains to be proven whether our

findings are generalizable to patients with hs-cTnT measurements during the postacute phase. Moreover, there is evidence that the extent of myocardial injury is relatively stable over time in the majority of patients with ischemic stroke.[8] Lastly, hs-cTnT is only one candidate biomarker that may be useful for risk stratification after ischemic stroke or TIA. Future studies should test the additive prognostic performance of other biomarkers such as NTproBNP or MRproANP (among others).

In conclusion, there was a robust association between myocardial injury (hs-cTnT levels above URL) and an increased risk of recurrent cardiovascular events in this population of patients with minor stroke or TIA. If these results are validated in confirmatory studies, stratification for hs-cTnT may help to identify patients at high risk for recurrent cardiovascular events among patients otherwise considered to be at lower risk based on their $ABCD^2$ score. Further studies are warranted to address the question whether hs-cTnT can be used for risk stratification after stroke and whether hs-cTnT is useful to identify stroke patients who especially benefit from advanced cardiac workup and intensified secondary prevention measures.

Acknowledgments

This work was supported by grants from Center for Stroke Research Berlin from the German Federal Ministry of Education and Research (01 EO 0801), Pfizer, and the German Stroke Foundation. M.E. received funding from Deutsche Forschungsgemeinschaft under Germany's Excellence Strategy (EXC-2049–390688087). Open Access funding enabled and organized by Projekt DEAL.

Author Contributions

J.F.S, S.H., and H.J.A. contributed to the concept and design of the study; S.H., T.I., R.G., I.L., M.A., and M.S. contributed to the acquisition and analysis of data; J.F.S., S.H., J.E.W., M.E., and H.J.A. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

H.J.A. reports speaker fees and consultancy honoraria received during the conduct of the study from Pfizer (Pfizer was involved as a funding source of the study). All other authors reported no relationships with commercial firms whose products could be affected by the present study.

References

1. Amarenco P, Lavallee PC, Monteiro Tavares L, et al. Five-year risk of stroke after TIA or minor ischemic stroke. N Engl J Med 2018;378: 2182–2190.
2. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369:283–292.
3. Wardlaw JM, Brazzelli M, Chappell FM, et al. ABCD2 score and secondary stroke prevention: meta-analysis and effect per 1,000 patients triaged. Neurology 2015;85:373–380.
4. Beatty AL, Ku IA, Bibbins-Domingo K, et al. Traditional risk factors versus biomarkers for prediction of secondary events in patients with stable coronary heart disease: from the heart and soul study. J Am Heart Assoc 2015;4:e001646.
5. Matusik PT. Biomarkers and cardiovascular risk stratification. Eur Heart J 2019;40:1483–1485.
6. Farmakis D, Mueller C, Apple FS. High-sensitivity cardiac troponin assays for cardiovascular risk stratification in the general population. Eur Heart J 2020;41:4050–4056.
7. Broersen LHA, Stengl H, Nolte CH, et al. Association between high-sensitivity cardiac troponin and risk of stroke in 96 702 individuals: a meta-analysis. Stroke 2020;51:1085–1093.
8. Scheitz JF, Nolte CH, Doehner W, et al. Stroke-heart syndrome: clinical presentation and underlying mechanisms. Lancet Neurol 2018; 17:1109–1120.
9. Willeit P, Welsh P, Evans JDW, et al. High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. J Am Coll Cardiol 2017;70:558–568.
10. Hijazi Z, Lindback J, Alexander JH, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J 2016;37:1582–1590.
11. Scheitz JF, Pare G, Pearce LA, et al. High-sensitivity cardiac troponin T for risk stratification in patients with embolic stroke of undetermined source. Stroke 2020;51:2386–2394.
12. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160–2236.
13. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–2381.
14. Ahmadi M, Laumeier I, Ihl T, et al. A support programme for secondary prevention in patients with transient ischaemic attack and minor stroke (INSPiRE-TMS): an open-label, randomised controlled trial. Lancet Neurol 2020;19:49–60.
15. Leistner S, Michelson G, Laumeier I, et al. Intensified secondary prevention intending a reduction of recurrent events in TIA and minor stroke patients (INSPiRE-TMS): a protocol for a randomised controlled trial. BMC Neurol 2013;13:11.
16. Amarenco P, Lavallee PC, Labreuche J, et al. One-year risk of stroke after transient ischemic attack or minor stroke. N Engl J Med 2016; 374:1533–1542.
17. Merwick A, Albers GW, Amarenco P, et al. Addition of brain and carotid imaging to the ABCD(2) score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. Lancet Neurol 2010;9:1060–1069.

18. Song B, Fang H, Zhao L, et al. Validation of the ABCD3-I score to predict stroke risk after transient ischemic attack. Stroke 2013;44: 1244–1248.

19. Scheitz JF, Mochmann HC, Erdur H, et al. Prognostic relevance of cardiac troponin T levels and their dynamic changes measured with a high-sensitivity assay in acute ischaemic stroke: analyses from the TRELAS cohort. Int J Cardiol 2014;177:886–893.

20. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50: e344–e418.

21. Giannitsis E, Kurz K, Hallermayer K, et al. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56: 254–261.

22. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237–269.

23. Gu XS, Rosenbaum PR. Comparison of multivariate matching methods: structures, distances, and algorithms. J Comput Graph Stat 1993;2:405–420.

24. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399–424.

25. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011;10:150–161.

26. Stuart EA, Lee BK, Leacy FP. Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research. J Clin Epidemiol 2013;66:S84–S90.e1.

27. Vansteelandt S, Daniel RM. On regression adjustment for the propensity score. Stat Med 2014;33:4053–4072.

28. Thoemmes F. Propensity score matching in SPSS2012. Available at: https://arxiv.org/ftp/arxiv/papers/1201/1201.6385.pdf. Accessed on March 3, 2021.

29. Stahrenberg R, Niehaus CF, Edelmann F, et al. High-sensitivity troponin assay improves prediction of cardiovascular risk in patients with cerebral ischaemia. J Neurol Neurosurg Psychiatry 2013;84: 479–487.

30. Blankenberg S, Salomaa V, Makarova N, et al. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. Eur Heart J 2016;37:2428–2437.

31. Lindholm D, Lindback J, Armstrong PW, et al. Biomarker-based risk model to predict cardiovascular mortality in patients with stable coronary disease. J Am Coll Cardiol 2017;70:813–826.

32. Marston NA, Bonaca MP, Jarolim P, et al. Clinical application of high-sensitivity troponin testing in the atherosclerotic cardiovascular disease framework of the current cholesterol guidelines. JAMA Cardiol 2020;5:1255–1262.

33. Desai JA, Abuzinadah AR, Imoukhuede O, et al. Etiologic classification of TIA and minor stroke by A-S-C-O and causative classification system as compared to TOAST reduces the proportion of patients categorized as cause undetermined. Cerebrovasc Dis 2014;38: 121–126.

34. Merkler AE, Gialdini G, Murthy SB, et al. Association between troponin levels and embolic stroke of undetermined source. J Am Heart Assoc 2017;6:e005905.

35. Yaghi S, Chang AD, Ricci BA, et al. Early elevated troponin levels after ischemic stroke suggests a cardioembolic source. Stroke 2018; 49:121–126.

36. White HD, Tonkin A, Simes J, et al. Association of contemporary sensitive troponin I levels at baseline and change at 1 year with long-term coronary events following myocardial infarction or unstable angina: results from the LIPID Study (Long-Term Intervention With Pravastatin in Ischaemic Disease). J Am Coll Cardiol 2014;63: 345–354.

37. Bonaca MP, O'Malley RG, Jarolim P, et al. Serial cardiac troponin measured using a high-sensitivity assay in stable patients with ischemic heart disease. J Am Coll Cardiol 2016;68:322–323.

4.3 Zeitliche Veränderungen in der Verschreibepraxis gerinnungsaktiver Substanzen bei Schlaganfallpatienten mit bekanntem Vorhofflimmern

Hellwig S., Grittner U., Herm J., Ruschmann R., Konieczny M., Endres M., Haeusler K. G.: Temporal Trends in Pharmacological Stroke Prevention in Patients with Acute Ischemic Stroke and Known Atrial Fibrillation. *J Stroke Cerebrovasc Dis.* 2020 Dec;29(12):105266. DOI: 10.1016/j.jstrokecerebrovasdis.2020.105266.

Schlaganfallpatient*innen mit bekanntem Vorhofflimmern sollten mit einer oralen Antikoagulation behandelt werden, sofern keine Kontraindikationen vorliegen[26, 27, 34]. Mehrere randomisierte, kontrollierte Studien untersuchten den Einsatz des Vitamin K-Antagonisten Warfarin im Vergleich zu ASS und/oder Placebo in der Primär- und Sekundärprävention des Schlaganfalls bei Patient*innen mit Vorhofflimmern ab 1989[117]. Eine Meta-Analyse dieser Studien aus dem Jahr 1994 errechnete eine 68%ige Risikoreduktion für das Auftreten ischämischer Schlaganfälle unter der Therapie mit Warfarin[118]. Eine weitere Meta-Analyse errechnete eine um 62% reduzierte Schlaganfallrate (95% KI 48%-72%) bei einer jährlichen absoluten Risikoreduktion von 2,7% in der Primärprävention und 8,4% für den Einsatz von Warfarin in der Sekundärprävention ischämischer Schlaganfälle[119]. Die EAFT Studie adressierte speziell den Einsatz von Vitamin K-Antagonisten in der Sekundärprävention schwerwiegender kardialer Folgeereignisse (MACE) nach ischämischem Schlaganfall bei Patient*innen mit Vorhofflimmern[120]. Über einen durchschnittlichen Nachverfolgungszeitraum von 2,3 Jahren zeigte sich eine um 9% verringerte jährliche MACE-Rate (8% unter OAK vs. 17% unter Placebo, Hazard Ratio 0,53 [95% KI 0,36-0.79]) sowie eine um 8% verringerte jährliche Schlaganfallrate (4% vs. 12%, HR 0,34 [95% KI 0,20-0,57])[120].
Trotz dieses belegten Nutzens ist eine dramatische Unterversorgung von Patient*innen mit Vorhofflimmern und einer Indikation für eine OAK mit einem VKA belegt[121]. Als Gründe hierfür werden die Notwendigkeit zur individuellen Dosis-Findung und ggf. Anpassung beim Einsatz von VKA (gesteuert nach dem Zielbereich der International Normalized Ratio (INR), i.d.R. zwischen 2,0 und 3,0) und den damit verbundenen regelmäßigen Blutentnahmen, multiple potentielle Arzneimittelinteraktionen, Interaktionen mit Nahrungsmitteln, eine vergleichsweise geringe therapeutische Breite und das erhöhte Blutungsrisiko genannt[122].

Seit Ende 2010 stehen die sog. Nicht-Vitamin K-abhängigen oralen Antikoagulanzien (NOAK) zur Verfügung[122]. Für alle vier Substanzen (Dabigatran, Rivaroxaban, Apixaban und Edoxaban) wurde in großen, randomisierten Studien eine Nichtunterlegenheit gegenüber Warfarin bei einem um ca. 50% reduzierten relativen Risiko für eine intrazerebrale Blutung und einem um ca. 10% reduzierten Risiko für Tod aus jeglicher Ursache nachgewiesen[123]. Während es bei NOAKs wesentlich seltener zu Arznei- und Nahrungsmittelinteraktionen kommt und es keiner individuellen Dosisfindung und/oder Therapiemonitoring bedarf, kann eine Niereninsuffizienz die Anwendbarkeit einschränken und die vergleichsweise kurze Plasmahalbwertszeit setzt eine strikte Einnahmeadhärenz voraus[124].

Ziel dieser Arbeit war es zu untersuchen, ob durch die Verfügbarkeit der NOAKs eine Verbesserung der Sekundärprävention bei Schlaganfallpatient*innen mit Vorhofflimmern zu belegen ist[122]. Zur Beantwortung dieser Fragestellung wurden monozentrisch 1.209 Datensätze von Patient*innen mit bestehender Indikation für eine OAK vor dem Schlaganfall (d.h. bekanntes VHF und CHA_2DS_2-VASc Score ≥1) aus drei repräsentativen Zeiträumen (2003-2004; 2008-2010 und 2013-2015) analysiert und verglichen[122]. Im Vergleich der Zeiträume vor und nach 2010 zeigte sich eine deutlich erhöhte Rate einer vorbestehenden OAK unter Verfügbarkeit der NOAKs (49,6% vs. 28,2%, p<0,001)[122]. Auch die Verschreiberate einer OAK bei Krankenhausentlassung stieg signifikant an (69,5% vs. 45,2%, p<0.001)[122]. Mit einer OAK-Einnahme vor Schlaganfall waren dabei jüngeres Alter (Odds Ratio 0,74 pro Dekade [95% KI 0,64-0,85]), vorausgegangener Schlaganfall oder TIA (OR 1,29 [95% KI 1,00-1,67]), Abwesenheit einer Herzinsuffizienz (OR 0,63 [95% KI 0,47-0,85]) und Aufnahme 2013-2015 (OR 2,45 [95% KI 1,91-3,15]) als unabhängige Faktoren assoziiert[122].

Zusammenfassend belegt diese Analyse, dass es mit der Verfügbarkeit von NOAKs zwar zu einem signifikanten Anstieg der OAK-Rate sowohl vor Auftreten des Index-Schlaganfalls als auch bei Krankenhausentlassung kam, jedoch weiterhin nicht einmal die Hälfte aller Patient*innen mit VHF und einer bestehenden Indikation zur OAK leitliniengerecht behandelt wurden[122].

https://www.doi.org/10.1016/j.jstrokecerebrovasdis.2020.105266

*4.4 Ätiologie, Strategien der Sekundärprävention und Behandlungsergebnisse bei ischämischem Schlaganfall trotz oraler Antikoagulation bei Patient*innen mit Vorhofflimmern*

Polymeris A. A., Meinel T. R., Oehler H., Hölscher K., Zietz A., Scheitz J. F., Nolte C. H., Stretz C., Yaghi S., Stoll S., Wang R., Haeusler K. G., **Hellwig S.**, Klammer M. G., Litmeier S., Leon Guerrero C. R., Moeini-Naghani I., Michel P., Strambo D., Salerno A., Bianco G., Cereda C., Uphaus T., Gröschel K., Katan M., Wegener S., Peters N., Engelter S. T., Lyrer P. A., Bonati L. H., Grunder L., Ringleb P. A., Fischer U., Kallmünzer B., Purrucker J. C., Seiffge D. J.: Aetiology, secondary prevention strategies and outcomes of ischaemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *J Neurol Neurosurg Psychiatry*. 2022 Jun;93(6):588-98. DOI: 10.1136/jnnp-2021-328391

Eine orale Antikoagulation reduziert das Schlaganfallrisiko bei Patientinnen und Patienten mit Vorhofflimmern um etwa 60%, wobei die „neuen“, nicht Vitamin-K abhängigen oralen Antikoagulanzien (NOAK) ein verbessertes Risiko-Nutzen-Verhältnis im Vergleich zu Vitamin K-Antagonisten aufweisen[123, 125]. In der zuvor dargestellten Arbeit ergab sich trotz Verfügbarkeit der NOAKs ab 2011 weiterhin das Bild einer fortbestehenden erheblichen Unterversorgung von Patient*innen mit VHF und einer Indikation für eine OAK[122]. Darüber hinaus besteht auch bei Patient*innen unter OAK ein residuelles Schlaganfallrisiko, dass in der Literatur mit 0,7% bis 2,3% in der Primär- und Sekundärprävention angegeben wird[126]. Dabei scheint es so zu sein, dass Patient*innen mit einem Schlaganfall trotz bestehender Antikoagulation ein besonders hohes Rezidivrisiko haben im Vergleich zu Patient*innen ohne vorbestehende Antikoagulation[127-129]. Hierbei sind die pathophysiologischen Hintergründe nur unzureichend verstanden: einerseits könnten konkurrierende Schlaganfallursachen wie Makro- oder Mikroangiopathie (→ *3.5 Schlaganfallätiologien*) oder aber Dosierungsfehler sowie mangelnde Einnahmetreue eine Rolle spielen[128, 130]. Ziel der vorliegenden Arbeit war es, die Schlaganfallursachen, nachfolgende Sekundärprävention und Behandlungsergebnisse bei Patient*innen mit VHF und ischämischem Schlaganfall trotz bestehender Antikoagulation zu analysieren[126].

Es wurden insgesamt 2.946 individuelle Datensätze aus den Jahren 2012-2020 von elf verschiedenen Zentren weltweit (Deutschland, Schweiz, USA) für die Analyse gepoolt[126]. Informationen über Behandlungsergebnisse („Outcome“) nach drei Monaten lagen für 1.906 Patient*innen vor, wobei der primäre Endpunkt eine Kombination aus erneutem ischämischem Schlaganfall, intrazerebraler Blutung und Tod und der sekundäre Endpunkt erneuter ischämischer Schlaganfall war[126]. Von allen untersuchten Patient*innen nahmen 1.272 (43,2%) einen VKA und 1.674 (56.8%) ein NOAK ein, wobei 925 (56,3%) die volle Dosis und 717 (43,7%) eine reduzierte Dosis einnahmen[126]. Informationen über die medikamentöse Sekundärprävention bei Entlassung lag für 2.875 Patient*innen vor, wobei 2.437 Patient*innen (84,8%) eine OAK erhielten (VKA: 13,4%; NOAK: 86,6%)[126]. Hinsichtlich der vermuteten Schlaganfallursachen handelte es sich bei 713 Patient*innen (24,2%) um konkurrierende Ursachen (Makroangiopathie: 60,6%; Mikroangiopathie: 26,3%; Andere: 13,1%), um eine unzureichende Antikoagulation bei 934 Patient*innen (31,7%) und um einen kardioembolischen Schlaganfall trotz suffizienter Antikoagulation bei 1.299 Patient*innen (44,1%)[126].

Insgesamt fand sich eine hohe Rate schwerwiegender vaskulärer Ereignisse bereits nach drei Monaten: der primäre Endpunkt trat bei 516 Patient*innen (27,1%) auf, wobei 84 Patient*innen (4,6%) einen Rezidivschlaganfall erlitten[126]. Hierbei hatte einzig die Einnahme eines NOAK einen protektiven Einfluss auf das Auftreten der beschriebenen Endpunkte (adjustierte Odds Ratio für Auftreten des primären Endpunktes 0,49 [95% KI 0,32-0,73] und für das Auftreten des sekundären Endpunktes 0,44 [95% KI 0,24-0,80])[126]. Eine Umstellung bei bestehender Einnahme eines NOAK auf ein anderes NOAK zeigte keine signifikante Assoziation mit dem Auftreten des primären Endpunktes (adjustierte Odds Ratio 1,28 [95% KI 0,65-2,51])[126]. Interessanterweise war eine additive Therapie mit einem Thrombozytenfunktionshemmer zusätzlich zur OAK positiv mit dem Auftreten des primären und sekundären Endpunktes assoziiert (adjustierte Odds Ratio 1,99 [95% KI 1,25-3,15] bzw. 2,66 [95% KI 1,40-5,04])[126].

Die Genese ischämischer Schlaganfälle trotz bestehender Antikoagulation bei Patient*innen mit Vorhofflimmern ist heterogen und mehr als jede*r vierte Patient*in erleidet bereits nach drei Monaten ein schwerwiegendes Folgeereignis[126]. Die Einnahme eines NOAK scheint mit einer niedrigeren Rate, eine additive Therapie mit einem Thrombozytenfunktionshemmer mit einer höheren Rate an Folgeereignissen assoziiert zu sein[126]. Dies sollte bei der Wahl der Sekundärprävention für dieses Patientenkollektiv Berücksichtigung finden.

Original research

Aetiology, secondary prevention strategies and outcomes of ischaemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation

Alexandros A Polymeris ,[1] Thomas R Meinel ,[2] Hannah Oehler,[3] Kyra Hölscher,[3] Annaelle Zietz,[1] Jan F Scheitz,[4] Christian H Nolte ,[4] Christoph Stretz ,[5] Shadi Yaghi ,[5] Svenja Stoll,[6] Ruihao Wang,[6] Karl Georg Häusler,[7] Simon Hellwig,[4] Markus G Klammer,[4] Simon Litmeier,[4] Christopher R Leon Guerrero,[8] Iman Moeini-Naghani,[8] Patrik Michel,[9] Davide Strambo ,[9] Alexander Salerno ,[9] Giovanni Bianco,[10] Carlo Cereda,[10] Timo Uphaus ,[11] Klaus Gröschel,[11] Mira Katan,[1,12] Susanne Wegener ,[12] Nils Peters,[1,13,14] Stefan T Engelter,[1,14] Philippe A Lyrer,[1] Leo H Bonati,[1] Lorenz Grunder,[15] Peter Arthur Ringleb,[3] Urs Fischer,[1,2] Bernd Kallmünzer,[6] Jan C Purrucker ,[3] David J Seiffge [2]

ABSTRACT

Objective To investigate the aetiology, subsequent preventive strategies and outcomes of stroke despite anticoagulation in patients with atrial fibrillation (AF).

Methods We analysed consecutive patients with AF with an index imaging-proven ischaemic stroke despite vitamin K-antagonist (VKA) or direct oral anticoagulant (DOAC) treatment across 11 stroke centres. We classified stroke aetiology as: (i) competing stroke mechanism other than AF-related cardioembolism; (ii) insufficient anticoagulation (non-adherence or low anticoagulant activity measured with drug-specific assays); or, (iii) AF-related cardioembolism despite sufficient anticoagulation. We investigated subsequent preventive strategies with regard to the primary (composite of recurrent ischaemic stroke, intracranial haemorrhage, death) and secondary endpoint (recurrent ischaemic stroke) within 3 months after index stroke.

Results Among 2946 patients (median age 81 years; 48% women; 43% VKA, 57% DOAC), stroke aetiology was competing mechanism in 713 patients (24%), insufficient anticoagulation in 934 (32%) and cardioembolism despite sufficient anticoagulation in 1299 (44%). We found high rates of the primary (27% of patients; completeness 91.6%) and secondary endpoint (4.6%; completeness 88.5%). Only DOAC (vs VKA) treatment after index stroke showed lower odds for both endpoints (primary: adjusted OR (aOR) (95% CI) 0.49 (0.32 to 0.73); secondary: 0.44 (0.24 to 0.80)), but not switching between different DOAC types. Adding antiplatelets showed higher odds for both endpoints (primary: aOR (95% CI) 1.99 (1.25 to 3.15); secondary: 2.66 (1.40 to 5.04)). Only few patients (1%) received left atrial appendage occlusion as additional preventive strategy.

Conclusions Stroke despite anticoagulation comprises heterogeneous aetiologies and cardioembolism despite sufficient anticoagulation is most common. While DOAC were associated with better outcomes than VKA, adding antiplatelets was linked to worse outcomes in these high-risk patients. Our findings indicate that individualised and novel preventive strategies beyond the currently available anticoagulants are needed.

Trial registration number ISRCTN48292829.

INTRODUCTION

Oral anticoagulation with either direct oral anticoagulants (DOAC) or vitamin K-antagonists (VKA) reduces the risk of ischaemic stroke in patients with non-valvular atrial fibrillation (AF). However, there is a substantial residual stroke risk in patients with AF despite anticoagulation ranging from 0.7% to 2.3% annually in primary and secondary prevention, respectively.[1–4] Since the introduction of DOAC, the overall use of oral anticoagulants for stroke prevention in patients with AF has increased steadily, particularly in patients with AF at the highest stroke risk.[5] Due to this development, the number of patients with AF suffering a stroke despite anticoagulation is expected to increase, too.[6 7] Accumulating evidence suggests that patients with AF and stroke despite anticoagulation are at a higher risk for future recurrence than patients who were naive to anticoagulation treatment before stroke.[8–10]

For stroke physicians, ischaemic stroke despite anticoagulation in patients with AF represents a challenge in everyday clinical practice, as its aetiology is not well-understood.[11] Competing stroke mechanisms such as large artery and small vessel disease, as well as non-adherence or inappropriately dosed anticoagulation have been discussed as potential causes of stroke despite anticoagulation,[8–11] but few data on their relative frequency exist.[6] A better understanding of the aetiology of stroke despite

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-328391).

For numbered affiliations see end of article.

Correspondence to
David J Seiffge, Department of Neurology, Inselspital University Hospital Bern, Bern, 3010, Switzerland; david.seiffge@insel.ch

AAP and TRM contributed equally.
JCP and DJS contributed equally.

AAP and TRM are joint first authors.
JCP and DJS are joint senior authors.

For 'Presented at statement' see end of article.

Received 4 November 2021
Accepted 5 March 2022
Published Online First 8 April 2022

Watch Video
jnnp.bmj.com

Check for updates

To cite: Polymeris AA, Meinel TR, Oehler H, *et al*. *J Neurol Neurosurg Psychiatry* 2022;**93**:588–598.

anticoagulation is needed to inform strategies to prevent recurrence after a stroke despite anticoagulation.[11] So far, limited data suggested no benefit from switching the anticoagulant type.[8 9] Indeed, the optimal management of patients with stroke despite anticoagulation remains unclear, and the latest guidelines offer no recommendations on this.[12]

We therefore sought to (i) describe the aetiology of stroke despite oral anticoagulation and (ii) investigate subsequent preventive strategies and outcomes in a large collaborative study of patients with AF and stroke despite anticoagulation from 11 experienced stroke centres.

METHODS

Study design, patient population and data collection

We pooled individual data of patients with consecutive stroke in a collaborative effort across 11 experienced stroke centres from Switzerland, Germany and the USA with a special research interest in stroke despite anticoagulation. Patients who had a stroke were identified using local prospective registries complemented by hospital admission records, as in prior research.[6 7] Local investigators collected data that were not available in the prospective databases by retrospectively reviewing patient charts. All data were collected using predefined variables in a standardised manner. De-identified patient data were pooled and analysed at the University Hospitals Basel and Bern.

We included patients with previously known AF and an imaging-proven acute ischaemic stroke (hereafter referred to as index stroke) occurring while on oral anticoagulant therapy (ie, prescribed anticoagulation for long-term stroke prevention, excluding non-persistent patients and those with physician-initiated pauses for medical reasons at the time of the stroke). We excluded patients with missing data on anticoagulant treatment, and those with mechanical heart valves. The reporting period was limited to patients presenting no earlier than January 2012 and no later than December 2020.

A detailed description of collected baseline clinical, neuroimaging and laboratory variables, as well as preventive treatments following the index stroke, is presented in the online supplemental file 1.

Aetiology of stroke despite anticoagulation

The presumed most likely aetiology of stroke was determined by local investigators according to the following predefined categories:

1. Competing stroke mechanism other than AF-related cardioembolism (such as small vessel disease, large artery atherosclerosis or other established pathologies as the most likely stroke mechanism in line with the TOAST classification criteria, that is, 'two or more mechanisms'[13]);
2. Insufficient anticoagulation defined (adapting prior research[6]) as (i) self-reported non-adherence (ie, history of missing intake of anticoagulants within the last 3 days before index stroke); (ii) low anticoagulant activity on admission (ie, international normalised ratio (INR) <2.0 in VKA-treated patients; plasma level <30 ng/mL in DOAC-treated patients[14]; or, (iii) inappropriately low DOAC dose or dosing frequency (according to current product labelling by the Swiss Agency for Therapeutic Products, European Medicines Agency and the United States Food and Drug Administration, as applicable). Patients with evidence for both (1) and (2) were classified solely as (1), that is, competing stroke mechanism;
3. AF-related cardioembolism despite sufficient anticoagulation, defined as stroke without evidence for either (1) or (2).

To investigate the reproducibility of the classification, a random sample from the two largest data sets (Basel and Bern, 25 patients each) was reclassified by a different local investigator, showing high inter-rater agreement (82%, kappa 0.73). Additionally, a random sample of 25 patients from the entire data set was reclassified based on available baseline variables by blinded raters from three of the largest centres (Basel, Bern and Heidelberg), showing high inter-centre agreement (87%, kappa 0.80).

3-month outcomes

Out of 11 centres, 8 routinely collected standardised information on the following 3-month outcomes: (i) recurrent ischaemic stroke, (ii) intracranial haemorrhage (ICH), (iii) all-cause death and (iv) functional outcome on the modified Rankin Scale (mRS). The primary endpoint was the composite of recurrent ischaemic stroke, ICH and all-cause death within 3 months, defined as in previous research.[8 15] Secondary endpoint was recurrent ischaemic stroke within 3 months. An additional combined endpoint of recurrent ischaemic stroke and ICH within 3 months was defined post hoc.

Statistical analyses

Main analysis

We presented data on the aetiology of stroke despite anticoagulation using descriptive statistics. We stratified patient characteristics according to stroke aetiology and type of anticoagulant (DOAC vs VKA) at the time of the index stroke. Categorical data are presented using frequencies and percentages and continuous data using the median and IQR. We compared categorical variables using the χ^2 test or Fisher's exact test, as appropriate, and continuous variables using the Mann-Whitney U test.

Secondary analyses

To investigate the prognostic significance of the aetiology of stroke despite anticoagulation with regard to the primary and secondary endpoints, we used univariable and multivariable logistic models adjusted for preselected common risk factors (ie, age, sex, hypertension, diabetes, ischaemic heart disease, dyslipidaemia, renal impairment, prior ischaemic stroke or ICH, current smoking and active malignancy).

To explore the association of preventive strategies with the primary and secondary endpoints, we fitted univariable and multivariable logistic models adjusted for preselected common outcome predictors, as described in detail in the online supplemental file 1. As a post-hoc analysis we additionally examined the association of all preventive strategies with the combined endpoint of recurrent ischaemic stroke and ICH.

For all models, we report the (adjusted) OR ((a)OR) along with 95% CIs and two-sided p values. Additionally, the number of missing values are indicated for all data. We fitted all models using only complete cases without data imputation and report the number of patients (and number of events) included in each model.

Statistical analyses were performed using Stata V.17.0 (StataCorp). We conducted this study in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Statement for observational studies.[16] This study is registered with the International Standard Registered Clinical/Social Study Number Registry.

This study complies with the Declaration of Helsinki.

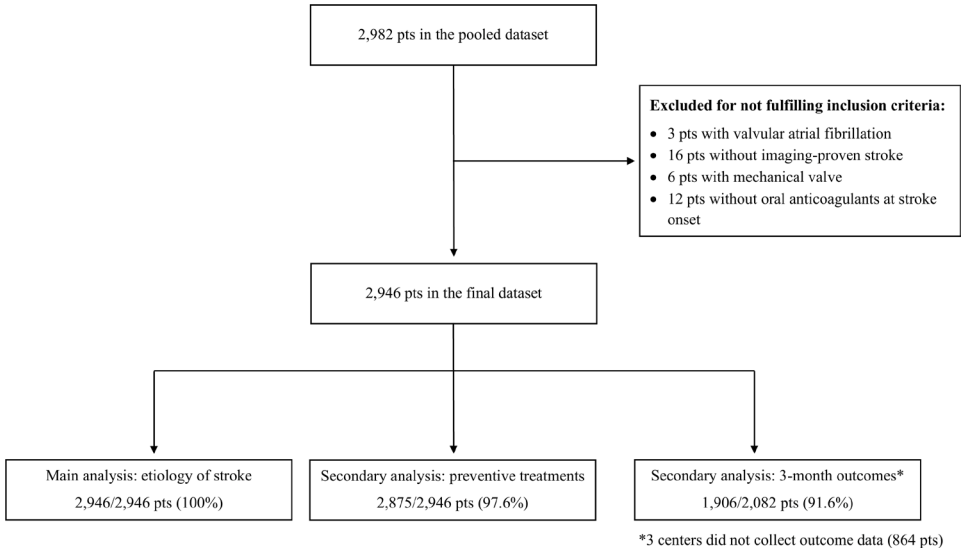


Figure 1 Study flowchart.

RESULTS

In total, 2946 patients were eligible for analysis. Figure 1 shows the study flowchart and online supplemental Table 1 the centre contributions. The median (IQR) age was 81 (76–86) years, 1404 patients were women (47.7%) and stroke was moderate to severe (National Institutes of Health Stroke Scale 6 (2–14)). At the time of the index stroke, 1674 patients (56.8%) were taking DOAC and 1272 (43.2%) were taking VKA; their detailed characteristics are shown in online supplemental table 2. Plasma level on admission was available for 913 patients on DOAC (54.5%), and INR on admission was available in 1267 patients on VKA (99.6%).

Aetiology of stroke despite anticoagulation

Information on the presumed most likely aetiology of stroke was available for all patients and was classified as competing stroke mechanism in 713 (24.2%), insufficient anticoagulation in 934 (31.7%) and cardioembolism despite sufficient anticoagulation in 1299 (44.1%) patients. The distribution of stroke aetiologies in patients with stroke from January 2012 to June 2016 versus July 2016 to December 2020 did not differ substantially (online supplemental figure 1). The detailed characteristics of all patients stratified to stroke aetiology are presented in table 1.

Among patients with competing mechanisms other than AF-related cardioembolism as stroke aetiology, information on the exact competing mechanism was available for 685 of 713 patients (96.1%). Of those, 658 patients (96.1%) had one and 27 (3.9%) had more than one competing stroke mechanism as the most likely stroke aetiology. The most common competing mechanism was large artery atherosclerosis, which was present in 415 (60.6%) patients, followed by small vessel disease (present in 180 (26.3%) patients). Less common aetiologies included coagulopathies (ie, cancer-related coagulopathy, antiphospholipid syndrome and others; 5.3%), peri-interventional stroke (3.4%), endocarditis (3.2%) and other cardio-aortic pathologies (3.8%). There were no substantial differences in the distribution of competing mechanisms among patients with DOAC versus VKA therapy at the time of the index stroke. Details are given in table 2.

Preventive treatments

Information on antithrombotic treatment after the index stroke was available for 2875 of 2946 patients (completeness 97.6%). At hospital discharge, 2437 patients (84.8%) were treated with oral anticoagulants, 120 (4.2%) received antiplatelets alone, 286 (9.9%) received no antithrombotic treatment and 32 (1.1%) received parenteral anticoagulation.

Of patients who received oral anticoagulants, 13.4% were prescribed VKA and 86.8% DOAC, whereby 80.5% received a two times per day DOAC and 66.6% received DOAC at full dose. Antiplatelets as add-on therapy to anticoagulation were prescribed in 367 patients (12.8% of all patients; 15.1% of all patients with anticoagulation), which was more common among those with competing mechanism as stroke aetiology. Most patients were prescribed statins and antihypertensives after the index stroke, and both drug types were more commonly prescribed after stroke due to competing mechanisms than due to other aetiologies. The detailed preventive treatments stratified to stroke aetiology are given in online supplemental table 3. An overview of the changes in oral anticoagulant therapy before versus after stroke is presented in figure 2.

Information on non-pharmacological preventive treatments was available for revascularisation treatments in 2774 of 2946 patients (94.2%) and for left atrial appendage occlusion in 1762 of 2496 patients (59.8%). Revascularisation treatments including carotid endarterectomy or stenting were administered to 94 patients (3.4%) and left atrial appendage occlusion was performed in 17 patients (1.0%), both more commonly among patients with competing mechanisms as stroke aetiology (online supplemental table 3).

3-month outcomes and their association with stroke aetiology

Information on 3-month outcomes was available in all but three centres for 2082 patients in total. Here, information on the primary and secondary endpoint was complete in 1906 (91.6%) and 1842 (88.5%) patients, respectively. The primary endpoint (ie, the composite of recurrent ischaemic stroke, ICH or all-cause death) occurred in 516 patients (27.1%) and the secondary endpoint (ie, recurrent ischaemic stroke) in 84 patients (4.6%)

Table 1 Patient characteristics stratified to stroke aetiology

Characteristic	All (N=2946)	N missing	Aetiology of stroke despite anticoagulation			P value
			Competing mechanism (N=713)	Insufficient anticoagulation (N=934)	Cardioembolism despite sufficient anticoagulation (N=1299)	
Demographics						
Age, median (IQR), years	81 (76–86)	0	80 (74–85.1)	82.45 (77–86.9)	81 (75–86)	<0.001
Female sex, N (%)	1404 (47.7)	0	254 (35.6)	533 (57.1)	617 (47.5)	<0.001
Risk factors						
Hypertension, N (%)	2649 (89.9)	0	632 (88.6)	844 (90.4)	1173 (90.3)	0.430
Diabetes, N (%)	871 (29.6)	0	239 (33.5)	264 (28.3)	368 (28.3)	0.029
Dyslipidaemia, N (%)	1768 (60.3)	13	458 (64.6)	569 (61.1)	741 (57.3)	0.005
Renal impairment, N (%)	959 (33.2)	58	229 (32.8)	318 (34.7)	412 (32.4)	0.510
Prior ischaemic stroke, N (%)	984 (33.4)	0	262 (36.7)	290 (31.0)	432 (33.3)	0.052
History of ICH, N (%)	60 (2.0)	0	13 (1.8)	14 (1.5)	33 (2.5)	0.210
Ischaemic heart disease, N (%)	905 (30.7)	0	232 (32.5)	275 (29.4)	398 (30.6)	0.400
Bioprosthetic heart valve, N (%)	151 (5.1)	0	54 (7.6)	34 (3.6)	63 (4.8)	0.001
Current smoking, N (%)	249 (8.8)	103	79 (11.8)	69 (7.6)	101 (8.0)	0.006
Active malignancy, N (%)	236 (8.1)	15	79 (11.1)	63 (6.8)	94 (7.3)	0.002
Prestroke mRS ≥3, N (%)	567 (22.1)	381*	118 (18.5)	198 (24.6)	251 (22.3)	0.021
Ipsilateral stenosis ≥50%, N (%)	452 (15.6)	54	307 (43.4)	65 (7.2)	80 (6.3)	<0.001
Ipsilateral stenosis <50%, N (%)	496 (17.1)	50	100 (14.1)	200 (21.9)	196 (15.3)	<0.001
Medication at the time of stroke onset						
Oral anticoagulant		0				
VKA, N (%)	1272 (43.2)		249 (34.9)	548 (58.7)	475 (36.6)	<0.001
DOAC, N (%)	1674 (56.8)		464 (65.1)	386 (41.3)	824 (63.4)	
DOAC dose		32				
Full, N (%)	925 (56.3)		292 (63.8)	121 (32.0)	512 (63.5)	<0.001
Reduced, N (%)	717 (43.7)		166 (36.2)	257 (68.0)	294 (36.5)	
DOAC dosing frequency		215†				
One time per day, N (%)	848 (58.1)		247 (57.7)	221 (66.4)	380 (54.4)	<0.001
Two times per day, N (%)	611 (41.9)		181 (42.3)	112 (33.6)	318 (45.6)	
DOAC mechanism of action		0				
Thrombin inhibitor, N (%)	152 (9.1)		39 (8.4)	29 (7.5)	84 (10.2)	0.270
Factor Xa inhibitor, N (%)	1522 (90.9)		425 (91.6)	357 (92.5)	740 (89.8)	
Additional antiplatelet, N (%)	363 (12.3)	4	119 (16.7)	112 (12.0)	132 (10.2)	<0.001
Statin, N (%)	1354 (46.4)	30	371 (52.3)	387 (41.7)	596 (46.6)	<0.001
Antihypertensive(s), N (%)	2683 (91.9)	27	652 (91.8)	842 (90.7)	1189 (92.8)	0.210
Stroke details						
NIHSS on admission, median (IQR)	6 (2–14)	33	4 (2–10)	8 (3–16)	6 (2–14)	<0.001
Intravenous thrombolysis, N (%)	351 (11.9)	2	46 (6.5)	211 (22.6)	94 (7.2)	<0.001
Endovascular treatment, N (%)	787 (26.8)	6	110 (15.4)	293 (31.4)	384 (29.7)	<0.001
Embolic infarct pattern, N (%)	2317 (81.7)	111	468 (67.3)	805 (89.6)	1044 (84.1)	<0.001
Large vessel occlusion, N (%)	1345 (46.2)	32	241 (34.2)	513 (55.6)	591 (46.0)	<0.001
Laboratory parameters on admission						
INR, median (IQR)	1.4 (1.1–1.9)	100	1.4 (1.1–2.0)	1.3 (1.1–1.6)	1.4 (1.2–2.2)	<0.001
Low anticoagulant activity, N (%)‡	957 (43.9)	766§	128 (26.9)	633 (82.1)	196 (21.0)	<0.001
Low VKA activity, N (%)	737 (58.2)		96 (39.3)	528 (96.4)	113 (23.8)	<0.001
Low DOAC activity, N (%)	220 (24.1)		32 (13.8)	105 (47.1)	83 (18.1)	<0.001
DOAC plasma level, ng/mL, median (IQR)	83.9 (30–164)	761§	110.1 (54.9–193.6)	34.6 (1.0–93.5)	100.9 (44.3–192.6)	<0.001
Outcome at discharge						
mRS ≥3, N (%)	1543 (63.3)	508¶	393 (62.8)	516 (67.9)	634 (60.3)	0.004
In-hospital death, N (%)	204 (8.4)		35 (5.6)	78 (10.3)	91 (8.7)	0.007

*Not collected in the centre Berlin (reporting period 2013–2015).
†Not collected in the centre Erlangen.
‡Defined in VKA-treated patients as INR <2.0 and in DOAC-treated patients as plasma level <30 ng/mL.
§DOAC plasma level on admission not collected in the centres Berlin, Mainz and George Washington University.
¶Not collected in the centre Mainz.
.DOAC, direct oral anticoagulant; ICH, intracranial haemorrhage; INR, international normalised ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; VKA, vitamin K-antagonist.

Table 2 Details of competing mechanisms

Competing mechanism	All (N=685)*	DOAC (N=441)	VKA (N=244)
Large artery atherosclerosis, N (%)	415 (60.6)	255 (57.8)	160 (65.6)
Small vessel disease, N (%)	180 (26.3)	120 (27.2)	60 (24.6)
Coagulopathy†, N (%)	36 (5.3)	28 (6.3)	8 (3.3)
Peri-interventional stroke‡, N (%)	23 (3.4)	18 (4.1)	5 (2.0)
Endocarditis, N (%)	22 (3.2)	14 (3.2)	8 (3.3)
Other cardio-aortic causes§, N (%)	26 (3.8)	13 (2.9)	13 (5.3)
Cervical artery dissection, N (%)	9 (1.3)	6 (1.4)	3 (1.2)
Vasculitis, N (%)	4 (0.6)	2 (0.5)	2 (0.8)

*Details were available for 685/713 patients (96.1%) who had competing mechanism as stroke aetiology.
†Including suspected cancer-related coagulopathy, hereditary thrombophilia, myeloproliferative disorders and antiphospholipid syndrome.
‡Including percutaneous transluminal coronary angioplasty, transcatheter aortic valve implantation, pulmonary vein isolation, cardioversion and other cardiovascular procedures.
§Including intracardiac thrombus, aortic dissection, patent foramen ovale/atrial septal defect, heart valve fibroelastoma and other structural heart abnormalities.
.DOAC, direct oral anticoagulant; VKA, vitamin K-antagonist.

within 3 months. Detailed information on 3-month outcomes is given in table 3.

Compared with patients with cardioembolism despite sufficient anticoagulation, those with competing mechanisms had higher odds for recurrent ischaemic stroke in unadjusted and adjusted analyses, but not for the composite outcome. The outcomes of patients with stroke due to insufficient anticoagulation did not differ from those with cardioembolism despite sufficient anticoagulation with regard to the primary and secondary endpoints (table 3).

Association of preventive strategies with the primary and secondary endpoint

Figure 3 shows the adjusted estimates for the association of preventive strategies after the index stroke with the primary and secondary endpoints; the detailed unadjusted and adjusted models are given in table 4. Among patients who received oral anticoagulant treatment at hospital discharge and for whom outcome data were available, 1279 (85.4%) patients received DOAC and 219 (14.6%) patients received VKA. Treatment with DOAC versus VKA was associated with lower odds for the primary and secondary endpoints, both in unadjusted and adjusted analyses (table 4). This remained true independent of the type of anticoagulant (DOAC vs VKA) at the time of the index stroke and whether the drug was switched or not after the index stroke in additional models accounting for the anticoagulant type at the time of the index stroke and its interaction with the type of anticoagulant after stroke (composite outcome: $aOR_{DOACvs.VKA}$ (95% CI) 0.50 (0.31 to 0.81), $p_{interaction\ (before*after)}=0.855$; recurrent ischaemic stroke: $aOR_{DOACvs.VKA}$ (95% CI) 0.47 (0.21 to 1.03), $p_{interaction\ (before*after)}=0.429$).

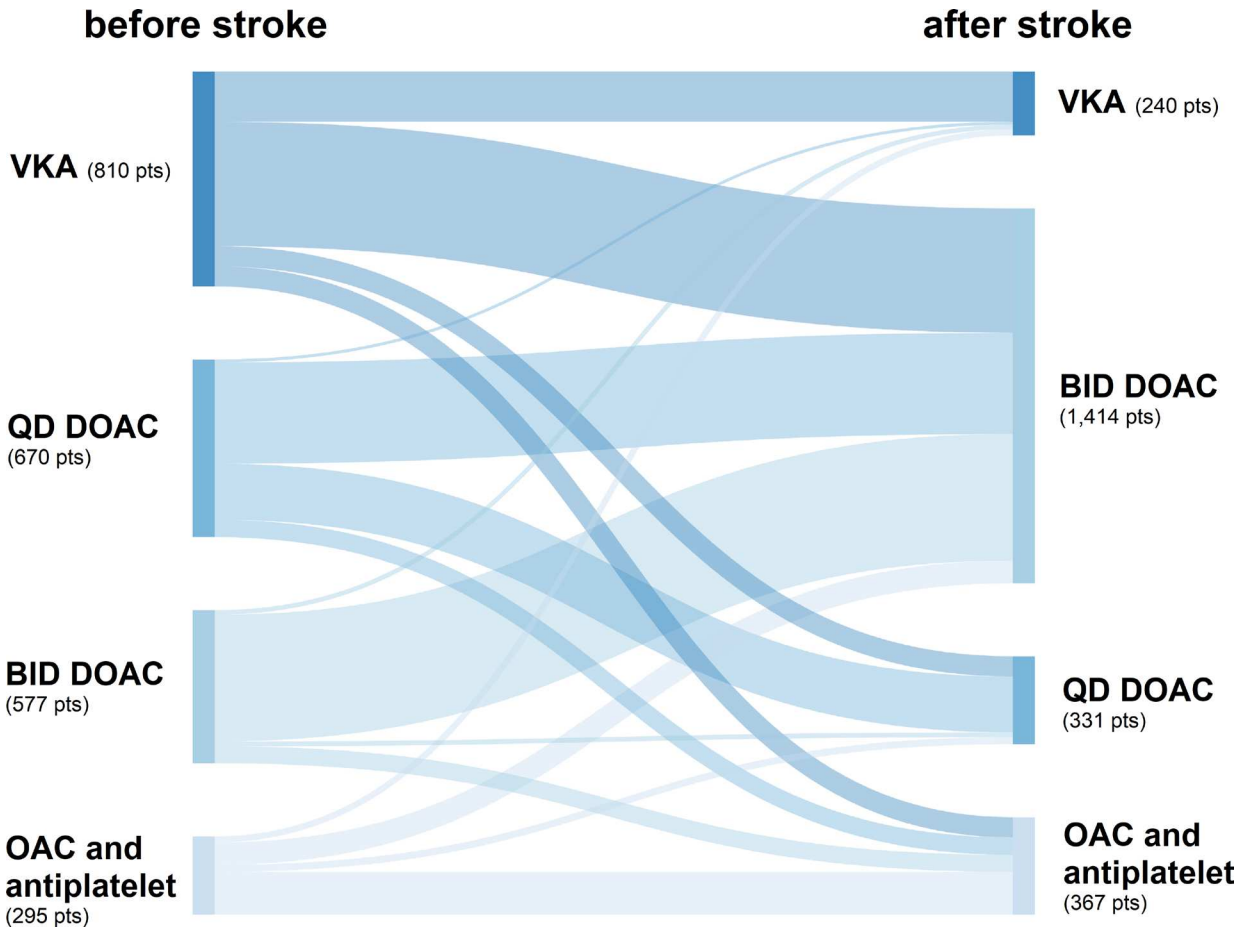


Figure 2 Changes in oral anticoagulant therapy at the time of the index stroke (before) versus at hospital discharge (after stroke). Patients not receiving oral anticoagulants after stroke and patients with missing type and dosing frequency of anticoagulants before or after stroke are not depicted. BID, two times per day; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; QD, one time per day; VKA, vitamin K-antagonist.

Table 3 3-month outcomes according to stroke aetiology

A. all 3-month outcomes stratified to stroke etiology

			Stroke etiology		
3-month outcome	**All (N=2082)***	**N missing**	**Competing mechanism (N=533)**	**Insufficient anticoagulation (N=729)**	**Cardioembolism despite sufficient anticoagulation (N=820)**
composite outcome, N (%)	516 (27.1%)	176	125 (25.4%)	186 (27.8%)	205 (27.5%)
recurrent ischemic stroke, N (%)	84 (4.6%)	240	33 (6.8%)	23 (3.6%)	28 (3.9%)
intracranial hemorrhage, N (%)	15 (0.8%)	238	3 (0.6%)	6 (0.9%)	6 (0.8%)
all-cause death, N (%)	434 (22.8%)	177	93 (18.9%)	164 (24.5%)	177 (23.8%)
mRS ≥3, N (%)	1,081 (56.7%)	177	258 (52.5%)	421 (62.9%)	402 (54.0%)

B. Association of stroke etiology with the primary and secondary endpoint

	Composite outcome						**Recurrent ischemic stroke**					
	unadjusted			**adjusted†**			**unadjusted**			**adjusted†**		
Stroke etiology	**OR [95%CI]**	**p value**	**N events/ total N in model**	**aOR [95%-CI]**	**p value**	**N events/ total N in model**	**OR [95%-CI]**	**p value**	**N events/ total N in model**	**aOR [95%-CI]**	**p value**	**N events/ total N in model**
competing stroke mechanism	0.90 (0.69 to 1.16)	0.4	516/1906	1.18 (0.83 to 1.66)	0.363	473/1773	1.80 (1.07 to 3.02)	0.026	84/1842	1.83 (1.05 to 3.20)	0.034	77/1697
insufficient anticoagulation	1.02 (0.81 to 1.28)	0.891		0.93 (0.68 to 1.27)	0.648		0.91 (0.52 to 1.60)	0.751		0.99 (0.55 to 1.79)	0.968	
cardioembolism despite sufficient anticoagulation	(reference)			(reference)			(reference)			(reference)		

*Adjusted for age, sex, hypertension, diabetes, ischaemic heart disease, dyslipidaemia, renal impairment, prior ischaemic stroke, intracranial haemorrhage, current smoking and active malignancy.
†3-month outcomes not collected in the centres Berlin, Heidelberg and Mainz.
aOR, adjusted OR; mRS, modified Rankin Scale.

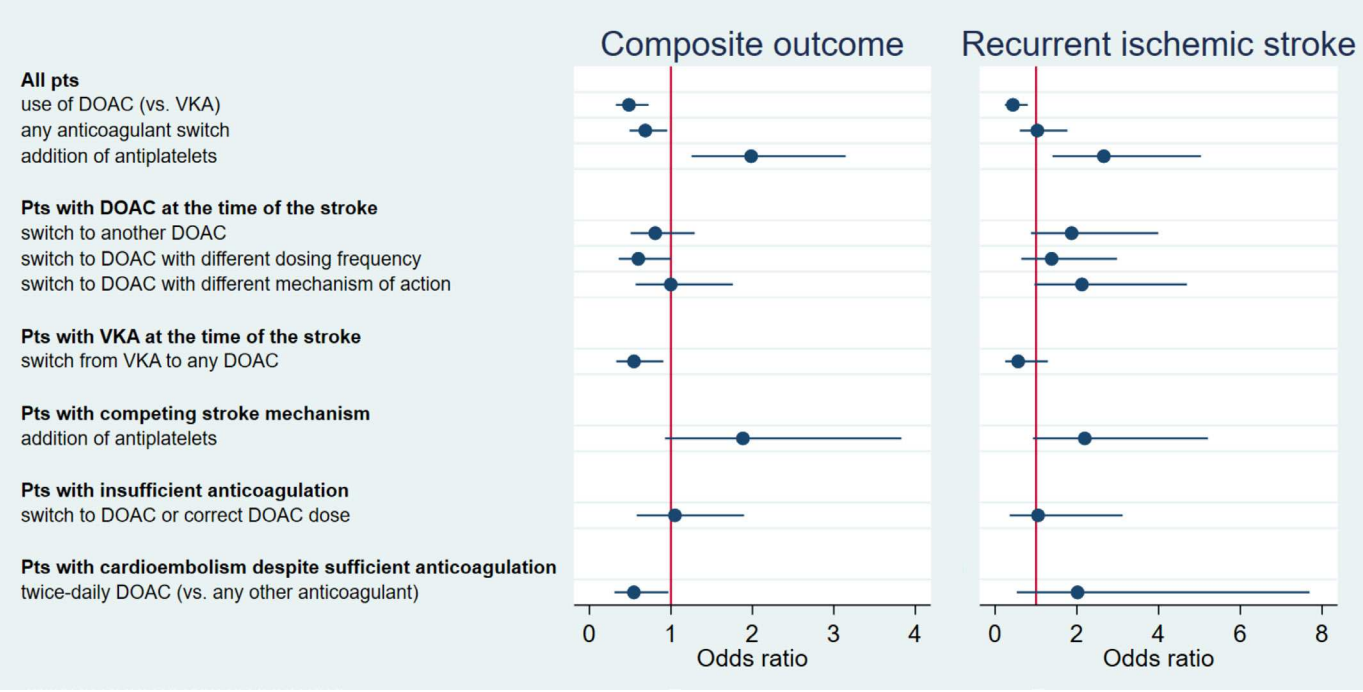


Figure 3 Association of preventive strategies after stroke despite anticoagulation with the primary and secondary endpoints from the adjusted models. DOAC, direct oral anticoagulant; Pts, patients; VKA, vitamin K-antagonist; estimates adjusted for age, sex, hypertension, diabetes, ischaemic heart disease, dyslipidaemia, renal impairment, prior ischaemic stroke, history of intracranial haemorrhage, current smoking, active malignancy, use of statins and use of antihypertensives.

Any anticoagulant switch and switch from VKA to DOAC were associated with lower odds for the composite outcome, but not for recurrent stroke. Among patients with cardioembolism despite sufficient anticoagulation, the use of two times per day DOAC was associated with lower odds for the composite outcome, but not for recurrent stroke. No other strategy was associated with lower odds for any of the endpoints, while the addition of antiplatelets to anticoagulants was even associated with higher odds for the primary and secondary endpoints.

A post-hoc analysis focusing on the combined endpoint of recurrent ischaemic stroke and ICH revealed largely consistent results. Among patients treated with VKA at the time of the index stroke, switching to any DOAC was associated with lower odds for this combined endpoint (online supplemental table 4).

DISCUSSION

This study revealed the following key findings: (1) The aetiology of stroke despite anticoagulation in patients with AF is heterogeneous, with about one out of four cases attributable to competing stroke mechanisms and about one out of three to insufficient anticoagulation, while AF-related cardioembolism despite sufficient anticoagulation was the most common aetiology. (2) Following stroke despite anticoagulation, unfavourable outcomes are common and recurrence rate is high. (3) Anticoagulation with DOAC was linked to better outcomes than VKA after stroke despite anticoagulation, while additional antiplatelet therapy was not associated with better outcomes.

Among patients with a competing mechanism other than AF-related cardioembolism as the most likely stroke aetiology, large artery atherosclerosis and small vessel disease were the most frequent mechanisms. Previous case–control and cohort studies on anticoagulated patients with AF demonstrated that vascular risk factors such as diabetes[17] and dyslipidaemia,[17 18] but also large artery atherosclerosis[17 19] and small vessel disease[20] per se were associated with higher stroke risk. In line with this, a previous single-centre study on patients with AF and stroke despite anticoagulation using the ASCOD classification (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: dissection) indicated that the coexistence of competing stroke mechanisms is common.[6] These findings stress the importance of a thorough work-up in patients with AF and stroke despite anticoagulation in order to uncover non-cardioembolic pathologies that might be less responsive to anticoagulation and warrant additional preventive therapies. Of note, our data indicated that underlying coagulopathies may—less commonly—also account for stroke despite anticoagulation in patients with AF. In these cases, abnormal blood count findings, elevated lactate dehydrogenase, C-reactive protein and particularly D-dimer levels should raise suspicion and prompt further testing including haematological work-up and cancer screening with imaging of the chest and abdomen to uncover potential relevant comorbidities such as myeloproliferative or other neoplasms.[21–23]

Our study further highlights the problem of insufficient anticoagulation as an important aetiology of stroke despite anticoagulation in patients with AF. Prior reports either lacked this information[8–10] or were of small sample size.[18] Our definition of insufficient anticoagulation comprised not only self-reported non-adherence and inappropriately low DOAC dosing, combining findings from previous studies,[18 24 25] but also included the anticoagulant activity measured on admission. For this, DOAC level was available in over 50% of DOAC-treated patients and INR in almost all VKA-treated patients in our data set. While low time in therapeutic range among VKA-treated patients has been previously reported as a contributor to stroke risk in patients with AF,[26] only few data about DOAC levels existed in this context so far.[6 27] Our finding that a relevant proportion of stroke despite anticoagulation is attributable to insufficient anticoagulation

Table 4 Association of preventive strategies after index stroke with the primary and secondary endpoint

		Composite outcome						Recurrent ischaemic stroke					
		Unadjusted			Adjusted*			Unadjusted			Adjusted*		
Patients	Preventive strategy	OR (95%, CI)	P value	N events/ total N in model	aOR (95%, CI)	P value	N events/ total N in model	OR (95%, CI)	P value	N events/ total N in model	aOR (95%, CI)	P value	N events/ total N in model
All patients	Use of DOAC (vs VKA) after stroke	0.49 (0.34 to 0.71)	<0.001	194/1498	0.49 (0.32 to 0.73)	<0.001	179/1394	0.51 (0.29 to 0.90)	0.020	69/1489	0.44 (0.24 to 0.80)	0.007	62/1368
	Any anticoagulant switch	0.71(0.52 to 0.96)	0.024	194/1498	0.69 (0.49 to 0.96)	0.026	179/1394	1.03 (0.62 to 1.69)	0.916	69/1489	1.03 (0.60 to 1.77)	0.909	62/1368
	Addition of antiplatelets	1.34 (0.89 to 2.03)	0.164	251/1564	1.99(1.25 to 3.15)	0.004	225/1448	2.38 (1.31 to 4.32)	0.004	69/1505	2.66 (1.40 to 5.04)	0.003	62/1382
Patients with DOAC at the time of the stroke	Switch to another DOAC	0.83 (0.54 to 1.27)	0.380	94/829	0.81(0.51 to 1.29)	0.372	86/761	1.76 (0.89 to 3.47)	0.105	39/826	1.87 (0.88 to 3.99)	0.105	33/757
	Switch to DOAC with different dosing frequency	0.65 (0.41 to 1.03)	0.069	89/798	0.60 (0.36 to 1.00)	0.051	81/730	1.31 (0.67 to 2.58)	0.436	35/794	1.38 (0.64 to 2.98)	0.410	29/725
	Switch to DOAC with different mechanism of action	0.91 (0.55 to 1.52)	0.722	89/799	1.00 (0.57 to 1.76)	0.994	81/731	2.17 (1.09 to 4.33)	0.027	35/795	2.12 (0.96 to 4.69)	0.063	29/726
Patients with VKA at the time of the stroke	Switch to any DOAC	0.51 (0.33 to 0.79)	0.002	100/669	0.55 (0.33 to 0.91)	0.019	93/621	0.50 (0.24 to 1.06)	0.070	30/663	0.56 (0.25 to 1.29)	0.174	29/611
Patients with competing stroke mechanism	Addition of antiplatelets	1.02 (0.56 to 1.87)	0.936	70/414	1.88 (0.93 to 3.83)	0.080	63/361	1.83 (0.84 to 3.99)	0.128	30/409	2.19 (0.92 to 5.21)	0.075	27/359
Patients with insufficient anticoagulation	Switch to DOAC or correct DOAC dose	0.84 (0.50 to 1.41)	0.501	69/498	1.05 (0.58 to 1.90)	0.874	62/467	0.87 (0.33 to 2.32)	0.778	17/480	1.05 (0.35 to 3.12)	0.930	16/402
Patients with cardioembolism despite sufficient anticoagulation	Two times per day DOAC (vs any other anticoagulant)	0.29 (0.18 to 0.45)	<0.001	96/617	0.55 (0.31 to 0.97)	0.039	86/576	2.20 (0.64 to 7.56)	0.212	21/592	2.02 (0.53 to 7.69)	0.305	18/555

*Adjusted for age, sex, hypertension, diabetes, ischaemic heart disease, dyslipidaemia, renal impairment, prior ischaemic stroke, intracranial haemorrhage, current smoking, active malignancy, use of statins, use of antihypertensives.
.aOR, adjusted OR; DOAC, direct oral anticoagulant; VKA, vitamin K-antagonist.

is important because these strokes may potentially be preventable. Such prevention strategies would entail interventions to increase physicians' awareness about the importance of per-label dosing, and also ways of identifying patients at high risk for non-adherence,[28] a more nuanced evaluation of drug intake behaviour[29] and adherence-enhancing interventions.[30]

Another main finding of our study is that the largest proportion of stroke despite anticoagulation was attributable solely to AF-related cardioembolism without evidence for insufficient anticoagulation or competing mechanisms. The profile of these patients resembled more the profile of patients with insufficient anticoagulation in terms of traditional cardiovascular risk factors and neuroimaging characteristics than the profile of patients with competing stroke mechanisms. This suggests shared stroke mechanisms in these patients, in whom inadequate anticoagulant activity might be ultimately implicated. Besides non-adherence and inappropriate dosing leading to insufficient anticoagulation, emerging evidence suggests that a high inter-individual variation in DOAC pharmacokinetics and pharmacodynamics exists, which may be attributable to genetic factors.[31] More research is needed to evaluate whether tailored pharmacogenomics approaches might mitigate the risk of AF-related cardioembolism despite anticoagulation.

Furthermore, our data show that the burden of unfavourable outcomes within 3 months after stroke despite anticoagulation is high, expanding on findings from previous smaller studies that focused mostly on ischaemic stroke recurrence.[8–10] In our study, over one out of five patients died and over one out of two patients had a mRS ≥3 at 3 months. While ICH occurred infrequently at <1%, 4.6% of patients suffered ischaemic stroke recurrence, clearly identifying this patient group as high risk and stressing the need to define optimal treatment strategies.

Overcoming limitations of previous studies, the large sample size of this pooled analysis enabled us to comprehensively investigate a series of preventive strategies. Regardless of the type of anticoagulant at the time of the index stroke, treatment with DOAC after the index stroke was associated with lower odds for both the primary and secondary endpoints as opposed to treatment with VKA, even after adjustment for several outcome-modifying variables. Although residual confounding by indication—potentially left unaccounted for despite adjustment—may have influenced this finding by introducing bias against VKA, our data are reassuring for the use of DOAC and support the current guidelines for recurrent stroke prevention which recommend DOAC in preference over VKA,[12] providing new evidence for patients with stroke despite anticoagulation.

In contrast to widespread practice, our data do not suggest that any specific switch between DOAC (including switching to different DOAC, or to DOAC with different dosing frequency or mechanism of action) may lead to better outcomes in patients with stroke while on DOAC therapy. Importantly, we found that adding antiplatelets to anticoagulants was not linked to better outcomes, but was instead associated with higher odds for both the primary and secondary endpoints. This finding expands on previous research showing no better or even worse cardiovascular outcomes in anticoagulated patients with AF and add-on antiplatelets,[32 33] indicating that this seems to apply also to patients with stroke despite anticoagulation. It is possible that residual confounding by indication that remained unaccounted for despite extensive adjustment for comorbidities may have influenced this finding, as discussed previously.[33]

The rates of the primary and secondary endpoints in our study were high, although most patients were treated with DOAC after stroke. This indicates that novel approaches to prevent stroke recurrence are needed in these patients. Besides strategies to optimise the currently available drug treatments discussed above, novel pharmacological approaches, such as factor XIa inhibitors,[34] or non-pharmacological interventional treatments, including the percutaneous occlusion of the left atrial appendage,[35] might advance stroke prevention in AF. Notably, surgical occlusion of the left atrial appendage was shown to confer additional protection against stroke when added to anticoagulation in a recent trial.[36]

Strengths and limitations

The strengths of this study include (i) its large sample size; (ii) the detailed patient characterisation with high data completeness, allowing for a large number of analyses with extensive adjustment for confounders and limiting the risk of spurious findings; (iii) the standardised classification of the stroke aetiology incorporating DOAC plasma levels, which were available in the majority of participating centres; and (iv) the homogeneity of the study population, which included only patients with imaging-confirmed stroke and previously known AF as the sole indication for anticoagulation.

We are aware of the following limitations: (i) Data were in part collected retrospectively rather than prospectively ascertained; (ii) Although experienced investigators determined the most likely stroke aetiology, inherent limitations in the determination of competing stroke mechanisms may have led to misclassification of the stroke aetiology, and heterogeneity among the participating centres may have introduced bias in the classification; (iii) Local investigators classified the stroke aetiology as insufficient anticoagulation using a standardised definition, but availability of coagulation measurements (DOAC plasma levels vs INR for VKA) differed. This is a potential source of bias, as it decreases the likelihood of patients on VKA (and increases the likelihood of patients on DOAC) to be classified as 'AF-related cardioembolism despite sufficient anticoagulation' and may have caused more patients on VKA (and less patients on DOAC) to be classified as 'insufficient anticoagulation'; (iv) The observational design of the study allowed only the assessment of association between treatment strategies and outcomes, but not causality thereof. Importantly, despite extensive adjustment for comorbidities, indication bias may still have confounded our findings, potentially contributing to the worse outcomes of patients treated with VKA or add-on antiplatelets after stroke despite anticoagulation. These results should therefore be interpreted cautiously, better serving as hypothesis-generating for potential future randomised trials that are necessary to provide robust evidence; (v) Despite the large sample size, the short follow-up time of 3 months may have limited the number of outcomes, thus disallowing the detection of their association with treatment strategies; (vi) With only 17 patients undergoing left atrial appendage occlusion in our observational data set, no meaningful statistical analyses for this preventive strategy were possible; (vii) The limited number of ICH events disallowed statistical analysis of ICH as a separate outcome. Finally, we did not consider extracranial bleeding in our analyses, as this outcome was not collected during follow-up.

In conclusion, this study on ischaemic stroke despite anticoagulant therapy in patients with AF showed that the aetiology of stroke is heterogeneous and unfavourable outcomes are common. While DOAC treatment after stroke despite anticoagulation was associated with better outcomes than VKA, add-on antiplatelets were linked to worse outcomes; further research into more personalised and novel preventive strategies is warranted.

Author affiliations
[1]Department of Neurology and Stroke Center, University Hospital Basel and University of Basel, Basel, Switzerland
[2]Department of Neurology, Inselspital University Hospital and University of Bern, Bern, Switzerland
[3]Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany
[4]Department of Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany
[5]Department of Neurology, The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA
[6]Department of Neurology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg (FAU), Erlangen, Germany
[7]Department of Neurology, University Hospital Würzburg, Würzburg, Germany
[8]Department of Neurology, The George Washington University, Washington, DC, USA
[9]Service of Neurology, Department of Clinical Neurosciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[10]Stroke Center, Neurology Department, Neurocenter of Southern Switzerland EOC, Lugano, Ticino, Switzerland
[11]Department of Neurology, University Hospital Mainz, Mainz, Germany
[12]Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland
[13]Stroke Center, Klinik Hirslanden Zurich, Zurich, Switzerland
[14]Neurology and Neurorehabilitation, University Department of Geriatric Medicine Felix Platter, University of Basel, Basel, Switzerland
[15]Department of Neuroradiology, Inselspital University Hospital and University of Bern, Bern, Switzerland

Presented at
European Stroke Organisation Conference 2021

Correction notice This article has been corrected since it was first published. The open access licence has been updated to CC BY.

Twitter Thomas R Meinel @TotoMynell and Alexander Salerno @TweetNeuroLine

Acknowledgements We thank all collaborators, listed in Supplementary Table 1, for their contribution to data collection.

Collaborators Stefan T Engelter, Philippe A Lyrer, Leo H Bonati, Christopher Traenka, Alexandros A Polymeris, Annaelle Zietz, Lilian Kriemler, Nils Peters, Gian Marco De Marchis, Sebastian Thilemann, Henrik Gensicke, Lisa Hert, Benjamin Wagner, Fabian Schaub, Louisa Meya, Nikolaos Symeon Avramiotis, Joachim Fladt, Tolga Dittrich, Urs Fisch, Jan F Scheitz, Christian H Nolte, Karl Georg Haeusler, Simon Hellwig, Markus G Klammer, Simon Litmeier, Thomas R Meinel, Urs Fischer, David J Seiffge, Lorenz Grunder, Marcel Arnold, Simon Jung, Jan Gralla, Christoph Stretz, Shadi Yaghi, Xing (Cathy) Dai, Svenja Stoll, Ruihao Wang, Bernd Kallmünzer, Christopher R Leon Guerrero, Iman Moeini-Naghani, Hannah Oehler, Kyra Hoelscher, Peter Ringleb, Jan C Purrucker, Patrik Michel, Davide Strambo, Alexander Salerno, Giovanni Bianco, Carlo W Cereda, Timo Uphaus, Klaus Gröschel, Mira Katan, Susanne Wegener

Contributors DJS acts as guarantor for this study and takes full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. AAP, TRM, JCP, DJS: design and study conception; data acquisition and analysis; first manuscript draft. All authors: data acquisition and analysis; critical manuscript revision.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JFS: grant from Corona-Stiftung, outside the submitted work. CHN: grants from German Ministry of Research and Education, German Center for Neurodegenerative Diseases, German Center for Cardiovascular Research; speaker and/or consultation fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Pfizer, Alexion, Daiichi-Sankyo, Abbott, W.L. Gore and Associates. CS: departmental funding from Massachusetts General Hospital for the Neuro-AF study. SY: steering committee member Neuro-AF study, non-funded; research collaboration Medtronic, non-funded. KGH: speaker's honoraria, consulting fees, lecture honoraria and/or grants from Abbott, Alexion, AMARIN, AstraZeneca, Bayer, Sanofi, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, BMS, Biotronik, Medtronic, Premier Research, Portola, W.L. Gore and Associates, Sun Pharma, Edwards Lifesciences. CC: grants from Swiss Heart Foundation (SHF); other support from iSchemaView and Bayer, outside the submitted work. KG: personal fees and/or non-financial support from Alexion Germany GmbH, Abbott Medical, Bayer Vital GmbH, Boehringer Ingelheim, BMS, Daiichi Sankyo, outside the submitted work. MK: funding from Swiss National Science Foundation (SNSF), SHF; contributions from BRAHMS Thermo Fisher, Roche; advisory fees from Bayer, AstraZeneca, Medtronic. SW: research support from SNSF, Olga Mayenfisch Foundation, University of Zurich CRPP stroke; speaker honoraria from Amgen; travel honoraria from Bayer; research grant from Boehringer Ingelheim. STE: research grants from SNSF, SHF, research support from Daiichi Sankyo; educational grant from Pfizer, compensation from Stago for educational material; travel/speaker honoraria from Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo; advisory board Bayer, Boehringer Ingelheim, BMS. PAR: speaker's honoraria and lecture fees from Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, outside the submitted work. UF: research support from the SNSF (32003B_197009), SHF, Medtronic; consultant for Medtronic, Stryker, CSL Behring; advisory board Portola/Alexion (money paid to institution). BK: consultant fees and travel expenses from Bayer, Daiichi Sankyo, Pfizer, Medtronic, outside the submitted work. JCP: consultation fees and travel expenses from Akcea, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, outside the submitted work. DJS: advisory board for Bayer Switzerland AG and Portola/Alexion, research funding from SNSF, SHF, Bangerter-Rhyner Foundation, Swiss Society of Neurology, Bayer Foundation. The remaining authors declare no conflicts of interest.

Patient consent for publication Not applicable.

Ethics approval The use and pooling of de-identified patient data from all Swiss centres participating in the study and the study itself were approved by the responsible ethics committee (Cantonal Ethics Committee Bern (Kantonale Ethikkommission (KEK) Bern) 2019–01010). The requirement for additional local ethical approval differed among non-Swiss participating centres and was acquired by the local principal investigators if necessary.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Not applicable.

ORCID iDs
Alexandros A Polymeris http://orcid.org/0000-0002-9475-2208
Thomas R Meinel http://orcid.org/0000-0002-0647-9273
Christian H Nolte http://orcid.org/0000-0001-5577-1775
Christoph Stretz http://orcid.org/0000-0003-4125-4077
Shadi Yaghi http://orcid.org/0000-0003-0031-1004
Davide Strambo http://orcid.org/0000-0003-4429-2714
Alexander Salerno http://orcid.org/0000-0001-8494-5527
Timo Uphaus http://orcid.org/0000-0001-5526-0510
Susanne Wegener http://orcid.org/0000-0003-4369-7023
Jan C Purrucker http://orcid.org/0000-0003-2978-4972
David J Seiffge http://orcid.org/0000-0003-3890-3849

REFERENCES

1 Diener H-C, Connolly SJ, Ezekowitz MD, *et al*. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol* 2010;9:1157–63.
2 Hankey GJ, Patel MR, Stevens SR, *et al*. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of rocket AF. *Lancet Neurol* 2012;11:315–22.
3 Easton JD, Lopes RD, Bahit MC, *et al*. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol* 2012;11:503–11.
4 Rost NS, Giugliano RP, Ruff CT, *et al*. Outcomes with edoxaban versus warfarin in patients with previous cerebrovascular events: findings from engage AF-TIMI 48 (effective anticoagulation with factor Xa next generation in atrial Fibrillation-Thrombolysis in myocardial infarction 48). *Stroke* 2016;47:2075–82.
5 Gadsbøll K, Staerk L, Fosbøl EL, *et al*. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. *Eur Heart J* 2017;38:658–906.
6 Purrucker JC, Hölscher K, Kollmer J, *et al*. Etiology of ischemic strokes of patients with atrial fibrillation and therapy with anticoagulants. *J Clin Med* 2020;9. doi:10.3390/jcm9092938. [Epub ahead of print: 11 09 2020].
7 Meinel TR, Branca M, De Marchis GM, *et al*. Prior anticoagulation in patients with ischemic stroke and atrial fibrillation. *Ann Neurol* 2021;89:42–53.
8 Seiffge DJ, De Marchis GM, Koga M, *et al*. Ischemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *Ann Neurol* 2020;87:677–87.

9 Yaghi S, Henninger N, Giles JA, *et al*. Ischaemic stroke on anticoagulation therapy and early recurrence in acute cardioembolic stroke: the IAC study. *J Neurol Neurosurg Psychiatry* 2021;92:1062–7.
10 Tanaka K, Koga M, Lee K-J, *et al*. Atrial fibrillation-associated ischemic stroke patients with prior anticoagulation have higher risk for recurrent stroke. *Stroke* 2020;51:1150–7.
11 Stretz C, Wu TY, Wilson D, *et al*. Ischaemic stroke in anticoagulated patients with atrial fibrillation. *J Neurol Neurosurg Psychiatry* 2021;92:1164–72.
12 Kleindorfer DO, Towfighi A, Chaturvedi S. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American heart Association/American stroke association. *Stroke* 2021;52:e364–467.
13 Adams HP, Bendixen BH, Kappelle LJ, *et al*. Classification of subtype of acute ischemic stroke. definitions for use in a multicenter clinical trial. TOAST. trial of ORG 10172 in acute stroke treatment. *Stroke* 1993;24:35–41.
14 Drouet L, Bal Dit Sollier C, Steiner T, *et al*. Measuring non-vitamin K antagonist oral anticoagulant levels: when is it appropriate and which methods should be used? *Int J Stroke* 2016;11:748–58.
15 Seiffge DJ, Paciaroni M, Wilson D, *et al*. Direct oral anticoagulants versus vitamin K antagonists after recent ischemic stroke in patients with atrial fibrillation. *Ann Neurol* 2019;85:823–34.
16 von Elm E, Altman DG, Egger M, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806–8.
17 Paciaroni M, Agnelli G, Ageno W, *et al*. Risk factors for cerebral ischemic events in patients with atrial fibrillation on warfarin for stroke prevention. *Atherosclerosis* 2010;212:564–6.
18 Paciaroni M, Agnelli G, Caso V, *et al*. Causes and risk factors of cerebral ischemic events in patients with atrial fibrillation treated with non-vitamin K antagonist oral anticoagulants for stroke prevention. *Stroke* 2019;50:2168–74.
19 Lehtola H, Airaksinen KEJ, Hartikainen P, *et al*. Stroke recurrence in patients with atrial fibrillation: concomitant carotid artery stenosis doubles the risk. *Eur J Neurol* 2017;24:719–25.
20 Du H, Wilson D, Ambler G, *et al*. Small vessel disease and ischemic stroke risk during anticoagulation for atrial fibrillation after cerebral ischemia. *Stroke* 2021;52:91–9.
21 Kargiotis O, Psychogios K, Safouris A, *et al*. The role of transcranial Doppler monitoring in patients with Multi-Territory acute embolic strokes: a review. *J Neuroimaging* 2019;29:309–22.
22 Stefanou MI, Richter H, Härtig F, *et al*. Recurrent ischaemic cerebrovascular events as presenting manifestations of myeloproliferative neoplasms. *Eur J Neurol* 2019;26:903–64.
23 Navi BB, Iadecola C. Ischemic stroke in cancer patients: a review of an underappreciated pathology. *Ann Neurol* 2018;83:873–83.
24 Ozaki AF, Choi AS, Le QT, *et al*. Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2020;13:e005969.
25 Steinberg BA, Shrader P, Pieper K, *et al*. Frequency and outcomes of reduced dose non-vitamin K antagonist anticoagulants: results from ORBIT-AF II (the outcomes Registry for better informed treatment of atrial fibrillation II). *J Am Heart Assoc* 2018;7. doi:10.1161/JAHA.117.007633. [Epub ahead of print: 16 02 2018].
26 Lehto M, Niiranen J, Korhonen P, *et al*. Quality of warfarin therapy and risk of stroke, bleeding, and mortality among patients with atrial fibrillation: results from the nationwide FinWAF registry. *Pharmacoepidemiol Drug Saf* 2017;26:657–65.
27 Seiffge DJ, Kägi G, Michel P, *et al*. Rivaroxaban plasma levels in acute ischemic stroke and intracerebral hemorrhage. *Ann Neurol* 2018;83:451–9.
28 Polymeris AA, Traenka C, Hert L, *et al*. Frequency and determinants of adherence to oral anticoagulants in stroke patients with atrial fibrillation in clinical practice. *Eur Neurol* 2016;76:187–93.
29 Albert V, Polymeris AA, Dietrich F, *et al*. Insights into direct oral anticoagulant therapy implementation of stroke survivors with atrial fibrillation in an ambulatory setting. *J Stroke Cerebrovasc Dis* 2021;30:105530.
30 Polymeris AA, Albert V, Hersberger KE, *et al*. Protocol for MAAESTRO: electronic monitoring and improvement of adherence to direct oral anticoagulant Treatment-A randomized crossover study of an educational and Reminder-Based intervention in ischemic stroke patients under polypharmacy. *Front Neurol* 2018;9:1134.
31 Raymond J, Imbert L, Cousin T, *et al*. Pharmacogenetics of direct oral anticoagulants: a systematic review. *J Pers Med* 2021;11. doi:10.3390/jpm11010037. [Epub ahead of print: 11 01 2021].
32 Flaker GC, Gruber M, Connolly SJ, *et al*. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials. *Am Heart J* 2006;152:967–73.
33 Fox KAA, Velentgas P, Camm AJ, *et al*. Outcomes associated with oral anticoagulants plus antiplatelets in patients with newly diagnosed atrial fibrillation. *JAMA Netw Open* 2020;3:e200107.
34 Katsanos AH, Kamel H, Healey JS, *et al*. Stroke prevention in atrial fibrillation: looking forward. *Circulation* 2020;142:2371–88.
35 Osmancik P, Herman D, Neuzil P, *et al*. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol* 2020;75:3122–35.
36 Whitlock RP, Belley-Cote EP, Paparella D, *et al*. Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med* 2021;384:2081–91.

*4.5 Die Einnahme nicht-Vitamin K-abhängiger oraler Antikoagulanzien hat einen positiven Einfluss auf den Schweregrad des ischämischen Schlaganfalls bei Patient*innen mit bekanntem Vorhofflimmern*

Hellwig S., Grittner U., Audebert H. J., Endres M., Haeusler K. G.: Non-vitamin K-dependent oral anticoagulants have a positive impact on ischaemic stroke severity in patients with atrial fibrillation. *Europace*. 2018 Apr 1;20(4):569-574. DOI: 10.1093/europace/eux087.

Ein protektiver Effekt durch eine orale Antikoagulation hinsichtlich des Auftretens von erstmaligen und erneuten Schlaganfällen bei Patient*innen mit Vorhofflimmern ist gut belegt[119, 123]. Dabei bleibt unklar, ob auch sich auch ein Effekt auf den Schlaganfallschweregrad unter bestehender NOAK-Therapie belegen lässt, wie zuvor schon für eine Therapie mit Vitamin K-Antagonisten beschrieben[131, 132]. Tierexperimentelle Daten in einem Schlaganfallmodell der Ratte legen dies zumindest für Rivaroxaban nahe[133].

Ziel der Arbeit war es, die Assoziation einer bestehenden OAK mit a) einem NOAK, b) einem VKA und INR ≥2 bei Aufnahme und c) einem VKA und INR <2 bei Aufnahme mit dem Auftreten eines schweren Schlaganfalls (definiert als ein NIHSS Score ≥11 bei Aufnahme) bzw. einem schlechten funktionellen Status bei Entlassung (definiert als ein mRS Score >2) zu untersuchen[134]. Grundgesamtheit für diese retrospektive, monozentrische Analyse der Jahre 2013-2015 waren 655 Patient*innen mit vorbekanntem Vorhofflimmern und einem CHA_2DS_2-VASc Score ≥2 vor dem Index-Ereignis[134]. Insgesamt nahmen 325 Patient*innen (49,6%) eine OAK ein: 159 Patient*innen (24,3%) ein NOAK, 75 Patient*innen (11,5%) ein VKA mit einer INR ≥2 bei Aufnahme und 91 Patient*innen (13,9%) ein VKA mit einer INR <2 bei Aufnahme[134]. Einen Thrombozytenfunktionshemmer erhielten 206 Patienten (31,5%; mono: 28,4%, dual: 3,1%), 25 Patient*innen (3,8%) eine andere gerinnungshemmende Medikation (Heparin in prophylaktischer Dosierung: 3,1%; Heparin in therapeutischer Dosierung: 0,3%; Fondaparinux: 0,5%) und 99 Patient*innen (15,1%) erhielten keine gerinnungswirksame Medikation bei Aufnahme[134].

Die durchschnittliche Dauer der Krankenhausbehandlung der gesamten Kohorte lag bei 5 Tagen (IQR 4-8 Tage), wobei Patient*innen, die ein NOAK einnahmen, eine sta-

tistisch signifikant kürzere mediane Behandlungsdauer aufwiesen im Vergleich zu Patient*innen mit einem VKA und INR <2 (5 vs. 6 Tage, p=0,012), zu Patient*innen, die mit einem Thrombozytenfunktionshemmer behandelt wurden (5 vs. 6 Tage, p=0,004) und zu Patient*innen ohne gerinnungswirksame Medikation (5 vs. 6 Tage, p=0,003)[134].
Hinsichtlich des primären Endpunktes war sowohl die Einnahme eines NOAK (adjustierte Odds Ratio 0,48 [95% KI 0,27-0,86]) als auch eines VKA mit einer INR ≥2 bei Aufnahme (ad. OR 0,23 [95% KI 0,10-0,53]) mit einer signifikant geringeren Wahrscheinlichkeit verbunden, einen schweren Schlaganfall zu erleiden[134]. Keine signifikante Assoziation zeigte sich für die Einnahme eines VKA mit einer INR <2 bei Aufnahme (ad. OR 0,62 [95% KI 0,33-1,16])[134].
Hinsichtlich eines schlechten funktionellen Outcomes bei Entlassung war ebenfalls sowohl die Einnahme eines NOAK (adjustierte Odds Ratio 0,47 [95% KI 0,27-0,84]) als auch eines VKA mit einer INR ≥2 bei Aufnahme (ad. OR 0,33 [95% KI 0,17-0,65]) mit einer signifikant geringeren Wahrscheinlichkeit verbunden, zum Zeitpunkt der Entlassung funktionell abhängig zu sein (mRS >2)[134]. Keine signifikante Assoziation zeigte sich für die Einnahme eines VKA mit einer INR <2 bei Aufnahme (ad. OR 0,61 [95% KI 0,32-1,16])[134].
Die hier vorgelegten Daten belegen erneut, dass auch nach Markteinführung der NOAKs eine relevante Unterversorgung von Patient*innen mit bekanntem Vorhofflimmern und einer Indikation zur oralen Antikoagulation besteht[134]. Gleichzeitig konnte gezeigt werden, dass eine bestehende Therapie mit einem NOAK die Wahrscheinlichkeit, einen schweren Schlaganfall zu erleiden oder bei Entlassung aus dem Krankenhaus funktionell abhängig zu sein, in vergleichbarem Maß reduziert wie eine wirksame OAK mit einem VKA (INR ≥2)[134].

ESC European Society of Cardiology

Europace (2018) **20**, 569–574
doi:10.1093/europace/eux087

CLINICAL RESEARCH
Atrial fibrillation

Non-vitamin K-dependent oral anticoagulants have a positive impact on ischaemic stroke severity in patients with atrial fibrillation

Simon Hellwig[1,2], Ulrike Grittner[1,3], Heinrich Audebert[1,2], Matthias Endres[1,2,4,5,6], and Karl Georg Haeusler[1,2]*

[1]Center for Stroke Research Berlin, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; [2]Department of Neurology, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; [3]Department of Biostatistics and Clinical Epidemiology, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; [4]Berlin Institute of Health, Kapelle-Ufer 2, 10117 Berlin, Germany; [5]German Center for Neurodegenerative Diseases (DZNE), Partner Site Berlin, Germany; and [6]German Center for Cardiovascular Diseases (DZHK), Partner Site Berlin, Germany

Received 23 December 2016; editorial decision 8 March 2017; accepted 8 March 2017; online publish-ahead-of-print 27 April 2017

Aims Several studies showed reduced stroke severity in patients with atrial fibrillation (AF) if the international normalized ratio (INR) was ≥2 at stroke onset. There are no respective data for non-vitamin K-dependent oral anticoagulants (NOACs). The aim of this study was to compare the impact of NOAC or phenprocoumon intake on stroke severity.

Methods and results In this single-centre observational study, 3669 patients with acute ischaemic stroke were retrospectively analysed regarding AF status and medication immediately before admission. Using multivariable regression, we analysed the association of pre-admission anticoagulation with severe stroke (National Institutes of Health Stroke Scale score ≥ 11) on admission and poor outcome at discharge (modified Rankin scale score > 2). Before the index stroke, 655 patients had known AF and a CHA_2DS_2-VASc score ≥ 2. While 325 (49.6%) patients were anticoagulated, 159 (24.3%) were prescribed a NOAC and 75 (11.5%) phenprocoumon patients had an INR ≥ 2 on admission. Compared with AF patients without medical stroke prevention, an INR ≥ 2 [OR 0.23 (95% CI 0.10–0.53)] or NOAC intake [OR 0.48 (95% CI 0.27–0.86)] were associated with a lower probability of severe stroke after adjustment for confounders, while an INR < 2 [OR 0.62 (95% CI 0.33–1.16)] was not. Adjusted odds ratios for poor functional outcome at hospital discharge were 0.47 (95% CI 0.27–0.84) for NOAC patients, 0.33 (95% CI 0.17–0.65) for INR ≥ 2 and 0.61 (95% CI 0.32–1.16) for INR < 2.

Conclusion NOAC intake before stroke did reduce the probability of severe stroke on hospital admission and poor functional outcome at hospital discharge as similarly demonstrated for phenprocoumon patients with an INR ≥ 2 on admission.

Keywords Atrial fibrillation • Ischaemic stroke • Morbidity • NOAC (Non-vitamin K oral anticoagulants) • Stroke aetiology

Introduction

Non-valvular atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide. AF increases the individual stroke risk about four- to five-fold, and at least 15% of all ischaemic strokes are caused by AF. Oral anticoagulation significantly reduces the risk of (recurrent) stroke in patients with AF, and relevant guidelines strongly recommend oral anticoagulation in AF patients with at least one additional risk factor for stroke.[1–3] Four phase III studies have demonstrated that non-vitamin K-dependent oral anticoagulants (NOACs) are at least equally effective to the vitamin K antagonist (VKA) warfarin with a median time in therapeutic range between 58

* Corresponding author. Tel: +49 30 450560663; fax: +49 30 450560979. *E-mail address*: georg.haeusler@charite.de

What's new?

- Despite the availability of non-vitamin K-dependent oral anticoagulants, there is a significant under-treatment in primary and secondary stroke prevention in patients with known atrial fibrillation and a CHA_2DS_2-VASc score ≥ 2 presenting with acute ischaemic stroke in a German university hospital.
- The intake of a non-vitamin K-dependent oral anticoagulant before stroke onset reduces the probability of severe stroke on hospital admission as well as poor functional outcome at hospital discharge, as similarly demonstrated for phenprocoumon treated patients with an international normalized ratio ≥ 2 on hospital admission.

and 68% in these trials.[4] However, the use of oral anticoagulants is restricted by contraindications such as renal failure or previous bleeds. In addition, the feared risk of bleeding leads to non-compliance with guideline recommendations.[5,6] Consecutively, only a subset of all acute ischaemic stroke patients with known AF before stroke is (sufficiently) anticoagulated when stroke occurs, as demonstrated in multiple observational studies.[7,8] Insufficient long-term persistence to VKAs or NOACs is another major problem in stroke patients.[9,10] While platelet inhibitors are a cornerstone of secondary stroke prevention in non-AF patients, they are no longer recommended by current guidelines for stroke prevention in AF patients.[1–3]

Stroke in patients with AF is more often disabling and associated with increased morbidity and mortality compared with stroke in patients without AF.[11] In addition to the reduction of stroke risk, the intake of VKA reduces stroke severity and improves long-term outcome if the international normalized ratio (INR) is within therapeutic range at stroke onset.[8,12] One could argue that there might be a similar effect of pre-admission NOAC intake on stroke-related morbidity and mortality but there is—besides a retrospective analysis including nine patients with NOAC intake before ischaemic stroke—no published analysis so far.[13,14] Interestingly, recently published experimental data showed a beneficial effect of rivaroxaban pretreatment on stroke severity in rats.[15] Consequently, we analysed this assumption in a cohort of stroke patients consecutively admitted at our department within 3 years.

Methods

Study design

This single-centre observational study was conducted at the Department of Neurology, Charité - Universitätsmedizin Berlin and approved by the local Ethics Committee (EA2/022/15). Medical records of 3669 patients consecutively admitted to the stroke unit of the Department of Neurology, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin, between 1 January 2013 and 31 December 2015 were retrospectively analysed. Patients suffering an ischaemic stroke or transient ischaemic attack (TIA) (labeled as 'index stroke') were identified by using relevant ICD-10 discharge diagnoses (I63.x; G45.x). All patients with ischaemic stroke or TIA and known AF before admission for their index stroke were included in the primary analysis. We did not include patients suffering from haemorrhagic stroke. The following information was assessed from medical records: demographic details, cardiovascular risk factors (e.g. atrial fibrillation, congestive heart failure, hypertension, diabetes mellitus, previous stroke or TIA, intracerebral haemorrhage or non-stroke vascular events), potential contraindications for oral anticoagulation (such as malignant tumours or epilepsy), CHA_2DS_2-VASc score before the index stroke, antithrombotic medication before admission, INR on admission, thrombin time, activated partial thromboplastin time (aPTT), iv thrombolysis or mechanical intervention, diagnostic results during the hospital stay (echocardiography, ultrasound of the brain-supplying arteries, brain imaging), stroke severity on admission according to the National Institutes of Health Stroke Scale (NIHSS) score as well as functional outcome at hospital discharge according to the modified Rankin Scale (mRS).[16–18] Severe stroke was defined as NIHSS ≥ 11 points.[8] Poor functional outcome was defined as mRS > 2 at hospital discharge.

Statistical analysis

The results are reported as frequencies and percentages for categorical variables. In the case of continuous variables, mean and standard deviation (SD) are reported for sufficiently normally distributed data ($|\text{skewness}| < 1$) or median and inter-quartile range (IQR) for quantitatively skewed variables. Differences regarding baseline parameters between patients with different pre-stroke antithrombotic medication were tested using either χ^2, Fisher's exact test, or Student's *t*-test for independent samples (*Table 1*). First, we tested overall differences between six cohorts using χ^2 test or one-way ANOVA (for age). In case of $P \leq 0.1$, we performed post-hoc exploratory tests for the NOAC cohort vs. other cohorts. A two sided significance-level of $\alpha = 0.05$ was applied. Severe stroke (NIHSS ≥ 11) and poor functional outcome (mRS > 2) were the main outcomes. *P*-values testing different characteristics with regard to these outcomes were age-adjusted using binary logistic regression models (Supplementary material online, *Table S2*). In multiple logistic regression, associations between antithrombotic treatment and stroke severity at admission and functional outcome at discharge were tested after adjustment for age, sex, diabetes mellitus, previous stroke, coronary artery disease, congestive heart failure, peripheral artery disease, renal insufficiency, epilepsy, and malignant tumour (*Table 2*). In addition, endovascular treatment was added to the model regarding the functional outcome at hospital discharge. Stroke severity and iv thrombolysis however are affected by oral anticoagulation at stroke onset and have an impact on functional outcome. Instead of being mere confounders, they are factors on the 'causal pathway' from anticoagulation treatment to functional outcome at discharge and cannot simply be adjusted for in multiple regression analysis.[19] Therefore, we performed a structural equation analysis to evaluate the causal relationship between anticoagulatory treatment, NIHSS score on admission as well as iv thrombolysis and functional outcome at hospital discharge (Supplementary material online, *Figure S1*). Odds ratios (OR) with 95% confidence intervals (CI) are reported. Despite of comparably small groups, we performed a sensitivity analysis comparing NOAC patients with or without altered routine anticoagulation tests to those patients without medical stroke prevention. Data were analysed using SPSS statistics 23 and SPSS AMOS 24 (IBM Corp., Armonk, NY, USA).

Results

Out of 3669 patients suffering from acute ischaemic stroke or TIA, 671 (18.3%) had a medical history of AF before index stroke. Sixteen patients had a CHA_2DS_2-VASc score < 2 and were not included in further analysis because anticoagulation was not (definitively)

Table 1 Baseline characteristics in 655 patients with known AF, acute ischaemic stroke or TIA and a CHA_2DS_2-VASc score ≥ 2

	$\sum$ ($n = 655$)	NOAC ($n = 159$)	VKA INR$\geq$2 ($n = 75$)	VKA INR<2 ($n = 91$)	Platelet inhibitor ($n = 206$)	No med. ($n = 99$)	Others ($n = 25$)	P (over all)	P NOAC vs. INR$\geq$2	P NOAC vs. INR<2	P NOAC vs. Platelet inhibitor	P NOAC vs. No med.
Age in years; mean (SD)	80 (9)	79 (8)	79 (7)	80 (7)	82 (9)	80 (11)	80 (7)	0.011	0.438	0.752	0.003	0.664
Female sex; *n* (%)	363 (55.4)	74 (46.5)	35 (46.7)	60 (65.9)	122 (59.2)	59 (59.6)	13 (52.0)	0.019	0.986	0.003	0.016	0.041
Previous stroke/TIA; *n* (%)	250 (38.2)	80 (50.3)	23 (30.7)	32 (35.4)	73 (35.4)	30 (30.3)	12 (48.0)	0.006	0.005	0.020	0.004	0.002
Diabetes; *n* (%)	188 (28.7)	56 (35.2)	22 (29.3)	27 (29.7)	58 (28.2)	21 (21.2)	4 (16.0)	0.152				
Hypertension[a]; *n* (%)	599 (91.6)	145 (91.2)	72 (96.0)	85 (93.4)	191 (92.7)	84 (85.7)	22 (88.0)	0.188				
Heart failure; *n* (%)	139 (21.2)	23 (14.5)	9 (12.0)	20 (22.0)	61 (29.6)	22 (22.2)	4 (16.0)	0.004	0.608	0.130	0.001	0.110
Coronary artery disease; *n* (%)	166 (25.3)	48 (30.2)	17 (22.7)	21 (23.1)	58 (28.2)	15 (15.2)	7 (28.0)	0.113				
Peripheral artery disease; *n* (%)	53 (8.1)	15 (9.4)	5 (6.7)	8 (8.8)	17 (8.3)	6 (6.1)	2 (8.0)	0.944				
Renal insufficiency; *n* (%)	150 (22.9)	37 (23.3)	10 (13.3)	15 (16.5)	56 (27.2)	25 (25.3)	7 (28.0)	0.116				
Malignant tumour; *n* (%)	94 (14.4)	22 (13.8)	9 (12.0)	14 (15.4)	32 (15.5)	8 (8.1)	9 (36.0)	0.020	0.699	0.737	0.651	0.161
Epilepsy; *n* (%)	24 (3.7)	8 (5.0)	2 (2.7)	5 (5.5)	6 (2.9)	2 (2.0)	1 (4.0)	0.664				
Thrombolysis; *n* (%)	112 (17.1)	6 (3.8)[b]	–	16 (17.6)	52 (25.2)	36 (36.4)	2 (8.0)	<0.001	0.181	<0.001	<0.001	<0.001
Endovascular treatment; *n* (%)	31 (4.7)	6 (3.8)	1 (1.3)	8 (8.8)	12 (5.8)	3 (3.0)	1 (4.0)	0.262				
Admission NIHSS $\geq$ 11; *n* (%)	190 (29.0)	35 (22.0)	9 (12.0)	27 (29.7)	74 (35.9)	40 (40.4)	5 (20.0)	<0.001	0.067	0.177	0.004	0.002
Admission mRS > 2; *n* (%)	409 (62.4)	86 (54.1)	33 (44.0)	64 (70.3)	142 (68.9)	72 (72.7)	12 (48.0)	<0.001	0.150	0.012	0.004	0.003
In-hospital stay in days; median (IQR)	5 (4–8)	5 (4–7)	5 (4–7)	6 (4–8)	6 (4–7)	6 (4–8)	6 (5–10)	0.106				
In-hospital mortality; *n* (%)	43 (6.6)	7 (4.4)	3 (4.0)	5 (5.5)	17 (8.3)	9 (9.1)	2 (8.0)	0.487				

Cohorts are separated according to medical stroke prevention before the index stroke.
Overall test: χ^2 or Fisher's exact test/one way ANOVA for age, Kruskal–Wallis-Test for hospital stay.
[a]Missing values: $n = 3$.
[b]Individualized treatment decision after obtaining informed consent in four patients with normal PTT and INR. NOAC intake <24 h was not known at the time of treatment in two patients.

Table 2 Adjusted[a] odds ratios and 95% CI for antithrombotic medication taken prior to admission with regard to severe stroke on hospital admission (NIHSS ≥ 11) and poor functional outcome at hospital discharge (mRS > 2) in 655 AF patients with acute ischaemic stroke or TIA and a CHA_2DS_2-VASc score ≥2 before admission

	NIHSS ≥ 11 On admission	mRS > 2 At discharge
Nagelkerke R^2	0.14	0.23
No antithrombotic medication	1 [reference]	1 [reference]
Platelet inhibitors	0.80 (0.47–1.34)	0.82 (0.47–1.42)
Heparin, low-dose	0.41 (0.12–1.41)	0.39 (0.13–1.18)
VKA		
INR < 2	0.62 (0.33–1.16)	0.61 (0.32–1.16)
INR ≥ 2	0.23 (0.10–0.53)	0.33 (0.17–0.65)
NOAC	0.48 (0.27–0.86)	0.47 (0.27–0.84)
Other anticoagulants[b]	0.59 (0.06–5.76)	0.66 (0.10–4.52)

[a]Multiple logistic regression analysis was adjusted for: age, sex, diabetes mellitus, previous stroke, coronary artery disease, congestive heart failure, peripheral artery disease, renal insufficiency, epilepsy, malignant tumour, and additionally for endovascular treatment in the model for mRS > 2 at discharge (Supplementary material online, *Table S2*).
[b]Including fondaparinux ($n = 3$) or therapeutic dose heparin iv ($n = 2$).

indicated before the index stroke. Baseline characteristics of 655 patients with known AF and a CHA_2DS_2-VASc score ≥ 2 before the index stroke are depicted in *Table 1*. In total, 530 (80.9%) out of 655 patients (mean age 80 years; 55.4% female) suffered an ischaemic stroke and 125 (19.1%) patients had a TIA. Median NIHSS score was 5 (IQR 1–12) on admission, and 6 (IQR 3–14) after excluding TIA patients. Forty-three (6.6%) of 655 stroke patients with AF died during the in-hospital stay [median 5 days (IQR 4–8)].

Medical stroke prevention before admission in patients with known AF before index stroke

From all 655 patients with known AF and a CHA_2DS_2-VASc score ≥ 2 before the index stroke, 325 (49.6%) received oral anticoagulation before admission [VKA phenprocoumon $n = 166$ (25.3%), $n = 75$ (11.5%) with INR ≥ 2 on admission; NOAC $n = 159$ (24.3%)]. Forty-seven (14.5%) of 325 anticoagulated patients also took a platelet inhibitor (+VKA $n = 19$; +NOAC $n = 28$). Three patients received fondaparinux and two patients therapeutic-dose intravenous heparin. Furthermore, 206 (31.5%) out of 655 patients received a platelet inhibitor (dual therapy $n = 20$). While 20 (3.1%) patients had low-dose heparin, 99 (15.1%) patients had no antithrombotic medication (*Table 1*). Comparing patient cohorts receiving a NOAC, VKA, platelet inhibitor or no medical stroke prevention to each other, significant differences were observed regarding age, gender, previous stroke as well as co-existing heart failure, thrombolysis on admission, NIHSS as well as mRS on admission (*Table 1*). A reduced dose of rivaroxaban as well as apixaban was prescribed in 61% and 49% of the respective patient cohort (Supplementary material online, *Table S1*).

Impact of oral anticoagulants on stroke severity on admission

On hospital admission, 190 (29.0%) out of 655 patients with known AF and a CHA_2DS_2-VASc score ≥ 2 before the index stroke had a NIHSS ≥ 11 indicating severe stroke. In bivariate analysis, old age, female sex, co-existing heart failure, coronary artery disease, and malignant tumour were associated with a higher probability of severe stroke on admission (Supplementary material online, *Table S2*). After adjustment for confounders, VKA intake resulting in an INR ≥ 2 on admission [OR 0.23 (95% CI 0.10–0.53)] as well as NOAC intake [OR 0.48 (95% CI 0.27–0.86)] were inversely associated with severe stroke on admission when compared with patients without antithrombotic medication at stroke onset (*Table 2*).

Impact of oral anticoagulants on functional outcome at hospital discharge

Comparing patient cohorts receiving different therapeutic regimens before admission, significant differences were observed regarding the rate of intravenous thrombolysis and NIHSS score on admission but not regarding the duration of the in-hospital stay (*Table 1*). At discharge, 342 (52.2%) out of 655 patients with known AF and a CHA_2DS_2-VASc score ≥ 2 before the index stroke had a mRS > 2 indicating poor functional outcome. In bivariate analysis, old age, co-existing diabetes, heart failure, and higher NIHSS score on admission were associated with poor functional outcome (Supplementary material online, *Table S2*). In multivariable analysis, VKA intake resulting in an INR ≥ 2 on admission [OR 0.33 (95% CI 0.17–0.64)] as well as NOAC intake [OR 0.49 (95% CI 0.28–0.86)] were inversely associated with poor functional outcome at hospital discharge when compared with patients without antithrombotic medication at stroke onset (*Table 2*).

Adherence regarding NOAC intake before admission

According to documented patient statements, NOAC intake was not discontinued immediately before admission in 159 AF patients. Patient-reported daily dose and the results of routine coagulation tests (INR, aPTT, or thrombin time) on admission are depicted in Supplementary material online, *Table S2*. Overall, 90 (56.6%) NOAC patients had altered routine coagulation tests indicating an anticoagulatory effect at stroke onset. Compared with patients without antithrombotic medication, NOAC patients with altered coagulation tests had a significantly lower rate of severe stroke (NIHSS ≥ 11) on admission (18.9% vs. 40.4%; OR 0.41 (95% CI 0.20–0.83) adjusted for age, sex, coronary artery disease, malignant tumour, peripheral artery disease, heart failure), while NOAC patients without altered coagulation tests had a non-significant lower rate of severe stroke (26.1%; adjusted OR 0.62 (95% CI 0.31–1.25).

Discussion

One of the major findings of this study is that only half of the patients with known AF and a CHA_2DS_2-VASc score ≥ 2 before stroke were

taking oral anticoagulation despite given indication. This finding underlines the present shortcomings in primary and secondary stroke prevention in AF patients and furthermore demonstrates subsequent complications. However, we analysed only AF patients with acute ischaemic stroke; therefore, we cannot draw conclusions on the quality of stroke prevention in AF patients in the general population.

Compared with AF patients without antithrombotic medication before stroke (*Table 2*), self-reported NOAC intake pre-admission lowered the probability of severe ischaemic stroke on hospital admission, as similarly observed for phenprocoumon patients with an INR ≥ 2 on admission. In accordance with previous publications, there was no significant effect of VKA intake with an INR < 2 or the intake of platelet inhibitors on stroke severity on admission.[8,20] NOAC intake also lowered the probability of worse functional outcome at hospital discharge (*Table 2*), despite of a higher rate of previous stroke and a lower rate of thrombolysis in patients taking a NOAC when compared with AF patients without antithrombotic medication (*Table 1*). A similar effect on stroke severity at hospital discharge was observed in VKA patients with an INR ≥ 2 on admission (*Table 2*). Adjusted for various confounders, the multiple relations of stroke severity on admission, thrombolysis as well as endovascular treatment on functional outcome at hospital discharge are depicted in the Supplementary material online, *Figure S1*. As demonstrated, the NIHSS score on admission significantly impacts on the mRS score at discharge. Moreover, intake of phenprocoumon or NOAC was inversely related to stroke severity on admission, as indicated by the negative estimates.

NOACs are effective in primary and secondary stroke prevention without need for routine coagulation monitoring.[4] However, a non-temporal correlation was reported between (single) plasma concentrations of dabigatran and edoxaban and cerebrovascular events during follow-up of the respective phase III clinical trials.[21,22] Just recently, a single-centre case series including 19 patients admitted for acute stroke while taking dabigatran demonstrated that plasma concentrations of dabigatran were higher in four patients with intracerebral haemorrhage compared with 15 patients with ischaemic stroke.[23] Because NOAC plasma concentrations on admission or measurements of calibrated anti-Xa activity were not available in our stroke cohort, coagulation tests on hospital admission were analysed (as similarly reported in a German registry).[24] Despite uncertain sensitivity and specificity, these tests provide useful information to assess a residual anticoagulant effect of NOACs—in patients with abnormal results—indicating a recent intake.[25] Of note, NOAC patients with elevated routine coagulation tests had a significantly lower probability of severe stroke when compared to patients without antithrombotic medication on admission. This was not the case for NOAC patients without elevated routine coagulation tests. With regard to the published phase III randomized trials, the reduced dose of rivaroxaban as well as apixaban was more often prescribed in our stroke cohort (Supplementary material online, *Table S1*).

Limitations of the present study

Beside the reported strengths, our study has weaknesses that mitigate the validity of its results. First, this is a retrospective single-centre analysis and we cannot exclude that undocumented factors have influenced the physicians' choice of medical stroke prevention in an individual patient pre-stroke. Second, there are limitations in terms of statistical power to the various comparisons due to comparably small patient subgroups. Third, there were significant differences between patient subgroups regarding baseline characteristics and acute stroke treatment. Despite statistical adjustment, residual bias may still be present. Fourth, we were unable to assess the adherence to NOAC intake and the actual anticoagulatory effect at the time of stroke onset in more detail because specific tests like calibrated anti-Xa activity are not part of clinical routine so far.[24] We addressed this issue by comparing NOAC patients with and without altered routine coagulation tests to those patients without medical stroke prevention. Fifth, due to retrospective data assessment we were unable to assess the impact of pre-hospital time in therapeutic range (TTR) on stroke severity. Since the half-life of phenprocoumon is much longer compared to warfarin, we believe that INR on admission is sufficient to assess the quality of anticoagulation in the last week before stroke.[26] Finally, we missed an additional follow-up 3 months after stroke that would have strengthened our results. Therefore, our findings have to be validated in larger cohorts of stroke patients with known AF as suggested previously.[13]

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

We thank Julia Herde (CSB) for critically reviewing the manuscript.

Conflict of interest: S.H. and U.G. report no conflicts of interest. M.E. reports fees and grant support by Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Ever, Glaxo Smith Kline, MSD, Novartis, and Pfizer. H.J.A. reports fees and grant support by Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Ever Neuropharma, Lundbeck, Pfizer, ReNeuron, and Roche Diagnostics. K.G.H. reports lecture fees and study grants by Bayer Healthcare, a study grant by Sanofi-Aventis as well as lecture fees from Sanofi-Aventis, Pfizer, Bristol-Myers-Squibb and Boehringer Ingelheim.

Funding

The project has received funding from the German Federal Ministry of Education and Research via the grant Center for Stroke Research Berlin (01 EO 0801). M.E. received support from the Volkswagen-Stiftung, Deutsche Forschungsgemeinschaft, and the Federal Ministry of Education and Research.

References

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr. *et al.* 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;**64**:e1–76.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
3. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): S3-Leitlinie Sekundärprophylaxe ischämischer Schlaganfall und transitorische ischämische Attacke. http://www.awmf.org/uploads/tx_szleitlinien/030-133l_S3_Sekunärprophylaxe_ischämischer_Schlaganfall_2015-02.pdf (19 December 2016, date last accessed).
4. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD *et al.* Comparison of the efficacy and safety of new oral anticoagulants with

warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–62.
5. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med* 2010;**123**:638–45.
6. Haeusler KG, Gerth A, Limbourg T, Tebbe U, Oeff M, Wegscheider K *et al*. Use of vitamin K antagonists for secondary stroke prevention depends on the treating healthcare provider in Germany—results from the German AFNET registry. *BMC Neurol* 2015;**15**:129.
7. Glader EL, Stegmayr B, Norrving B, Terent A, Hulter-Asberg K, Wester PO *et al*. Large variations in the use of oral anticoagulants in stroke patients with atrial fibrillation: a Swedish national perspective. *J Intern Med* 2004;**255**:22–32.
8. Haeusler KG, Konieczny M, Endres M, Villringer A, Heuschmann PU. Impact of anticoagulation before stroke on stroke severity and long-term survival. *Int J Stroke* 2012;**7**:544–50.
9. Glader EL, Sjolander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. *Stroke* 2010;**41**:397–401.
10. Martinez C, Katholing A, Wallenhorst C, Freedman SB. Therapy persistence in newly diagnosed non-valvular atrial fibrillation treated with warfarin or NOAC. A cohort study. *Thromb Haemost* 2016;**115**:31–9.
11. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R *et al*. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 2005;**36**:1115–9.
12. Hannon N, Arsava EM, Audebert HJ, Ay H, Crowe M, Ni Chroinin D *et al*. Antithrombotic treatment at onset of stroke with atrial fibrillation, functional outcome, and fatality: a systematic review and meta-analysis. *Int J Stroke* 2015;**10**:808–14.
13. Stollberger C, Finsterer J. Presentation, therapy and outcome of patients with ischemic stroke under new oral anticoagulants. *Neurol Neurochir Pol* 2014;**48**:136–40.
14. Tomita H, Hagii J, Metoki N, Saito S, Shiroto H, Hitomi H *et al*. Severity and functional outcome of patients with cardioembolic stroke occurring during non-vitamin K antagonist oral anticoagulant treatment. *J Stroke Cerebrovasc Dis* 2015;**24**:1430–7.
15. Dittmeier M, Kraft P, Schuhmann MK, Fluri F, Kleinschnitz C. Pretreatment with rivaroxaban attenuates stroke severity in rats by a dual antithrombotic and anti-inflammatory mechanism. *Thromb Haemost* 2016;**115**:835–43.
16. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH *et al*. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. *Europace* 2012;**14**:1385–413.
17. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J *et al*. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989;**20**:864–70.
18. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;**19**:604–7.
19. McNamee R. Confounding and confounders. *Occup Environ Med* 2003;**60**:227–34.
20. Ottosen TP, Svendsen ML, Hansen ML, Brandes A, Andersen G, Husted SE *et al*. Preadmission oral anticoagulant therapy and clinical outcome in patients hospitalised with acute stroke and atrial fibrillation. *Dan Med J* 2014;**61**:A4904.
21. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW *et al*. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial. *J Am Coll Cardiol* 2014;**63**:321–8.
22. Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF *et al*. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* 2015;**385**:2288–95.
23. Volbers B, Kohrmann M, Kallmunzer B, Kurka N, Breuer L, Ringwald J *et al*. Dabigatran plasma levels in acute cerebrovascular events. *J Stroke Cerebrovasc Dis* 2016;**25**:877–82.
24. Purrucker JC, Haas K, Rizos T, Khan S, Poli S, Kraft P *et al*. Coagulation testing in acute ischemic stroke patients taking non-vitamin K antagonist oral anticoagulants. *Stroke* 2017;**48**:152–8.
25. Dale BJ, Chan NC, Eikelboom JW. Laboratory measurement of the direct oral anticoagulants. *Br J Haematol* 2016;**172**:315–36.
26. Kristiansen C, Lassen JF, Dahler-Eriksen BS, Dahler-Eriksen K, Larsen TB, Brandslund I. Evaluation of a simple dosage scheme for transition from phenprocoumon to warfarin in oral anticoagulation. *Thromb Res* 2000;**98**:157–63.

Erratum

doi:10.1093/europace/euy023
Online publish-ahead-of-print 9 February 2018

Erratum to: Occupational radiation exposure in the electrophysiology laboratory with a focus on personnel with reproductive potential and during pregnancy: A European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart rhythm Society (HRS) [*Europace* 2017;19:1909–1922].

In 10.1093/europace/eux252, Tatjana Potpara had not been mentioned among the members of the ESC Scientific Document Group, and another member had been added erroneously. This has now been corrected online. The Editors apologise for this error.

5. Diskussion

Die wissenschaftlichen Arbeiten, die in dieser Habilitationsschrift vorgelegt werden, befassen sich mit einer erweiterten kardialen Diagnostik nach ischämischem Schlaganfall, der prognostischen Bedeutung blutbasierter kardialer Biomarker für die Prognoseabschätzung nach ischämischem Schlaganfall oder TIA und der medikamentösen Sekundärprävention im Rahmen kardio-embolischer Schlaganfälle. Es ergeben sich drei Hauptbefunde: 1.) die Durchführung einer kardiovaskulären MRT in der Akutphase nach ischämischem Schlaganfall erhöht die Detektionsrate pathologischer kardialer Befunde signifikant im Vergleich zur Routinediagnostik und reduziert damit die Rate der als kryptogen klassifizierten Schlaganfälle; 2.) der blutbasierte kardiale Biomarker hs-cTnT als Surrogat für eine myokardiale Schädigung ist unabhängig mit dem Auftreten schwerwiegender kardiovaskulärer Folgeereignisse nach Schlaganfall assoziiert und 3.) die Therapie mit nicht-Vitamin K-abhängigen oralen Antikoagulanzien (NOAK) bei Patient*innen mit Vorhofflimmern hat einen positiven Einfluss auf den Schlaganfallschweregrad und zumindest das kurzfristige Behandlungsergebnis sowohl in der Primär- als auch Sekundärprävention; dennoch besteht bei der Versorgung Optimierungsbedarf.

5.1 Intensivierte kardiale Diagnostik nach ischämischem Schlaganfall

Während traditionell jeder fünfte Schlaganfall einer kardioembolischen Genese zugeordnet wird (→ *3.5 Schlaganfallätiologien*), bleibt zu vermuten, dass in der heterogenen Gruppe der „kryptogenen“ Schlaganfälle ein relevanter Anteil ebenfalls kardialen Ursprungs sein könnte[42, 45, 53]. In diesem Zusammenhang wurde das ESUS-Konzept entwickelt für Schlaganfälle mit embolischem Infarktmuster ohne identifizierte Emboliequelle trotz abgeschlossener Diagnostik[45]. Eine Meta-Analyse aus dem Jahr 2017 analysierte neun Studien und errechnete einen ESUS-Anteil an allen ischämischen Schlaganfällen von durchschnittlich 17%[47]. Eine kardiale Diagnostik ist Teil der diagnostischen Abklärung nach einem ischämischen Schlaganfall[29]. Im Kern besteht hierbei jedoch nur Konsens, allen Schlaganfallpatientinnen und -patienten ein EKG-Monitoring über die Dauer von mindestens 24 Stunden im Rahmen der Stroke Unit Behandlung zukommen zu lassen[29]. Bereits über die Indikation und Auswahl einer Echokardiographie herrscht Uneinigkeit: die deutschen Leitlinien empfehlen eine Echokardiographie, wenn die Schlaganfallätiologie durch die übrige Diagnostik nicht geklärt werden konnte[29]. Andererseits wird die transthorakale Echokardiographie (TTE) als Teil der

Routinediagnostik aufgeführt[29]. Es wird in den Leitlinien darauf hingewiesen, dass die transösophageale Echokardiographie (TOE) einer TTE zur Detektion potentiell für die Schlaganfallätiologie relevanter Befunde wie eines PFO, eines Vorhofseptumaneurysma, Plaques der thorakalen Aorta, endokarditischen Veränderungen oder Pathologien des linken Vorhofs überlegen sei[29, 74]. Gleichzeitig muss berücksichtigt werden, dass die TOE ein semi-invasives Verfahren ist, i.d.R. eine Analgosedierung notwendig macht, in seltenen Fällen mit relevanten medizinischen Komplikationen verbunden sein kann und einen vergleichsweise hohen apparativen und personellen Aufwand bedeutet[135-137]. Die Versorgungsrealität in Deutschland zeigt, dass nur ca. 2/3 aller Schlaganfallpatient*innen eine TTE und nur ca. jede*r fünfte eine TOE während des Aufenthalts auf der Stroke Unit erhalten[75]. Interessanterweise war die Rate an Echokardiographien von der Anzahl der behandelten Patient*innen pro Zentrum abhängig, wobei sowohl die TTE- als auch die TOE-Rate mit steigender Patient*innenzahl abnahm; ebenso waren die Raten in überregionalen Stroke Units niedriger als in regionalen[75]. Eine kanadische Arbeit aus dem Jahr 2021 berichtet eine TTE-Rate von 74% in einem regionalen Schlaganfallzentrum, wobei klinisch potentiell bedeutsame Befunde bei ca. 6% festgestellt wurden und die Befunde der TTE bei etwas mehr als 3% eine Behandlungskonsequenz hatten[138]. Gleichzeitig führte die Durchführung der TTE zu einem verlängerten Krankenhausaufenthalt bei knapp 5% der Patient*innen[138].

5.2 Bedeutung der kardiovaskulären MRT

Als diagnostische Alternative steht die kardiovaskuläre MRT (CMR) zur Verfügung[87]. Diese strahlungsfreie bildgebende Methode ermöglicht einen hervorragenden Gewebekontrast und moderne Sequenzen wie T1- und T2-Mapping sowie Kontrastmittelspätanreicherung (Late Gadolinium Enhancement, LGE) erlauben eine differenzierte Darstellung auch subtiler, ggf. subklinischer parenchymatöser Veränderungen[139]. Die CMR gilt insbesondere auch als Goldstandard für die Beurteilung der linksventrikulären Struktur und Funktion[140]. In Vorarbeiten konnte gezeigt werden, dass die CMR eine durchführbare und sichere Methode bei ausgewählten Schlaganfallpatient*innen ist[87]. Limitationen in der Anwendbarkeit bei Schlaganfallpatient*innen bestehen einerseits durch mögliche allgemeine Kontraindikationen für die Durchführung einer MRT (z.B. bestimmte Metallimplantate oder schwere Klaustrophobie, körperliche Voraussetzungen für flaches Liegen) sowie im spezifischen Fall der CMR die vergleichsweise lange Untersuchungsdauer sowie die Notwendigkeit, Atemkommandos

zu befolgen[141]. Überdies ist für relevante Sequenzen zur Gewebedifferenzierung die Applikation von MR-Kotrastmittel erforderlich[141].

Über die diagnostische Wertigkeit der CMR im Kontext des ischämischen Schlaganfalls herrscht indes Uneinigkeit[142]. Ein systematisches Review mit Meta-Analyse aus dem Jahr 2021 untersuchte die diagnostische Ausbeute der CMR im Vergleich zur Echokardiographie bei Schlaganfallpatient*innen[143]. Hier zeigte sich eine vergleichbare Detektionsrate kardio-aortaler Emboliequellen, wobei die Echokardiographie der CMR in der Detektion eines PFO überlegen war und die CMR der Echokardiographie in der Detektion linksventrikulärer Thromben[143]. Zumindest die deutschen Leitlinien sehen daher die kardiale MRT (wie auch die kardiale CT) aktuell als komplementäre Methode zur Echokardiographie bei ausgewählten Patient*innen mit ungeklärter Schlaganfallätiologie[29].

Die CMR gilt allgemein als Goldstandard zur Beurteilung der linksventrikulären Pumpfunktion[88]. In Vorarbeiten konnten wir zeigen, dass die CMR auch bei Patient*innen mit akutem ischämischem Schlaganfall eine verlässliche Methode zur Erhebung der systolischen und diastolischen Herzfunktion ist[144]. Hierbei fand sich in einem Kollektiv vergleichsweise junger Schlaganfallpatient*innen mit einer niedrigen Rate einer vorbekannten Herzinsuffizienz (n=229; durchschnittliches Alter 66 Jahre, Herzinsuffizienz bei 2% bekannt) zumindest bei jede*r Vierten eine systolische (LVEF <50%) und bei mehr als der Hälfte (59%) eine diastolische Funktionsstörung[144]. Weiterhin konnten wir zeigen, dass die Akquisitionszeit für die Kurzachsenpakete (*short axis stack*) durch die Anwendung sog. Cine real-time Sequenzen (CRT) im Vergleich zum Standard segmentierter SSFP-Cine Sequenzen (*steady state free precession*) signifikant und relevant verkürzt werden konnte (mediane Untersuchungszeit SSFP-Cine 3:41 min vs. CRT 0:22 min), bei vergleichbarer Aussagekraft hinsichtlich Schlüsselparameter der systolischen und diastolischen Herzfunktion[144]. In unserer Analyse im Rahmen der HEBRAS Studie fand sich unter Einsatz der CMR eine signifikant höhere Rate einer reduzierten LVEF (sowohl bei einem Grenzwert <45% gemäß Studienprotokoll als auch bei einem Grenzwert <30% gemäß ESUS-Definition)[108]. Sowohl der Nachweis myokardialer Wandbewegungsstörungen als auch eine reduzierte LVEF begünstigen die Formation eines intrakardialen Thrombus[68]. Nichtsdestotrotz kann die Frage nach der therapeutischen Konsequenz dieser Befunde ohne Thrombusnachweis und/oder konkomittantes Vorhofflimmern nicht pauschal beantwortet werden; die deutschen

Leitlinien empfehlen, dass eine OAK bei einer LVEF ≤35% anstelle einer Thrombozytenfunktionshemmung erwogen werden kann[61]. Dies unterstreicht erneut die Notwendigkeit einer individualisierten Therapieempfehlung ggf. auch in interdisziplinärer Zusammenarbeit mit Kardiologinnen und Kardiologen im Lichte solcher Befunde.
Ein weiteres Alleinstellungsmerkmal der CMR ist die exzellente Gewebedifferenzierung zur Detektion fokaler und diffuser myokardialer Fibrosierung[145]. Insbesondere von Interesse ist die Möglichkeit, durch die kontrastmittel-gestützte CMR fokale myokardiale Fibrosen (identifiziert durch Nachweis von LGE) auch bei Patient*innen ohne bekannte kardiale Erkrankung zu detektieren[146]. Weiterhin kann das Muster der myokardialen Fibrose als „KHK-typisch“ oder „nicht KHK-typisch“ klassifiziert werden[147]. In einer Pilot-Auswertung der CORONA-IS Studie fand sich bei jede*r Dritten mit akutem ischämischem Schlaganfall eine fokale myokardiale Fibrose, von denen drei Viertel als KHK-typisch klassifiziert wurden[148]. Patient*innen mit fokaler Fibrose hatten dabei höhere T1 Mapping-Werte als Zeichen der diffusen Fibrosierung auch in Arealen ohne fokale Fibrose im Vergleich zu Patient*innen ohne fokale Fibrose[148]. Überdies fanden sich in der Gruppe von Patient*innen mit fokaler Fibrose bei fast der Hälfte erhöhte T2 Mapping-Werte als Zeichen eines myokardialen Ödems und damit hinweisend auf ein akutes oder subakutes Geschehen[148]. In einer weiteren Analyse der HBERAS Studie untersuchten wir den Zusammenhang von kardialen Biomarkern (hs-cTnT und NT-proBNP) mit dem Vorliegen fokaler Fibrosen[149]. Hierbei fand sich eine solche fokale Fibrose bei einem Viertel der Patient*innen, wobei ca. 80% ein KHK-typisches Muster aufwiesen[149]. Auch in der adjustierten Analyse war ein erhöhtes hs-cTnT (>URL) mit dem Vorliegen einer fokaler Fibrose, und hier insbesondere mit Fibrosen in KHK-typischer Konfiguration assoziiert[149]. Die kontrastmittelgestützte CMR ist mithin dazu geeignet, auch klinisch stumme Myokardinfarkte zu detektieren (*unrecognized myocardial infarction*, UMI)[145]. Hinsichtlich der Prognose erneuter kardiovaskulärer Ereignisse war die Auftrittswahrscheinlichkeit in großen, populationsbasierten Studien bei Proband*innen mit UMI vergleichbar zu Proband*innen mit bekanntem Myokardinfarkt (*recognized myocardial infarction*, RMI)[150]. In zukünftigen Studien könnte also untersucht werden, ob der Nachweis einer fokalen Fibrose mittels CMR bei Patient*innen mit ischämischem Schlaganfall - und insbesondere bei solchen ohne vorbekannte Herzerkrankung - ein nützlicher prädiktiver Biomarker für das Auftreten erneuter kardiovaskulärer Ereignisse sein könnte.

5.3 Kardiales Troponin und kardiovaskuläres Risiko nach Schlaganfall

Eine Vielzahl blut-basierter Biomarker wurde im Kontext des ischämischen Schlaganfalls hinsichtlich ihrer prognostischen Bedeutung untersucht[102]. In einem systematischen Review analysierten wir Publikationen aus den Jahren 2007-2018 mit Daten zu 257 verschiedenen Biomarkern[102]. Bezüglich kardialer Biomarker waren neben natriuretischen Peptiden insbesondere kardiale Troponine (hs-cTn: Troponin I und Troponin T) Gegenstand wissenschaftlicher Untersuchungen[102]. In Vorarbeiten konnte bereits ein Zusammenhang zwischen hs-cTn und dem Risiko eines ischämischen Schlaganfalls sowohl in der Allgemeinbevölkerung als auch bei Patient*innen mit Vorhofflimmern und Patient*innen mit vorausgegangenem Schlaganfall dargestellt werden[151]. Weniger gut verstanden ist der Zusammenhang erhöhter Troponin-Werte mit dem Rezidivrisiko nach ischämischem Schlaganfall[152, 153]. Hinsichtlich der kurzfristigen Prognose zeigten sich erhöhte Troponinwerte bei Aufnahme assoziiert mit einem schlechten funktionellen Zustand bei Krankenhausentlassung (mRS ≥2) sowie Tod während des stationären Aufenthalts[154]. Der optimale Grenzwert für die Vorhersage eines schlechten funktionellen Zustands bei Krankenhausentlassung lag in dieser Analyse bei 16 ng/L[154].

Bezüglich einer längerfristigen Assoziation mit erneuten vaskulären Ereignissen nach ischämischem Schlaganfall konnte eine Subgruppenanalyse der Find-AF Studie bei 197 Patient*innen mit ischämischem Schlaganfall ohne bekanntes Vorhofflimmern eine unabhängige Assoziation erhöhter Troponinwerte sowohl mit erneuten vaskulären Ereignissen als auch mit Mortalität nach einem Jahr belegen[152]. In einer Biomarker-basierten Subgruppenanalyse der NAVIGATE ESUS Studie fand sich bei 1337 Patient*innen über einen durchschnittlichen Nachverfolgungszeitraum von 11 Monaten ebenfalls eine Assoziation von erhöhten Troponinwerten und dem kombinierten Endpunkt erneuter kardiovaskulärer Ereignisse (jährliche Ereignisrate 8,2% bei Patient*innen mit hs-cTnT ≥URL vs. 4,8% mit hs-cTnT <URL), die jedoch in der adjustierten Analyse keine statistische Signifikanz erreichte (adjustierte HR 1,3 95% KI 0,73-2,3)[153]. Kein relevanter Unterschied zeigte sich in dieser Analyse hinsichtlich des Endpunktes Rezidivschlaganfall (4,7% vs. 3,9%)[153]. Im Vergleich zu diesen Vorarbeiten zeigte sich hier eine stärkere Assoziation von Troponin und erneuten kardiovaskulären Ereignissen (9,3% vs. 4,4% aHR 1,63 95% KI 1,13-2,35), möglicherweise aufgrund des längeren Nachverfolgungszeitraums von durchschnittlich 3,2 Jahren[115].

5.4 Risikostratifizierung nach ischämischem Schlaganfall

Nach einem ischämischen Schlaganfall haben kardiovaskuläre Rezidiv- und Folgeereignisse einen relevanten Einfluss auf das Ausmaß an Behinderung und damit Abhängigkeit von anderen und die Lebensqualität allgemein[155, 156]. Gleichermaßen sind auch die gesamtgesellschaftlichen Kosten für das Gesundheitssystem hierdurch maßgeblich betroffen[157]. Die Identifikation von Patient*innen mit besonders hohem Risiko ist daher von hervorgehobener Bedeutung, um das diagnostische Vorgehen und die Sekundärprävention nach ischämischem Schlaganfall zu optimieren[158]. Eine Reihe verschiedener Vorhersagemodelle sowohl für das kurz- als auch das langfristige Risiko für Rezidivschlaganfälle, Mortalität oder kombinierte kardiovaskuläre Endpunkte wurden in verschiedenen Schlaganfallpopulationen entwickelt[92]. Konventionelle kardiovaskuläre Vorhersagemodelle basieren dabei in der Regel auf demographischen Informationen und Komorbiditäten und erreichen bestenfalls eine moderate prädiktive Genauigkeit[159]. Der in unserer Studie verwendete $ABCD^2$ Score wurde ursprünglich für die kurzfristige Risikoeinschätzung nach TIA entwickelt, hat sich aber auch für ein langfristiges Assessment etabliert[94, 160]. In einer Meta-Analyse aus dem Jahr 2015 konnte der $ABCD^2$ Score bei 13.766 analysierten Patient*innen nicht verlässlich das Risiko für einen Rezidivschlaganfall innerhalb der ersten sieben Tage diskriminieren (Sensitivität 87%, Spezifität 35%)[161].

Mehrere Studien belegen, dass Biomarker-basierte Risikomodelle z.B. im Kontext einer KHK oder Vorhofflimmern traditionellen Schemata überlegen sein können[114, 162, 163]. In einer Subgruppenanalyse der PEGASUS-TIMI 54 Studie wurde der additive Nutzen von Troponin (hs-TnI) zur leitliniengerechten Risikoklassifizierung bei Patient*innen mit vorausgegangenem Myokardinfarkt (ein bis drei Jahre vor Studieneinschluss) untersucht[164]. Hinsichtlich des kombinierten primären Endpunkts aus kardiovaskulärem Tod, erneutem Myokardinfarkt oder Schlaganfall zeigte sich, dass diejenigen Patient*innen mit niedrigem Risiko, die ein erhöhtes hs-TnI aufwiesen, eine vergleichbare Ereignisrate aufwiesen wie diejenigen Patient*innen mit ohnehin hohem Risiko[164]. Unter Berücksichtigung von hs-TnI führte dies zu einer Reklassifizierung des Risikos bei 11,9% der Patient*innen[164]. Ein vergleichbarer Effekt fand sich auch in unserer Analyse von INSPiRE-TMS: Patient*innen wurden nach dem $ABCD^2$ Score in eine Hochrisikogruppe ($ABCD^2 \geq 6$) und eine Niedrigrisikogruppe eingeteilt ($ABCD^2 < 6$)[93]. Unter Berücksichtigung von hs-cTnT zeigten nun diejenigen Patient*innen, die basierend auf

dem $ABCD^2$ Score allein ein niedriges Risiko attribuiert bekamen, ebenfalls eine vergleichbar hohe Ereignisrate wie die Patient*innen in der Hochrisikogruppe (9,5% vs. 8,9%). Sollten sich diese Ergebnisse in unabhängigen Kohorten validieren lassen, könnte die routinemäßige Bestimmung von hs-cTnT bei Patient*innen mit akutem ischämischem Schlaganfall dazu beitragen, Hochrisikopatient*innen zu identifizieren, die sich für eine weiterführende kardiale Abklärung qualifizieren. So wurde in der Vergangenheit auch ein Zusammenhang von erhöhten Troponinwerten und ESUS (auch nach Ausschluss von Patient*innen mit nachfolgend erstmalig detektiertem Vorhofflimmern) bzw. einer mutmaßlich kardio-embolischen Schlaganfallätiologie belegt[165, 166]. In einer post-hoc Analyse der HEBRAS Studie waren erhöhte kardiale Biomarker mit der Detektion pathologischer Befunde in der CMR assoziiert[167]. Die Detektion eines erhöhten kardialen Troponins in der Akutphase nach ischämischem Schlaganfall als Zeichen der myokardialen Schädigung könnte demgemäß auch als Auswahlkriterium für die Durchführung einer CMR, insbesondere bei Patient*innen ohne kardiale Vorerkrankung, nützlich sein.

5.5 Orale Antikoagulation im zeitlichen Verlauf

Eine OAK ist bei Patient*innen mit Vorhofflimmern und einem CHA_2DS_2-VASc Score >1 (Männer) bzw. >2 (Frauen) in der Abwesenheit von Kontraindikationen angezeigt. Nach stattgehabtem Schlaganfall ist dieses Kriterium bei Patient*innen mit Vorhofflimmern erfüllt. In der Ära der Vitamin K-Antagonisten (bis 2010) wurde wiederholt eine eklatante Unterversorgung bei Patient*innen mit Vorhofflimmern und Indikation zur OAK mit durchschnittlichen Behandlungsraten unter 50% belegt[121, 168, 169]. Eine landesweite Studie aus Dänemark mit >100.000 analysierten Patient*innen fand Behandlungsraten von 40-50% vor 2010 und konnte einen Anstieg auf 66,5% bis 2015 nachweisen, wobei zuletzt drei von vier Patient*innen mit neu diagnostiziertem Vorhofflimmern ein NOAK verschrieben bekamen[170]. Vergleichbare Daten aus Deutschland liegen nur begrenzt vor[171, 172]. in unserer Analyse aus den Jahren 2003-2004, 2008-2010 und 2013-2015 zeigte sich eine relevante Zunahme in der Behandlung mit einer OAK zum Zeitpunkt des Index-Schlaganfalls vor und nach Einführung der NOAK (28,2% vs. 49,6%)[122]. Interessanterweise zeigte sich bereits eine Zunahme der OAK-Rate vor Einführung der NOAKs (2003-2004: 22,2% vs. 2008-2010: 31,0%)[122]. Dabei muss berücksichtigt werden, dass internationale Leitlinien für die Behandlung bei Vorhofflimmern

bis 2006 eine OAK in der Regel bei Patient*innen mit hohem Schlaganfallrisiko empfahlen und Patient*innen mit niedrigerem Risiko i.d.R. mit ASS behandelt wurden[173]. Ebenso stieg die Behandlungsrate mit einer OAK bei Krankenhausentlassung mit der Zeit an (2003-2004 & 2008-2010: 45,2% vs. 2013-2015: 69,5%)[122]. Zu den unabhängigen Faktoren, die mit einer OAK vor dem Index-Schlaganfall assoziiert waren, zählten jüngeres Alter, vorausgegangener Schlaganfall oder TIA, die Abwesenheit einer bekannten Herzinsuffizienz und der Zeitraum 2013-2015[122]. Dies ist kongruent zu den Befunden aus Dänemark, wo ebenfalls jüngeres Alter, fehlende Komorbiditäten und ein erhöhtes Schlaganfallrisiko als Einflussfaktoren identifiziert werden konnten[170].

5.6 Ischämischer Schlaganfall trotz OAK

Trotz einer bestehenden OAK verbleibt bei Patient*innen mit Vorhofflimmern ein residuelles Schlaganfallrisiko, das in der Literatur mit jährlichen Raten zwischen 0,7% und 2,3% in Primär- und Sekundärprävention angegeben wird[126]. Zu den Ursachen zählen ein mögliches Therapieversagen (als Folge mangelnder Compliance bzw. Einnahmetreue, fehlerhafter Dosierung oder auch Nichtansprechen in seltenen Fällen) oder konkurrierende Schlaganfallursachen, für die ein Ansprechen auf eine OAK nicht belegt ist (z.B. mikroangiopathische Veränderungen)[128, 174]. Neben der Frage nach den zugrunde liegenden Ursachen solcher „Durchbruchschlaganfälle“ bleibt zunächst unzureichend verstanden, ob diese Patient*innen ein besonderes hohes Rezidivrisiko haben, und ob eine solche Konstellation Einfluss auf die weitere Sekundärprävention haben sollte[128]. In unserer gepoolten Analyse zu Schlaganfallursachen, Sekundärprävention und Behandlungsergebnissen bei fast 3.000 Patient*innen mit bekanntem Vorhofflimmern und ischämischem Schlaganfall trotz bestehender OAK fand sich bei einem Viertel eine konkurrierende Schlaganfallätiologie, eine unzureichende OAK bei einem Drittel und ein mutmaßlich kardioembolischer Schlaganfall trotz suffizienter Antikoagulation bei vier von zehn Patient*innen[126]. Der relevante Anteil konkurrierender Schlaganfallätiologien erscheint hierbei plausibel angesichts der Ergebnisse vorausgegangener Analysen, die in einem Kollektiv von Patient*innen mit Schlaganfall trotz OAK bei über 95% zumindest eine alternative Schlaganfallätiologie (potential, uncertain or unlikely nach ASCOD, → *3.5 Schlaganfallätiologien*) detektieren konnten[175]. Als Konsequenz hieraus ergibt sich die Notwendigkeit, auch bei Patient*innen mit bekanntem Vorhofflimmern unter oraler Antikoagulation eine vollständige ätiologische Abklärung im Falle eines „Durchbruchschlaganfalls“ durchzuführen. Überdies

sollte die Dosierung und Einnahmetreue der OAK kritisch evaluiert werden, ggf. auch unter früher Bestimmung der Plasmakonzentration im Falle eines NOAK. Ein Vorteil durch einen Therapiewechsel zu einem anderen Präparat hingegen konnte durch unsere Daten nicht belegt werden[126]. Eine additive Hemmung der Thrombozytenfunktion war sogar mit einem höheren Risiko verbunden, ein Rezidivereignis zu erleiden[126]. Ein solches Signal fand sich auch in Analysen großer, randomisierter Studien zur Antikoagulation bei Vorhofflimmern wie den SPORTIF Studien, wo für die zusätzliche Einnahme von ASS keine Reduktion an Schlaganfällen, systemischen Embolien oder Herzinfarkten festgestellt werden konnte bei einer gleichzeitig um 1,6% pro Jahr erhöhten Rate großer Blutungen[176]. Eine neuere Arbeit mit Daten aus dem GARFIELD-AF Register fand bei Patient*innen mit OAK und einer Thrombozytenfunktionshemmung sogar eine erhöhte Rate an inzidentellen Schlaganfällen und auch Blutungen nach einem Jahr ohne einen nachweisbaren positiven Einfluss auf Mortalität oder das Auftreten eines ACS[177]. Interessanterweise hatte insbesondere diejenigen Patient*innen mit einer konkurrierenden Schlaganfallätiologie ein erhöhtes Risiko für einen Rezidivschlaganfall, jedoch nicht für den primären Endpunkt[126].

5.7 Behandlungsergebnisse bei Schlaganfällen trotz OAK

Insgesamt fand sich in unserer Analyse eine vergleichsweise hohe Rate an Endpunkten innerhalb des Beobachtungszeitraums von drei Monaten: mehr als ein Viertel aller Patient*innen erlitten den zusammengesetzten Endpunkt aus erneutem Schlaganfall, intrazerebraler Blutung oder Tod, wobei Tod der wesentliche Einflussfaktor war (84% aller Ereignisse)[126]. Diese hohen Ereignissraten unterstreichen den Bedarf einer weiteren Verbesserung der Sekundärprävention ischämischer Schlaganfälle bei Patient*innen mit Vorhofflimmern. Neben nicht-pharmakologischen Ansätzen wie dem Vorhofohrverschluss werden aktuell auch sog. Faktor XIa-Inhibitoren (Milvexian, Asundexian) der klinischen Prüfung unterzogen[178-180]. Die klinische Phase III Studie zur Sicherheit und Wirksamkeit von Asundexian im Vergleich zu Apixaban bei Patient*innen mit Vorhofflimmern und erhöhtem Schlaganfallrisiko (OCEANIC-AF) wurde durch den Sponsor der Studie auf Empfehlung des unabhängigen Data Monitoring Committees im November 2023 bei unterlegener Wirksamkeit vorzeitig beendet[181]. In den unlängst publizierten Ergebnissen der LAAOS III Studie reduzierte ein operativer Vorhofohrverschluss bei Patient*innen mit Vorhofflimmern, die sich aus anderer Indikation einer

Operation am Herzen unterzogen, nachfolgend das Risiko eines ischämischen Schlaganfalls oder einer systemischen Embolie[182]. Dies könnte eine weitere mögliche Behandlungsalternative bei Schlaganfallpatient*innen mit Vorhofflimmern und Schlaganfall trotz OAK oder bei einer Kontraindiktion für eine OAK darstellen.

6. Zusammenfassung

Herz und Hirn sind in Gesundheit und Krankheit eng miteinander verbunden[183]. Kardiale Pathologien sind häufige und überdies auch häufig unentdeckte Ursachen eines ischämischen Schlaganfalls[45, 53]. Gleichzeitig treten nach einem Schlaganfall vermehrt kardiale Komplikationen auf, die einen entscheidenden Einfluss auf die kurz- und langfristige Prognose haben[184].

Neben einem Rhythmusmonitoring greift die klinische Routine im Wesentlichen auf die Echokardiographie zur morphologischen und funktionellen Beurteilung des Herzens in der Akutphase nach ischämischem Schlaganfall zurück[29, 75]. Darüber hinaus stehen weitere Methoden wie die kardiovaskuläre MRT zur Verfügung[29, 87]. In der prospektiven Beobachtungsstudie HEBRAS konnten wir zeigen, dass ein kombinierter Einsatz der kardiovaskulären MRT einschließlich MR-Angiographie des Aortenbogens sowie eines prolongierten EKG-Monitorings für die Dauer von bis zu zehn Tagen die Detektionsrate präspezifizierter pathologischer Befunde im Vergleich zur Routinediagnostik signifikant erhöhen konnte[108]. Dies führte entsprechend zu einer signifikanten Reduktion der als kryptogen klassifizierten Schlaganfälle[108]. Diese Befunde können Grundlage dafür sein, in nachfolgenden Studien zu untersuchen, ob die Anwendung eines solchen intensivierten diagnostischen Ansatzes möglicherweise Einfluss auf eine veränderte Sekundärprävention haben und hierdurch ggf. zu einer Reduktion kardiovaskulärer Komplikationen nach ischämischem Schlaganfall führen kann.

In einer zweiten Arbeit wurde die Bedeutung des kardialen Biomarkers Troponin T für das Auftreten kardiovaskulärer Komplikationen im langfristigen Verlauf nach ischämischem Schlaganfall oder TIA untersucht[115]. Dies war eine post-hoc Analyse der prospektiven, randomisierten, multizentrischen INSPiRE-TMS Studie[116]. Hierbei war ein Troponinwert über dem Assay-spezifischen Referenzlimit bei Aufnahme mit einem bis zu zweifach erhöhten Risiko für ein schwerwiegendes kardiovaskuläres Ereignis während eines durchschnittlichen Nachverfolgungszeitraums von über drei Jahren assoziiert[115]. Interessanterweise fand sich bei denjenigen Patient*innen, die gemäß einem etablierten Prognoseinstrument (dem $ABCD^2$ Score) als Niedrigrisikokollektiv eingestuft wurden, eine vergleichbare Ereignisrate wie in der Gruppe mit hohem Risiko, wenn das Troponin bei Aufnahme erhöht war[115]. Während eine individualisierte vaskuläre Risikoprädiktion nach ischämischem Schlaganfall oder TIA eine hohe klinische Bedeutung hat, sagen etablierte Risikoscores das Auftreten von Folge- und Rezidive-

reignissen mit nur unzureichender Genauigkeit voraus[92]. Die Ergebnisse dieser Analyse unterstreichen das Potential von Troponin T als vaskulärer Risikomarker im Kontext des ischämischen Schlaganfalls. Hierauf aufbauend könnte in nachfolgenden Studien untersucht werden, ob sich die Testgenauigkeit von Prädiktionsmodellen unter Hinzunahme von Troponin optimieren lässt.

Für bestimmte kardiale Pathologien stellt eine orale Antikoagulation die leitliniengerechte Sekundärprävention nach Schlaganfall dar, wobei hier insbesondere das Vorhofflimmern zu nennen ist[29]. Bis Ende 2010 standen hierfür als orale Medikation nur Vitamin K-Antagonisten (in Deutschland i.d.R. Phenprocoumon, in Nordamerika Warfarin) zur Verfügung. Trotz des belegten Nutzens ist eine erhebliche Unterversorgung in der Behandlung von Patientinnen und Patienten mit bestehender Indikation für eine OAK in diesem Zeitraum gut belegt[121]. In einer retrospektiven Analyse von konsekutiven Patient*innendaten der Charité - Universitätsmedizin Berlin untersuchten wir, ob die Verfügbarkeit sog. Nicht-Vitamin K-abhängiger oraler Antikoagulanzien (NOAK) ab 2010/2011 einen Einfluss auf die Verschreibepraxis bei Patient*innen mit Vorhofflimmern und einer Indikation für eine OAK hatte[122]. Während hier annähernd eine Verdopplung der OAK-Rate von 28% auf 50% nachgewiesen werden konnte, blieb dennoch jede*r Zweite ohne eine adäquate Behandlung[122].

In diesem Kontext ist zu erwähnen, dass ischämische Schlaganfälle auch bei Patient*innen mit Vorhofflimmern unter bestehender Antikoagulation auftreten[128]. In einer retrospektiven, multizentrischen, gepoolten Analyse betrachteten wir die mutmaßliche Schlaganfallätiologie, Sekundärprävention und Behandlungsergebnisse in einem Kollektiv solcher Patient*innen[126]. Hier zeigte sich, dass jede*r Vierte eine konkurrierende Schlaganfallursache (zusätzlich zum bekannten Vorhofflimmern) aufwies, jede*r Dritte unzureichend antikoaguliert war und nahezu jede*r Zweite einen kardio-embolischen Schlaganfall trotz bestehender (suffizienter) Antikoagulation erlitt[126]. Nach drei Monaten hatten bereits mehr als jede*r Vierte ein schwerwiegendes Folgeereignis (erneuter Schlaganfall, intrazerebrale Blutung oder Tod), wobei einzig die Einnahme eines NOAK einen protektiven Einfluss aufwies[126]. Diese Analyse hebt die Heterogenität der Schlaganfallätiologien bei Patient*innen mit bestehender OAK hervor und unterstreicht die Notwendigkeit einer individualisierteren Sekundärprävention in diesem Kollektiv.

Abschließend untersuchten wir die Hypothese, dass die Einnahme eines NOAKs bei Patient*innen mit bekanntem VHF auch einen positiven Einfluss auf den Schlaganfall-

schweregrad haben könnte[134]. Patient*innen mit Einnahme eines NOAK erlitten hierbei signifikant seltener einen schweren Schlaganfall (NIHSS >10), vergleichbar zu Patient*innen unter wirksamer Einnahme eines VKA (INR ≥2)[134]. Eine solche Assoziation zeigte sich auch für eine für ein schlechtes funktionelles Behandlungsergebnis bei Entlassung (mRS >2) und die Aufenthaltsdauer im Krankenhaus[134].

Die hier vorgestellten Arbeiten tragen zum besseren Verständnis der pathophysiologischen Zusammenhänge zwischen Herz und Hirn im Kontext des ischämischen Schlaganfalls bei. Eine erweiterte kardiale Diagnostik erscheint zumindest bei ausgewählten Patient*innen eine sinnvolle Ergänzung. Der kardiale Biomarker Troponin ist mit dem langfristigen Auftreten kardiovaskulärer Rezidiv- und Folgeereignisse assoziiert. Diese Erkenntnisse können Grundlage für weiterführende Studien einer individualisierteren Risikoprädiktion und Sekundärprophylaxe sein.

7. Literaturangaben

1. Drenckhahn D. (Hrsg.), Benninghoff A. Anatomie - Makroksopische Anatomie, Histologie, Embryologie, Zellbiologie Band 2. 16. ed: Urban & Fischer Verlag/Elsevier GmbH; 2004.
2. Pötzsch B. (Hrsg)., Madlener K. (Hrsg). Hämostaseologie: Grundlagen, Diagnostik und Therapie. 2 ed: Springer; 2009.
3. Monahan-Earley R., Dvorak A. M., Aird W. C. Evolutionary origins of the blood vascular system and endothelium. J Thromb Haemost. 2013;11 Suppl 1(Suppl 1):46-66.
4. Werner E. Gerabek (Hrsg.) et al. Enzyklopädie Medizingeschichte: De Gruyter; 2007.
5. Mani N. Pathogenese, Diagnose und Prognose der Apoplexie bei Johann Jakob Wepfer (1658). Medizinische Diagnostik in Geschichte und Gegenwart: Festschrift für Heinz Goerke zum sechzigsten Geburtstag: Verlag Werner Fritsch; 1978. p. 235-9.
6. Schiller F. Concepts of stroke before and after Virchow. Med Hist. 1970;14(2):115-31.
7. Sacco R. L., Kasner S. E., Broderick J. P., Caplan L. R., Connors J. J., Culebras A., et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-89.
8. Aho K., Harmsen P., Hatano S., Marquardsen J., Smirnov V. E., Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. Bull World Health Organ. 1980;58(1):113-30.
9. Campbell B. C. V., Khatri P. Stroke. Lancet. 2020;396(10244):129-42.
10. Albers J.M., Dittrich R., Ritter M.A., Ringelstein E.B. Aktuelle Diagnostik und Therapie des Schlaganfalls. Intensivmedizin up2date. 2011;7(4):289-311.
11. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021;20(10):795-820.
12. Feigin V. L., Brainin M., Norrving B., Martins S., Sacco R. L., Hacke W., et al. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. Int J Stroke. 2022;17(1):18-29.

13. Pandian J. D., Kalkonde Y., Sebastian I. A., Felix C., Urimubenshi G., Bosch J. Stroke systems of care in low-income and middle-income countries: challenges and opportunities. Lancet. 2020;396(10260):1443-51.
14. Li L., Scott C. A., Rothwell P. M., Oxford Vascular Study. Trends in Stroke Incidence in High-Income Countries in the 21st Century: Population-Based Study and Systematic Review. Stroke. 2020;51(5):1372-80.
15. Heuschmann P. U., Busse O., Wagner M., Endres M., Villringer A., Röther J., et al. Frequency and Care of Stroke in Germany. Akt Neurol. 2010;37(7):333-40.
16. Robert Koch Institut. Gesundheitsberichterstattung des Bundes gemeinsam getragen von RKI und DESTATIS - Gesundheit in Deutschland 2015 [Available from: https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GesInDtld/gesundheit_in_deutschland_2015.pdf?__blob=publicationFile]
17. Heidemann C., Scheidt-Nave C., Beyer A., Baumert J., Thamm R., Maier B. , et al. Gesundheitliche Lage von Erwachsenen in Deutschland – Ergebnisse zu ausgewählten Indikatoren der Studie GEDA 2019/2020-EHIS. Journal of Health Monitoring. 2021;6(3):1-106.
18. Weber R., Krogias C., Eyding J., Bartig D., Meves S. H., Katsanos A. H., et al. Age and Sex Differences in Ischemic Stroke Treatment in a Nationwide Analysis of 1.11 Million Hospitalized Cases. Stroke. 2019;50(12):3494-502.
19. Stahmeyer J. T., Stubenrauch S., Geyer S., Weissenborn K., Eberhard S. The Frequency and Timing of Recurrent Stroke: An Analysis of Routine Health Insurance Data. Dtsch Arztebl Int. 2019;116(42):711-7.
20. Ward A., Payne K. A., Caro J. J., Heuschmann P. U., Kolominsky-Rabas P. L. Care needs and economic consequences after acute ischemic stroke: the Erlangen Stroke Project. Eur J Neurol. 2005;12(4):264-7.
21. Berliner Schlaganfallregister. Auswertung 2022 [Available from: https://www.aekb.de/fileadmin/01_aerzt-innen/qualitaetssicherung/berliner-schlaganfallregister/BSR_Gesamt_2022.pdf]
22. National Institute of Neurological Disorders, Stroke rt P. A. Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333(24):1581-7.
23. Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. Stroke Unit Trialists' Collaboration. BMJ. 1997;314(7088):1151-9.

24. Goyal M., Menon B. K., van Zwam W. H., Dippel D. W., Mitchell P. J., Demchuk A. M., et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723-31.
25. Hankey G. J. Secondary stroke prevention. Lancet Neurol. 2014;13(2):178-94.
26. Hamann G.F., Sander D., Röther J., Grau A. Deutsche Schlaganfall-Gesellschaft und Deutsche Gesellschaft für Neurologie. Sekundärprophylaxe ischämischer Schlaganfall und transitorische ischämische Attacke: Teil 1, S2k-Leitlinie. Deutsche Gesellschaft für Neurologie (Hrsg), Leitlinien für Diagnostik und Therapie in der Neurologie. 2022.
27. Kleindorfer D. O., Towfighi A., Chaturvedi S., Cockroft K. M., Gutierrez J., Lombardi-Hill D., et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021;52(7):e364-e467.
28. Bhatia K., Jain V., Aggarwal D., Vaduganathan M., Arora S., Hussain Z., et al. Dual Antiplatelet Therapy Versus Aspirin in Patients With Stroke or Transient Ischemic Attack: Meta-Analysis of Randomized Controlled Trials. Stroke. 2021;52(6):e217-e23.
29. Ringleb P., Köhrmann M., Jansen O. Akuttherapie des ischämischen Schlaganfalls, S2e-Leitlinie. Deutsche Gesellschaft für Neurologie (Hrsg), Leitlinien für Diagnostik und Therapie in der Neurologie. 2022.
30. Joglar J. A., Chung M. K., Armbruster A. L., Benjamin E. J., Chyou J. Y., Cronin E. M., et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149(1):e1-e156.
31. Lip G. Y., Frison L., Halperin J. L., Lane D. A. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. Stroke. 2010;41(12):2731-8.
32. Bosch R., Eckardt L., Gramlich M., Hindricks G., Hoffmann E., Sommer P. Pocket-Leitlinie: Diagnose und Behandlung von Vorhofflimmern (Version 2020). Leitlinien der Deutschen Gesellschaft für Kardiologie – Herz- und Kreislaufforschung eV. 2021.
33. Hindricks G., Potpara T., Dagres N., Arbelo E., Bax J. J., Blomstrom-Lundqvist C., et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation

developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42(5):373-498.

34. Dawson J., Bejot Y., Christensen L. M., De Marchis G. M., Dichgans M., Hagberg G., et al. European Stroke Organisation (ESO) guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack. Eur Stroke J. 2022;7(3):I-II.

35. Bailey R. R. Lifestyle Modification for Secondary Stroke Prevention. Am J Lifestyle Med. 2018;12(2):140-7.

36. Eckstein H., Kühnl A., Berkefeld J., Dörfler A., Kopp I., Langhoff R., et al. S3-Leitlinie zur Diagnostik, Therapie und Nachsorge der extracraniellen Carotisstenose 2. Auflage. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) e V. 2020.

37. Homma S., Sacco R. L. Patent foramen ovale and stroke. Circulation. 2005;112(7):1063-72.

38. Lechat P., Mas J. L., Lascault G., Loron P., Theard M., Klimczac M., et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med. 1988;318(18):1148-52.

39. Diener H. C., Grau A., Baldus S. Kryptogener Schlaganfall und offenes Foramen ovale, S2e-Leitlinie. Deutsche Gesellschaft für Neurologie (Hrsg), Leitlinien für Diagnostik und Therapie in der Neurologie. 2018.

40. Ntaios G., Papavasileiou V., Sagris D., Makaritsis K., Vemmos K., Steiner T., Michel P. Closure of Patent Foramen Ovale Versus Medical Therapy in Patients With Cryptogenic Stroke or Transient Ischemic Attack: Updated Systematic Review and Meta-Analysis. Stroke. 2018;49(2):412-8.

41. Chen P. H., Gao S., Wang Y. J., Xu A. D., Li Y. S., Wang D. Classifying Ischemic Stroke, from TOAST to CISS. CNS Neurosci Ther. 2012;18(6):452-6.

42. Adams H. P., Jr., Bendixen B. H., Kappelle L. J., Biller J., Love B. B., Gordon D. L., Marsh E. E., 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35-41.

43. Fisher C. M. Lacunes: Small, Deep Cerebral Infarcts. Neurology. 1965;15:774-84.
44. Landau W. M., Nassief A. Editorial comment--time to burn the TOAST. Stroke. 2005;36(4):902-4.
45. Hart R. G., Diener H. C., Coutts S. B., Easton J. D., Granger C. B., O'Donnell M. J., et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13(4):429-38.
46. Bogiatzi C., Hackam D. G., McLeod A. I., Spence J. D. Secular trends in ischemic stroke subtypes and stroke risk factors. Stroke. 2014;45(11):3208-13.
47. Hart R. G., Catanese L., Perera K. S., Ntaios G., Connolly S. J. Embolic Stroke of Undetermined Source: A Systematic Review and Clinical Update. Stroke. 2017;48(4):867-72.
48. Hart R. G., Sharma M., Mundl H., Kasner S. E., Bangdiwala S. I., Berkowitz S. D., et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. N Engl J Med. 2018;378(23):2191-201.
49. Diener H. C., Sacco R. L., Easton J. D., Granger C. B., Bernstein R. A., Uchiyama S., et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. N Engl J Med. 2019;380(20):1906-17.
50. Kamel H., Longstreth W. T., Jr., Tirschwell D. L., Kronmal R. A., Marshall R. S., Broderick J. P., et al. Apixaban to Prevent Recurrence After Cryptogenic Stroke in Patients With Atrial Cardiopathy: The ARCADIA Randomized Clinical Trial. JAMA. 2024;331(7):573-81.
51. Geisler T., Keller T., Martus P., Poli K., Serna-Higuita L. M., Schreieck J., et al. Apixaban versus Aspirin for Embolic Stroke of Undetermined Source. NEJM Evid. 2024;3(1):EVIDoa2300235.
52. Albers G. W., Bernstein R., Brachmann J., Camm A. J., Fromm P., Goto S., et al. Reexamination of the Embolic Stroke of Undetermined Source Concept. Stroke. 2021;52(8):2715-22.
53. Kamel H., Healey J. S. Cardioembolic Stroke. Circ Res. 2017;120(3):514-26.
54. Ferro J. M. Cardioembolic stroke: an update. Lancet Neurol. 2003;2(3):177-88.
55. Lin H. J., Wolf P. A., Kelly-Hayes M., Beiser A. S., Kase C. S., Benjamin E. J., D'Agostino R. B. Stroke severity in atrial fibrillation. The Framingham Study. Stroke. 1996;27(10):1760-4.

56. Stewart S., Hart C. L., Hole D. J., McMurray J. J. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med. 2002;113(5):359-64.
57. Go A. S., Hylek E. M., Phillips K. A., Chang Y., Henault L. E., Selby J. V., Singer D. E. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285(18):2370-5.
58. Berry J. D., Dyer A., Cai X., Garside D. B., Ning H., Thomas A., et al. Lifetime risks of cardiovascular disease. N Engl J Med. 2012;366(4):321-9.
59. Yiin G. S., Howard D. P., Paul N. L., Li L., Luengo-Fernandez R., Bull L. M., et al. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study. Circulation. 2014;130(15):1236-44.
60. Daher J., Da Costa A., Hilaire C., Ferreira T., Pierrard R., Guichard J. B., et al. Management of Left Ventricular Thrombi with Direct Oral Anticoagulants: Retrospective Comparative Study with Vitamin K Antagonists. Clin Drug Investig. 2020;40(4):343-53.
61. Olma M. C., Röther J., Grau A., Kurth T. Sekundärprophylaxe ischämischer Schlaganfall und transitorische ischämische Attacke – Teil 2, S2k-Leitlinie. Deutsche Gesellschaft für Neurologie (DGN) und Deutsche Schlaganfall-Gesellschaft (DSG). 2022.
62. Ferreira J. P., Girerd N., Gregson J., Latar I., Sharma A., Pfeffer M. A., et al. Stroke Risk in Patients With Reduced Ejection Fraction After Myocardial Infarction Without Atrial Fibrillation. J Am Coll Cardiol. 2018;71(7):727-35.
63. Chiang C. H., Hung W. T., Huang W. C., Jheng Y. C., Lai W. Y., Lin Y. Y., et al. The risk of stroke after acute myocardial infarction in patients with and without atrial fibrillation: A nationwide cohort study. J Chin Med Assoc. 2021;84(12):1126-34.
64. Mooe T., Eriksson P., Stegmayr B. Ischemic stroke after acute myocardial infarction. A population-based study. Stroke. 1997;28(4):762-7.
65. Saposnik G., Kapral M. K., Liu Y., Hall R., O'Donnell M., Raptis S., et al. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. Circulation. 2011;123(7):739-49.
66. Reeves M. J., Fonarow G. C., Smith E. E., Pan W., Olson D., Hernandez A. F., et al. Representativeness of the Get With The Guidelines-Stroke Registry: comparison

of patient and hospital characteristics among Medicare beneficiaries hospitalized with ischemic stroke. Stroke. 2012;43(1):44-9.
67. Playford D., Stewart S., Harris S. A., Chan Y. K., Strange G. Pattern and Prognostic Impact of Regional Wall Motion Abnormalities in 255 697 Men and 236 641 Women Investigated with Echocardiography. J Am Heart Assoc. 2023;12(22):e031243.
68. Levine G. N., McEvoy J. W., Fang J. C., Ibeh C., McCarthy C. P., Misra A., et al. Management of Patients at Risk for and With Left Ventricular Thrombus: A Scientific Statement From the American Heart Association. Circulation. 2022;146(15):e205-e23.
69. Freudenberger R. S., Hellkamp A. S., Halperin J. L., Poole J., Anderson J., Johnson G., et al. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Circulation. 2007;115(20):2637-41.
70. Bardy G. H., Lee K. L., Mark D. B., Poole J. E., Packer D. L., Boineau R., et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352(3):225-37.
71. Homma S., Thompson J. L., Pullicino P. M., Levin B., Freudenberger R. S., Teerlink J. R., et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012;366(20):1859-69.
72. Pullicino P. M., Qian M., Sacco R. L., Freudenberger R., Graham S., Teerlink J. R., et al. Recurrent stroke in the warfarin versus aspirin in reduced cardiac ejection fraction (WARCEF) trial. Cerebrovasc Dis. 2014;38(3):176-81.
73. Merkler A. E., Pearce L. A., Kasner S. E., Shoamanesh A., Birnbaum L. A., Kamel H., et al. Left Ventricular Dysfunction Among Patients With Embolic Stroke of Undetermined Source and the Effect of Rivaroxaban vs Aspirin: A Subgroup Analysis of the NAVIGATE ESUS Randomized Clinical Trial. JAMA Neurol. 2021;78(12):1454-60.
74. Holmes M., Rathbone J., Littlewood C., Rawdin A., Stevenson M., Stevens J., et al. Routine echocardiography in the management of stroke and transient ischaemic attack: a systematic review and economic evaluation. Health Technol Assess. 2014;18(16):1-176.
75. Rizos T., Jenetzky E., Nabavi D. G., Haeusler K. G., Wachter R., Ossenbrink M., et al. Echocardiography in acute stroke patients: a nationwide analysis in departments with certified stroke units in Germany. Neurol Res Pract. 2023;5(1):3.

76. Pagan R. J., Parikh P. P., Mergo P. J., Gerber T. C., Mankad R., Freeman W. D., Shapiro B. P. Emerging role of cardiovascular CT and MRI in the evaluation of stroke. AJR Am J Roentgenol. 2015;204(2):269-80.
77. Hur J., Choi B. W. Cardiac CT Imaging for Ischemic Stroke: Current and Evolving Clinical Applications. Radiology. 2017;283(1):14-28.
78. Groeneveld N. S., Guglielmi V., Leeflang M. M. G., Matthijs Boekholdt S., Nils Planken R., Roos Ybwem, et al. CT angiography vs echocardiography for detection of cardiac thrombi in ischemic stroke: a systematic review and meta-analysis. J Neurol. 2020;267(6):1793-801.
79. Boussel L., Cakmak S., Wintermark M., Nighoghossian N., Loffroy R., Coulon P., et al. Ischemic stroke: etiologic work-up with multidetector CT of heart and extra- and intracranial arteries. Radiology. 2011;258(1):206-12.
80. Rinkel L. A., Beemsterboer C. F., Groeneveld N. S., Lobe N. H., Boekholdt S. M., Bouma B. J., et al. Cardiac thrombi detected by CT in patients with acute ischemic stroke: A substudy of Mind the Heart. Eur Stroke J. 2023;8(1):168-74.
81. Schroeder S., Achenbach S., Bengel F., Burgstahler C., Cademartiri F., de Feyter P., et al. Cardiac computed tomography: indications, applications, limitations, and training requirements: report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. Eur Heart J. 2008;29(4):531-56.
82. Oshinski J. N., Delfino J. G., Sharma P., Gharib A. M., Pettigrew R. I. Cardiovascular magnetic resonance at 3.0 T: current state of the art. J Cardiovasc Magn Reson. 2010;12(1):55.
83. Kammerlander A. A., Marzluf B. A., Zotter-Tufaro C., Aschauer S., Duca F., Bachmann A., et al. T1 Mapping by CMR Imaging: From Histological Validation to Clinical Implication. JACC Cardiovasc Imaging. 2016;9(1):14-23.
84. Messroghli D. R., Moon J. C., Ferreira V. M., Grosse-Wortmann L., He T., Kellman P., et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson. 2017;19(1):75.
85. Zahuranec D. B., Mueller G. C., Bach D. S., Stojanovska J., Brown D. L., Lisabeth L. D., et al. Pilot study of cardiac magnetic resonance imaging for detection

of embolic source after ischemic stroke. J Stroke Cerebrovasc Dis. 2012;21(8):794-800.
86. Baher A., Mowla A., Kodali S., Polsani V. R., Nabi F., Nagueh S. F., et al. Cardiac MRI improves identification of etiology of acute ischemic stroke. Cerebrovasc Dis. 2014;37(4):277-84.
87. Haeusler K. G., Wollboldt C., Bentheim L. Z., Herm J., Jäger S., Kunze C., et al. Feasibility and Diagnostic Value of Cardiovascular Magnetic Resonance Imaging After Acute Ischemic Stroke of Undetermined Origin. Stroke. 2017;48(5):1241-7.
88. Grothues F., Smith G. C., Moon J. C., Bellenger N. G., Collins P., Klein H. U., Pennell D. J. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol. 2002;90(1):29-34.
89. English C., Ramage E. Secondary stroke prevention: more questions than answers. Lancet Neurol. 2023;22(9):770-1.
90. Chandratheva A., Geraghty O. C., Rothwell P. M. Poor performance of current prognostic scores for early risk of recurrence after minor stroke. Stroke. 2011;42(3):632-7.
91. Mohan K. M., Wolfe C. D., Rudd A. G., Heuschmann P. U., Kolominsky-Rabas P. L., Grieve A. P. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke. 2011;42(5):1489-94.
92. Chaudhary D., Abedi V., Li J., Schirmer C. M., Griessenauer C. J., Zand R. Clinical Risk Score for Predicting Recurrence Following a Cerebral Ischemic Event. Front Neurol. 2019;10:1106.
93. Amarenco P., Lavallee P. C., Labreuche J., Albers G. W., Bornstein N. M., Canhao P., et al. One-Year Risk of Stroke after Transient Ischemic Attack or Minor Stroke. N Engl J Med. 2016;374(16):1533-42.
94. Amarenco P., Lavallee P. C., Monteiro Tavares L., Labreuche J., Albers G. W., Abboud H., et al. Five-Year Risk of Stroke after TIA or Minor Ischemic Stroke. N Engl J Med. 2018;378(23):2182-90.
95. Giles M. F., Albers G. W., Amarenco P., Arsava M. M., Asimos A., Ay H., et al. Addition of brain infarction to the ABCD2 Score (ABCD2I): a collaborative analysis of unpublished data on 4574 patients. Stroke. 2010;41(9):1907-13.
96. Merwick A., Albers G. W., Amarenco P., Arsava E. M., Ay H., Calvet D., et al. Addition of brain and carotid imaging to the ABCD(2) score to identify patients at early

risk of stroke after transient ischaemic attack: a multicentre observational study. Lancet Neurol. 2010;9(11):1060-9.
97. Lyden P. Using the National Institutes of Health Stroke Scale: A Cautionary Tale. Stroke. 2017;48(2):513-9.
98. Lyden P., Brott T., Tilley B., Welch K. M., Mascha E. J., Levine S., et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke. 1994;25(11):2220-6.
99. Duncan P. W., Jorgensen H. S., Wade D. T. Outcome measures in acute stroke trials: a systematic review and some recommendations to improve practice. Stroke. 2000;31(6):1429-38.
100. Banks J. L., Marotta C. A. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke. 2007;38(3):1091-6.
101. Saver J. L., Chaisinanunkul N., Campbell B. C. V., Grotta J. C., Hill M. D., Khatri P., et al. Standardized Nomenclature for Modified Rankin Scale Global Disability Outcomes: Consensus Recommendations From Stroke Therapy Academic Industry Roundtable XI. Stroke. 2021;52(9):3054-62.
102. Montellano F. A., Ungethum K., Ramiro L., Nacu A., Hellwig S., Fluri F., et al. Role of Blood-Based Biomarkers in Ischemic Stroke Prognosis: A Systematic Review. Stroke. 2021;52(2):543-51.
103. De Marchis G. M., Dankowski T., Konig I. R., Fladt J., Fluri F., Gensicke H., et al. A novel biomarker-based prognostic score in acute ischemic stroke: The CoRisk score. Neurology. 2019;92(13):e1517-e25.
104. Katan M., Fluri F., Schuetz P., Morgenthaler N. G., Zweifel C., Bingisser R., et al. Midregional pro-atrial natriuretic peptide and outcome in patients with acute ischemic stroke. J Am Coll Cardiol. 2010;56(13):1045-53.
105. De Marchis G. M., Schneider J., Weck A., Fluri F., Fladt J., Foerch C., et al. Midregional proatrial natriuretic peptide improves risk stratification after ischemic stroke. Neurology. 2018;90(6):e455-e65.
106. Haeusler K. G., Grittner U., Fiebach J. B., Endres M., Krause T., Nolte C. H. HEart and BRain interfaces in Acute ischemic Stroke (HEBRAS)--rationale and design of a prospective oberservational cohort study. BMC Neurol. 2015;15:213.
107. Kolominsky-Rabas P. L., Weber M., Gefeller O., Neundoerfer B., Heuschmann P. U. Epidemiology of ischemic stroke subtypes according to TOAST criteria:

incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke. 2001;32(12):2735-40.
108. Hellwig S., Krause T., Scheitz J. F., Herm J., Grittner U., Jauert N., et al. Enhanced diagnostic workup increases pathological findings in patients with acute ischaemic stroke: results of the prospective HEBRAS study. Stroke Vasc Neurol. 2023.
109. Thygesen K., Alpert J. S., Jaffe A. S., Chaitman B. R., Bax J. J., Morrow D. A., et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-64.
110. Giannitsis E., Kurz K., Hallermayer K., Jarausch J., Jaffe A. S., Katus H. A. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem. 2010;56(2):254-61.
111. Scheitz J. F., Endres M., Mochmann H. C., Audebert H. J., Nolte C. H. Frequency, determinants and outcome of elevated troponin in acute ischemic stroke patients. Int J Cardiol. 2012;157(2):239-42.
112. Mochmann H. C., Scheitz J. F., Petzold G. C., Haeusler K. G., Audebert H. J., Laufs U., et al. Coronary Angiographic Findings in Acute Ischemic Stroke Patients With Elevated Cardiac Troponin: The Troponin Elevation in Acute Ischemic Stroke (TRELAS) Study. Circulation. 2016;133(13):1264-71.
113. Willeit P., Welsh P., Evans J. D. W., Tschiderer L., Boachie C., Jukema J. W., et al. High-Sensitivity Cardiac Troponin Concentration and Risk of First-Ever Cardiovascular Outcomes in 154,052 Participants. J Am Coll Cardiol. 2017;70(5):558-68.
114. Hijazi Z., Lindback J., Alexander J. H., Hanna M., Held C., Hylek E. M., et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J. 2016;37(20):1582-90.
115. Hellwig S., Ihl T., Ganeshan R., Laumeier I., Ahmadi M., Steinicke M., et al. Cardiac Troponin and Recurrent Major Vascular Events after Minor Stroke or Transient Ischemic Attack. Ann Neurol. 2021;90(6):901-12.
116. Ahmadi M., Laumeier I., Ihl T., Steinicke M., Ferse C., Endres M., et al. A support programme for secondary prevention in patients with transient ischaemic attack and minor stroke (INSPiRE-TMS): an open-label, randomised controlled trial. Lancet Neurol. 2020;19(1):49-60.
117. Katsanos A. H., Kamel H., Healey J. S., Hart R. G. Stroke Prevention in Atrial Fibrillation: Looking Forward. Circulation. 2020;142(24):2371-88.

118. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154(13):1449-57.
119. Hart R. G., Benavente O., McBride R., Pearce L. A. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med. 1999;131(7):492-501.
120. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet. 1993;342(8882):1255-62.
121. Ogilvie I. M., Newton N., Welner S. A., Cowell W., Lip G. Y. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010;123(7):638-45 e4.
122. Hellwig S., Grittner U., Herm J., Ruschmann R., Konieczny M., Endres M., Haeusler K. G. Temporal Trends in Pharmacological Stroke Prevention in Patients with Acute Ischemic Stroke and Known Atrial Fibrillation. J Stroke Cerebrovasc Dis. 2020;29(12):105266.
123. Ruff C. T., Giugliano R. P., Braunwald E., Hoffman E. B., Deenadayalu N., Ezekowitz M. D., et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-62.
124. Diener H. C., Kleinschnitz C. Non-Vitamin K Oral Anticoagulants in Stroke Patients: Practical Issues. J Stroke. 2016;18(2):138-45.
125. Hart R. G., Pearce L. A., Aguilar M. I. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146(12):857-67.
126. Polymeris A. A., Meinel T. R., Oehler H., Holscher K., Zietz A., Scheitz J. F., et al. Aetiology, secondary prevention strategies and outcomes of ischaemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. J Neurol Neurosurg Psychiatry. 2022;93(6):588-98.
127. Tanaka K., Koga M., Lee K. J., Kim B. J., Park E. L., Lee J., et al. Atrial Fibrillation-Associated Ischemic Stroke Patients With Prior Anticoagulation Have Higher Risk for Recurrent Stroke. Stroke. 2020;51(4):1150-7.

128. Seiffge D. J., De Marchis G. M., Koga M., Paciaroni M., Wilson D., Cappellari M., et al. Ischemic Stroke despite Oral Anticoagulant Therapy in Patients with Atrial Fibrillation. Ann Neurol. 2020;87(5):677-87.
129. Yaghi S., Henninger N., Giles J. A., Leon Guerrero C., Mistry E., Liberman A. L., et al. Ischaemic stroke on anticoagulation therapy and early recurrence in acute cardioembolic stroke: the IAC study. J Neurol Neurosurg Psychiatry. 2021;92(10):1062-7.
130. Stretz C., Wu T. Y., Wilson D., Seiffge D. J., Smith E. E., Gurol M. E., Yaghi S. Ischaemic stroke in anticoagulated patients with atrial fibrillation. J Neurol Neurosurg Psychiatry. 2021;92(11):1164-72.
131. Haeusler K. G., Konieczny M., Endres M., Villringer A., Heuschmann P. U. Impact of anticoagulation before stroke on stroke severity and long-term survival. Int J Stroke. 2012;7(7):544-50.
132. Hannon N., Arsava E. M., Audebert H. J., Ay H., Crowe M., Ni Chroinin D., et al. Antithrombotic treatment at onset of stroke with atrial fibrillation, functional outcome, and fatality: a systematic review and meta-analysis. Int J Stroke. 2015;10(6):808-14.
133. Dittmeier M., Kraft P., Schuhmann M. K., Fluri F., Kleinschnitz C. Pretreatment with rivaroxaban attenuates stroke severity in rats by a dual antithrombotic and anti-inflammatory mechanism. Thromb Haemost. 2016;115(4):835-43.
134. Hellwig S., Grittner U., Audebert H., Endres M., Haeusler K. G. Non-vitamin K-dependent oral anticoagulants have a positive impact on ischaemic stroke severity in patients with atrial fibrillation. Europace. 2018;20(4):569-74.
135. Hilberath J. N., Oakes D. A., Shernan S. K., Bulwer B. E., D'Ambra M. N., Eltzschig H. K. Safety of transesophageal echocardiography. J Am Soc Echocardiogr. 2010;23(11):1115-27; quiz 220-1.
136. Herm J., Konieczny M., Jungehulsing G. J., Endres M., Villringer A., Malzahn U., et al. Should transesophageal echocardiography be performed in acute stroke patients with atrial fibrillation? J Clin Neurosci. 2013;20(4):554-9.
137. Tilz R.R., Busch S., Chun K.R.J., Frerker C., Gaede L., Steven D., et al. Analgosedierung in der Kardiologie. Konsensuspapier der DGK und DGAI 2024. Die Kardiologie. 2024;18:187-99.
138. Moores M., Yogendrakumar V., Bereznyakova O., Alesefir W., Thavorn K., Pettem H., et al. Clinical Utility and Cost of Inpatient Transthoracic Echocardiography Following Acute Ischemic Stroke. Neurohospitalist. 2021;11(1):12-7.

139. Rajiah P. S., Francois C. J., Leiner T. Cardiac MRI: State of the Art. Radiology. 2023;307(3):e223008.
140. von Knobelsdorff-Brenkenhoff F., Schulz-Menger J. Cardiovascular magnetic resonance in the guidelines of the European Society of Cardiology: a comprehensive summary and update. J Cardiovasc Magn Reson. 2023;25(1):42.
141. Saeed M., Van T. A., Krug R., Hetts S. W., Wilson M. W. Cardiac MR imaging: current status and future direction. Cardiovasc Diagn Ther. 2015;5(4):290-310.
142. Yaghi S., Liberman A. L., Atalay M., Song C., Furie K. L., Kamel H., Bernstein R. A. Cardiac magnetic resonance imaging: a new tool to identify cardioaortic sources in ischaemic stroke. J Neurol Neurosurg Psychiatry. 2017;88(1):31-7.
143. Meinel T. R., Eggimann A., Brignoli K., Wustmann K., Buffle E., Meinel F. G., et al. Cardiovascular MRI Compared to Echocardiography to Identify Cardioaortic Sources of Ischemic Stroke: A Systematic Review and Meta-Analysis. Front Neurol. 2021;12:699838.
144. Hellwig S., Grittner U., Elgeti M., Wyschkon S., Nagel S. N., Fiebach J. B., et al. Evaluation of left ventricular function in patients with acute ischaemic stroke using cine cardiovascular magnetic resonance imaging. ESC Heart Fail. 2020;7(5):2572-80.
145. Antiochos P., Ge Y., Steel K., Bingham S., Abdullah S., Mikolich J. R., et al. Imaging of Clinically Unrecognized Myocardial Fibrosis in Patients With Suspected Coronary Artery Disease. J Am Coll Cardiol. 2020;76(8):945-57.
146. Karamitsos T. D., Arvanitaki A., Karvounis H., Neubauer S., Ferreira V. M. Myocardial Tissue Characterization and Fibrosis by Imaging. JACC Cardiovasc Imaging. 2020;13(5):1221-34.
147. Barison A., Aimo A., Todiere G., Grigoratos C., Aquaro G. D., Emdin M. Cardiovascular magnetic resonance for the diagnosis and management of heart failure with preserved ejection fraction. Heart Fail Rev. 2022;27(1):191-205.
148. Blaszczyk E., Hellwig S., Saad H., Ganeshan R., Stengl H., Nolte C. H., et al. Myocardial injury in patients with acute ischemic stroke detected by cardiovascular magnetic resonance imaging. Eur J Radiol. 2023;165:110908.
149. von Rennenberg R., Herm J., Krause T., Hellwig S., Stengl H., Scheitz J. F., et al. Elevation of cardiac biomarkers in stroke is associated with pathological findings on cardiac MRI-results of the HEart and BRain interfaces in Acute Stroke study. Int J Stroke. 2023;18(2):180-6.

150. Acharya T., Aspelund T., Jonasson T. F., Schelbert E. B., Cao J. J., Sathya B., et al. Association of Unrecognized Myocardial Infarction With Long-term Outcomes in Community-Dwelling Older Adults: The ICELAND MI Study. JAMA Cardiol. 2018;3(11):1101-6.
151. Broersen L. H. A., Stengl H., Nolte C. H., Westermann D., Endres M., Siegerink B., Scheitz J. F. Association Between High-Sensitivity Cardiac Troponin and Risk of Stroke in 96 702 Individuals: A Meta-Analysis. Stroke. 2020;51(4):1085-93.
152. Stahrenberg R., Niehaus C. F., Edelmann F., Mende M., Wohlfahrt J., Wasser K., et al. High-sensitivity troponin assay improves prediction of cardiovascular risk in patients with cerebral ischaemia. J Neurol Neurosurg Psychiatry. 2013;84(5):479-87.
153. Scheitz J. F., Pare G., Pearce L. A., Mundl H., Peacock W. F., Czlonkowska A., et al. High-Sensitivity Cardiac Troponin T for Risk Stratification in Patients With Embolic Stroke of Undetermined Source. Stroke. 2020;51(8):2386-94.
154. Scheitz J. F., Mochmann H. C., Erdur H., Tutuncu S., Haeusler K. G., Grittner U., et al. Prognostic relevance of cardiac troponin T levels and their dynamic changes measured with a high-sensitivity assay in acute ischaemic stroke: analyses from the TRELAS cohort. Int J Cardiol. 2014;177(3):886-93.
155. Rutten-Jacobs L. C., Arntz R. M., Maaijwee N. A., Schoonderwaldt H. C., Dorresteijn L. D., van Dijk E. J., de Leeuw F. E. Long-term mortality after stroke among adults aged 18 to 50 years. JAMA. 2013;309(11):1136-44.
156. Sposato L. A., Lam M., Allen B., Shariff S. Z., Saposnik G., Group Paradise Study. First-Ever Ischemic Stroke and Incident Major Adverse Cardiovascular Events in 93 627 Older Women and Men. Stroke. 2020;51(2):387-94.
157. Ferrone S. R., Boltyenkov A. T., Lodato Z., O'Hara J., Vialet J., Malhotra A., et al. Clinical Outcomes and Costs of Recurrent Ischemic Stroke: A Systematic Review. J Stroke Cerebrovasc Dis. 2022;31(6):106438.
158. van Wijk I., Kappelle L. J., van Gijn J., Koudstaal P. J., Franke C. L., Vermeulen M., et al. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. Lancet. 2005;365(9477):2098-104.
159. DeFilippis A. P., Young R., Carrubba C. J., McEvoy J. W., Budoff M. J., Blumenthal R. S., et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med. 2015;162(4):266-75.

160. Johnston S. C., Rothwell P. M., Nguyen-Huynh M. N., Giles M. F., Elkins J. S., Bernstein A. L., Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007;369(9558):283-92.
161. Wardlaw J. M., Brazzelli M., Chappell F. M., Miranda H., Shuler K., Sandercock P. A., Dennis M. S. ABCD2 score and secondary stroke prevention: meta-analysis and effect per 1,000 patients triaged. Neurology. 2015;85(4):373-80.
162. Beatty A. L., Ku I. A., Bibbins-Domingo K., Christenson R. H., DeFilippi C. R., Ganz P., et al. Traditional Risk Factors Versus Biomarkers for Prediction of Secondary Events in Patients With Stable Coronary Heart Disease: From the Heart and Soul Study. J Am Heart Assoc. 2015;4(7).
163. Lindholm D., Lindback J., Armstrong P. W., Budaj A., Cannon C. P., Granger C. B., et al. Biomarker-Based Risk Model to Predict Cardiovascular Mortality in Patients With Stable Coronary Disease. J Am Coll Cardiol. 2017;70(7):813-26.
164. Marston N. A., Bonaca M. P., Jarolim P., Goodrich E. L., Bhatt D. L., Steg P. G., et al. Clinical Application of High-Sensitivity Troponin Testing in the Atherosclerotic Cardiovascular Disease Framework of the Current Cholesterol Guidelines. JAMA Cardiol. 2020;5(11):1255-62.
165. Merkler A. E., Gialdini G., Murthy S. B., Salehi Omran S., Moya A., Lerario M. P., et al. Association Between Troponin Levels and Embolic Stroke of Undetermined Source. J Am Heart Assoc. 2017;6(9).
166. Yaghi S., Chang A. D., Ricci B. A., Jayaraman M. V., McTaggart R. A., Hemendinger M., et al. Early Elevated Troponin Levels After Ischemic Stroke Suggests a Cardioembolic Source. Stroke. 2018;49(1):121-6.
167. von Rennenberg R., Herm J., Krause T., Hellwig S., Stengl H., Scheitz J. F., et al. Elevation of cardiac biomarkers in stroke is associated with pathological findings on cardiac MRI-results of the HEart and BRain interfaces in Acute Stroke study. Int J Stroke. 2022:17474930221095698.
168. Bungard T. J., Ghali W. A., Teo K. K., McAlister F. A., Tsuyuki R. T. Why do patients with atrial fibrillation not receive warfarin? Arch Intern Med. 2000;160(1):41-6.
169. Wilke T., Groth A., Mueller S., Pfannkuche M., Verheyen F., Linder R., et al. Oral anticoagulation use by patients with atrial fibrillation in Germany. Adherence to guidelines, causes of anticoagulation under-use and its clinical outcomes, based on claims-data of 183,448 patients. Thromb Haemost. 2012;107(6):1053-65.

170. Gadsboll K., Staerk L., Fosbol E. L., Sindet-Pedersen C., Gundlund A., Lip G. Y. H., et al. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. Eur Heart J. 2017;38(12):899-906.
171. Gulker J. E., Kroger K., Kowall B., Dingelstadt M., Stang A. Increasing Use of Anticoagulants in Germany and Its Impact on Hospitalization for Intracranial Bleeding. Circ Cardiovasc Qual Outcomes. 2018;11(5):e004470.
172. Patti G., Wang R., Marston X. L., Yeh Y. C., Zimmermann L., Ye X., et al. Anticoagulant Treatment Adherence and Persistence in German Patients with Atrial Fibrillation. Cardiol Ther. 2023;12(2):371-91.
173. Fuster V., Ryden L. E., Cannom D. S., Crijns H. J., Curtis A. B., Ellenbogen K. A., et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace. 2006;8(9):651-745.
174. Du H., Wilson D., Ambler G., Banerjee G., Shakeshaft C., Cohen H., et al. Small Vessel Disease and Ischemic Stroke Risk During Anticoagulation for Atrial Fibrillation After Cerebral Ischemia. Stroke. 2021;52(1):91-9.
175. Purrucker J. C., Holscher K., Kollmer J., Ringleb P. A. Etiology of Ischemic Strokes of Patients with Atrial Fibrillation and Therapy with Anticoagulants. J Clin Med. 2020;9(9).
176. Flaker G. C., Gruber M., Connolly S. J., Goldman S., Chaparro S., Vahanian A., et al. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials. Am Heart J. 2006;152(5):967-73.
177. Fox K. A. A., Velentgas P., Camm A. J., Bassand J. P., Fitzmaurice D. A., Gersh B. J., et al. Outcomes Associated With Oral Anticoagulants Plus Antiplatelets in Patients With Newly Diagnosed Atrial Fibrillation. JAMA Netw Open. 2020;3(2):e200107.
178. Shoamanesh A., Mundl H., Smith E. E., Masjuan J., Milanov I., Hirano T., et al. Factor XIa inhibition with asundexian after acute non-cardioembolic ischaemic stroke

(PACIFIC-Stroke): an international, randomised, double-blind, placebo-controlled, phase 2b trial. Lancet. 2022;400(10357):997-1007.
179. Sharma M., Molina C. A., Toyoda K., Bereczki D., Bangdiwala S. I., Kasner S. E., et al. Safety and efficacy of factor XIa inhibition with milvexian for secondary stroke prevention (AXIOMATIC-SSP): a phase 2, international, randomised, double-blind, placebo-controlled, dose-finding trial. Lancet Neurol. 2024;23(1):46-59.
180. Kar S., Doshi S. K., Alkhouli M., Camm A. J., Coylewright M., Gibson M. C., et al. Rationale and design of a randomized study comparing the Watchman FLX device to DOACs in patients with atrial fibrillation. Am Heart J. 2023;264:123-32.
181. HealthCare Bayer. OCEANIC-AF-Studie aufgrund mangelnder Wirksamkeit vorzeitig abgebrochen: Bayer HealthCare; 2023 [Available from: https://www.bayer.com/media/oceanic-af-studie-aufgrund-mangelnder-wirksamkeit-vorzeitig-abgebrochen/]
182. Whitlock R. P., Belley-Cote E. P., Paparella D., Healey J. S., Brady K., Sharma M., et al. Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. N Engl J Med. 2021;384(22):2081-91.
183. Scheitz J. F., Nolte C. H., Doehner W., Hachinski V., Endres M. Stroke-heart syndrome: clinical presentation and underlying mechanisms. Lancet Neurol. 2018;17(12):1109-20.
184. Sposato L. A., Hilz M. J., Aspberg S., Murthy S. B., Bahit M. C., Hsieh C. Y., et al. Post-Stroke Cardiovascular Complications and Neurogenic Cardiac Injury: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;76(23):2768-85.

8. Danksagung

Mein großer Dank gilt zunächst dem Direktor der Klinik für Neurologie der Charité, Herr Professor Dr. Matthias Endres, sowie dem Standortleiter am Campus Benjamin Franklin, Herr Professor Dr. Heinrich Audebert, dass ich an den von Ihnen geleiteten Institutionen meine klinische, wissenschaftliche und hochschuldidaktische Ausbildung absolvieren durfte. Weiterhin danke ich dem Berlin Institute of Health (BIH) für die großzügige Förderung im Rahmen des Clinician Scientist Programms.

Besonderen Dank möchte ich darüber hinaus meinen klinischen und wissenschaftlichen Lehrern, Mentoren und Vorbildern aussprechen, ohne deren großzügige Unterstützung, Anleitung und Kritik die wissenschaftlichen Arbeiten nicht möglich gewesen wären, an denen ich beteiligt sein durfte: Herr Professor Dr. Karl Georg Häusler, Herr Professor Dr. Christian Nolte und Herr Professor Dr. Jan Scheitz. Bedanken möchte ich mich auch bei dem Leiter der akademischen Neuroradiologie, Herr Professor Dr. Jochen Fiebach, für seinen fortwährenden Rat und Unterstützung!

Überdies bedanke ich mich bei allen ärztlichen und pflegenden Kolleginnen und Kollegen der Neurologie am Campus Benjamin Franklin, die mich während meiner Ausbildung begleitet und unterstützt haben, insbesondere bei den Mitgliedern der AG Integrative Kardio-Neurologie sowie dem Trial Team des Centrums für Schlaganfallforschung. Ohne die Hilfe und Unterstützung der Studienassistenz, allen voran Kristin Simon und Tatjana Wittenberg, wäre eine erfolgreiche wissenschaftliche Arbeit nicht möglich gewesen! Gleiches gilt für die technische Assistenz der akademischen Neuroradiologie des CSB: Moritz Renner, Birgit Hansel und Claudia Lindner.

Zuletzt möchte ich mich bei meiner Familie bedanken: bei meinen Eltern, die mir meine Ausbildung ermöglicht und mich immer unterstützt haben; bei meiner Frau Sophie, für Ihre Großzügigkeit, Toleranz, Zuwendung und Unterstützung in allen Lebenslagen und bei unseren Kindern Anton, David und Jakob: einfach dafür, dass es sie gibt.

9. Eidesstattliche Erklärung

Erklärung gemäß § 4 Abs. 3 (l) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,

- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern und Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,

- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Berlin, den 02.05.2024 Dr. med. Simon Hellwig, M.Sc.