Acute cerebral infarcts in multiple arterial territories

The Bergen NORSTROKE study

Vojtech Novotny

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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UNIVERSITY OF BERGEN

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Haukeland University Hospital

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NORSTROKE
Bergen Stroke Research Group

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Abbreviations

Common nouns

ACA	anterior cerebral artery
ACI	acute cerebral infarct
ADC-MRI	apparent diffusion coefficient magnetic resonance imaging
AF	atrial fibrillation
APS	antiphospholipid syndrome
AV	anatomical variation
BA	basilar artery
BI	Barthel Index
CBF	cerebral blood flow
CCA	common carotid artery
CE	cardiogenic embolism
CI	cerebral infarct
CT	computed tomography
DALYs	disability adjusted life years
DM	diabetes mellitus
DVT	deep venous thrombosis
DWI-MRI	diffusion-weighted magnetic resonance imaging
ECG	electrocardiography
ESUS	embolic stroke of undetermined source
fPCA	fetal posterior cerebral artery
ICA	internal carotid artery
ICM	insertable cardiac monitor
ICH	intracranial hemorrhage
IE	Infective endocarditis
IS	ischemic stroke
IVT	intravenous thrombolysis
LAA	large artery atherosclerosis
LVO	large vessel occlusion
LVT	left ventricular thrombus
MACI	acute cerebral infarct(s) in multiple arterial territories
MACI-M	acute cerebral infarct(s) in multiple arterial territories with multi-territory clinical manifestation
MACI-S	acute cerebral infarct(s) in multiple arterial territories with single-territory clinical manifestation
MCA	middle cerebral artery
MI	myocardial infarction
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
MT	mechanical thrombectomy
NBTE	non-bacterial thrombotic endocarditis
NIHSS	The National Institutes of Health Stroke Scale
OD	other disease
PCA	posterior cerebral artery

PCI	percutaneous coronary intervention
PFO	patent foramen ovale
SACI	acute cerebral infarct(s) in a single arterial territory
SLE	systemic lupus erythematosus
STEMI	ST-elevation myocardial infarction
SVD	small vessel disease
TEE	transesophageal echocardiography
TIA	transient ischemic attack
TTE	transthoracic echocardiography
UE	undetermined etiology
VA	vertebral artery

Trials, organizations, etc.

ASA	American Stroke Association
ARCH trial	Aortic Arch Related Cerebral Hazard Trial
ASCO	Atherosclerosis, Small vessel disease, Cardiac source, Other cause
ASCOD	Atherosclerosis, Small vessel disease, Cardiac source, Other Cause. Dissection
CCS	The Causative Classification of Stroke system
CHANCE trial	Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events
NORSTROKE	the Norwegian Stroke Research Registry
REDUCE trial	Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke
RESPECT trial	Patent Foramen Ovale Closure or Medical Therapy After Stroke
SSS-TOAST	Stop Stroke Study TOAST system
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
WHO	World Health Organization

Abstract

Introduction

The majority of acute cerebral infarcts results from an occlusion of one single cerebral artery followed by loss of blood supply to the respective arterial territory. However, several independent arterial territories may be affected if more than one cerebral artery is occluded simultaneously. Acute cerebral infarcts in multiple arterial territories (MACI) account for 10 to 20 % of all ischemic strokes. MACI may have distinct pathophysiological and clinical features differing from acute cerebral infarct(s) in a single arterial territory (SACI).

Aims

In this dissertation, we sought to give a broad description of patients with MACI. The aim of the first two papers was to clarify pathophysiological mechanisms in regards to the etiology. In the third paper, we assessed short-term outcome and complications within the first week after the hospital admission. The fourth paper sheds light on the clinical manifestation on admission.

Methods

We used data from the Bergen NORSTROKE registry. We included only patients with acute cerebral infarct(s) (ACI) confirmed by diffusion-weighted magnetic resonance imaging (DWI-MRI) consecutively admitted to the stroke unit at Haukeland University Hospital. The first two papers are based on a cohort of 2125 patients admitted from 2006 to 2013. The last two papers are based on a cohort of 3343 patients admitted in an extended time frame from 2006 to 2016. MACI was defined as more than one non-continuous ischemic lesion in more than one arterial cerebral territory; either left and/or right carotid artery territory and/or basilar artery territory.

Results

The proportion of patients with MACI was approximately 9% of all ACI patients. The paper-I confirmed that cardiogenic embolism (CE), as defined by TOAST criteria, is the most frequent underlying etiology of MACI. The paper-II showed a positive correlation between the time from stroke onset to MRI examination and frequency of large artery atherosclerosis (LAA)-associated MACI. There was no correlation between the time from stroke onset to MRI examination and frequency of CE-

associated MACI. These findings suggest that CE-associated MACI occur simultaneously as a shower of emboli, while LAA-associated MACI happens rather successively over time. The paper-III showed that patients with MACI have a worse short-term outcome within the first week after the admission compared to patients with SACI. Moreover, MACI was associated with more in-hospital complications, namely deep venous thrombosis and myocardial infarction. The paper-IV showed that 72% of patients diagnosed with MACI presented with a single-territory clinical manifestation (MACI-S) on admission. MACI-S was associated with less than five ischemic lesions on DWI-MRI, involvement of the left hemisphere, and a partial anterior cerebral infarct stroke syndrome (PACI) as defined by the Oxfordshire Community Stroke Project (OCSP) classification. This finding emphasizes the essential role of MRI examination for final diagnosis of MACI.

Conclusion

The data presented in this dissertation show that patients with MACI differ in many clinical aspects from patients with SACI. Our findings add new knowledge to this less documented field of stroke medicine and may help to improve the diagnostic and therapeutic approaches in these patients.

List of publications

This dissertation is based on the following papers:

Paper-I **Acute cerebral infarcts in multiple arterial territories associated with cardioembolism**

V Novotny, L Thomassen, U Waje-Andreassen, H Næss

Acta Neurologica Scandinavica, 2017; 135:346-351

Paper-II **Time patterns in multiple acute cerebral infarcts**

V Novotny, AN Khanevski, L Thomassen, U Waje-Andreassen, H Næss

International Journal of Stroke, 2017; 12(9):969-975

Paper-III **Short-Term Outcome and In-Hospital Complications After Acute Cerebral Infarcts in Multiple Arterial Territories**

V Novotny, AN Khanevski, AT Bjerkreim, CE Kvistad, A Fromm, U Waje-Andreassen, H Næss, L Thomassen, N Logallo

Stroke, 2019; 50.12: 3625-3627

Paper-IV **Clinical manifestation of acute cerebral infarcts in multiple arterial Territories**

V Novotny, S Aarli, AN Khanevski, AT Bjerkreim, CE Kvistad, A Fromm, U Waje-Andreassen, H Naess, L Thomassen, N Logallo

Under review.

Introduction

Cerebral infarct

Definition

Cerebral infarct (CI) / Ischemic stroke represent the major category of stroke. CI is a focal brain injury due to acute disruption of nutrition and oxygen supply to the brain tissue. This is followed by a corresponding neurological deficit or death.

The latest consensus on CI definition follows the advances in medical technology achieved in the past decades. Previously, the definitions were based solely on the clinical manifestation, not reflecting the tissue-based verification of the CI. This resembles the former World Health Organization (WHO) definition from 1980: ”Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.”[1]

However, the additional implementation of modern neuroimaging changed the concept of CI diagnosis. The definition of CI also incorporates a silent CI, characterized by no clinical symptoms, yet by a focal brain injury identified by neuroimaging.[2] A more precise definition of central nervous system infarct endorsed by American Stroke Association (ASA) from 2013 is: “Brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury.”[3] This change has an implication for the stroke epidemiology worldwide since the prevalence of silent CI ranges from 10% to 20% among patients over 70 years.[4] The unavailability of MRI in less developed countries may, however, potentially underestimate the true rates.

The introduction of diffusion-weighted magnetic resonance imaging (DWI-MRI) in the routine diagnostic work-up of stroke also led to a tissue-based redefinition of transient ischemic attack (TIA). Several studies have shown that up to 50% of patients diagnosed with TIA based on the clinical, time-based definition, have evidence of focal brain injury on MRI. These findings left behind the arbitrary 24 hours period as obsolete. The assumption that transient neurological deficit could not be accompanied by irreversible brain injury is not valid anymore. The new definition endorsed by ASA

is: “A transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction”.[5]

Epidemiology & burden of stroke

A significant improvement in stroke therapy and prevention has been achieved in most of the developed countries. However, comparing the years 1990 and 2010, stroke remains the second most frequent cause of mortality after ischemic heart disease. Moreover, stroke moved from the 5th to the 3rd most common cause of disability worldwide.[6] These epidemiological data reflect both regional and ethnic differences, but also the availability of healthcare resources and public stroke awareness. All of these factors have an impact on morbidity, mortality, etiology of stroke and their trends over time.

In 2016, there were 13.7 million new stroke cases worldwide, with a reduction of age-standardized incidence by 8.1% from the year 1990. Furthermore, there was a clear reduction in global age-standardized mortality rate and disability-adjusted life years (DALYs) by 34.2% and 36.2%, respectively.[7] The relative numbers have satisfying progression, however the absolute numbers are moving the opposite direction, mostly due to rapid population growth and ageing. Furthermore, there are significant regional differences. While the incidence of stroke is decreasing in high-income countries; the incidence, mortality and DALYs in many low- and middle-income countries are increasing. This phenomenon reflects the so-called epidemiological transition of developing countries caused by an increase in modifiable risk factors, which so far were reduced effectively in the developed countries.

Thus, despite relatively positive progression in high income-countries, the global burden of stroke is increasing, and further research within the field of implementing and improving primary prevention worldwide is crucial.

According to the national Norwegian and American reports, 87% of strokes are ischemic, and 13% are hemorrhagic.[8, 9] Globally, the rate of intracerebral hemorrhage (ICH) is higher than in the Caucasian population alone. This reflects a higher incidence of ICH in Asia, low- and middle-income countries where hypertension as

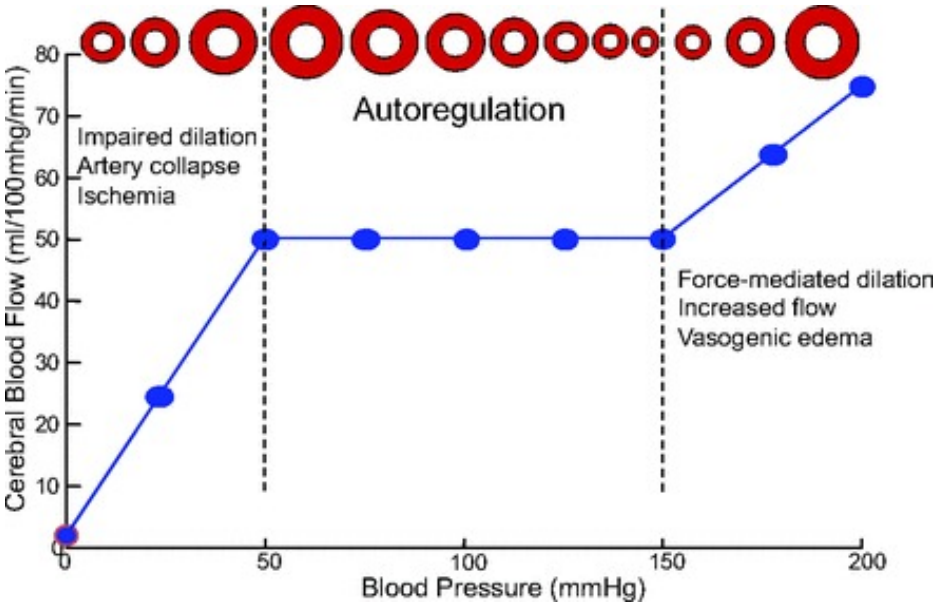
the critical factor in the pathogenesis is more prevalent.[10] Lower rates of ICH in the high-income countries reflect the effective prevention of modifiable risk factors, including hypertension. There are still huge gaps between regions regarding the prevention of modifiable risk factors, screening for conditions increasing risk of stroke such as diabetes mellitus (DM), atrial fibrillation (AF) or hypertension and availability of appropriate secondary prevention for recurrent stroke.

Pathophysiology

Cerebral blood flow and the penumbra concept

Around 20% of the cardiac output is directed to the brain, although the brain represents only 2% of the total body weight. In contrast to other organs of the human body, the brain tissue keeps only a very low amount or no reserves of nutrition and oxygen, which may be utilized in case of acute ischemia. The brain is, therefore, completely dependent on continuous blood supply. The primary defense mechanism against misbalance in cerebral blood flow (CBF) is cerebral autoregulation. It maintains a constant level of CBF via constriction or dilatation of cerebral blood vessels in response to, among others, variations in mean arterial pressure. However, the cerebral autoregulation is only effective in the range of mean arterial pressure from approximately 60 to 150 mmHg. Outside these thresholds, the compensatory capability of autoregulation collapses. (Figure 1) In ACI, the cerebral perfusion pressure within the affected area falls, followed by the compensatory response. However, an immediate lack of oxygen and glucose in the core of ischemia is unavoidable. If perfusion is not restored soon enough, irreversible ischemia-induced brain tissue damage occurs (infarct core).

Figure 1. Autoregulation of cerebral blood flow



Adapted from Pires et al., 2013

Perfusion imaging techniques based on computed tomography (CT) or magnetic resonance imaging (MRI) are able to measure the amount of blood passing through a defined area of brain tissue at a certain time - absolute CBF. An essential feature of perfusion techniques is the capability of measuring the relative CBF, thus distinguish salvageable brain tissue (penumbra) from an infarct core. The differentiation between salvageable brain tissue at risk and infarcted tissue irreversibly lost due to ischemia is nowadays utilized in acute reperfusion therapies.

The average values for CBF in the healthy brain are 50 +/- 15 ml/ 100 g / min for grey matter and 22 +/- 5 ml /100 g/ min for the white matter. If the CBF falls below these levels, the cerebral tissue enters the stage of ischemic risk (penumbra). The critical average threshold of CBF for penumbra based on CT/MRI perfusion imaging has been reported from 14 to 35 ml/100 g of brain tissue. CBF values under 4.8 to 8.4 ml/100 g defines an infarct core, where the neuronal electrical activity ceases, and the brain tissue is irreversibly damaged despite reperfusion therapy.[11]

The CBF is also secured by an extensive collateral blood circulation (CBC) preserving blood supply in case of cerebral artery occlusion. The primary CBC route is secured by the circle of Willis, connecting the left and right anterior and posterior circulations via corresponding communicating arteries. The secondary CBC routes are far more complex, comprising connections between the internal and external carotid artery but also deep connections between a middle cerebral artery (MCA), posterior cerebral artery (PCA) and anterior cerebral artery (ACA). Perforator and leptomeningeal collateral systems play a crucial role when occlusion of an intracranial artery occurs. In addition, branches of the external carotid artery, such as ophthalmic, meningeal and occipital arteries, are recruited in case of internal carotid artery (ICA) occlusion.[12]

However, human cerebral vasculature varies from person to person. The state and functionality of CBC and cerebral autoregulation determine the progress of cerebral ischemia as such. The transformation time of reversible penumbra into an irreversible infarct core is largely individual and relies strongly on the unique capability of the brain to compensate the ischemia.[13] Today, the efficacy of acute reperfusion therapy by either intravenous thrombolysis (IVT) or mechanical thrombectomy (MT) is based on the concept that the process of developing ACI is gradual, and the infarct core expands in time. The main goal of reperfusion therapies is to save the salvageable brain tissue, represented by the area of benign oligemia and penumbra surrounding the gradually expanding infarct core. This also supports the concept of individual time window-based acute reperfusion therapy. The current arbitrary time-window of 4.5 hours for IVT[14] and previous time-window of 6 hours for MT may exclude patients whose individual time window is wider due to great collateralizations, and who still benefit from reperfusion therapies beyond the formal time windows. The tissue-based patient selection to acute reperfusion therapy by MT using advanced CT and MRI techniques was recently proven successful.[15, 16] Advanced imaging techniques will likely increasingly become an essential part of acute stroke diagnostics and therapy.

Mechanism of arterial occlusion

Cerebral ischemia evolves after either sudden or gradual occlusion of a cerebral artery. The occlusive process usually occurs by either embolism or thrombosis, both leading to hyporfusion.[17]

Embolism

Embolism is a broad term comprising all ischemic events where the occlusion is caused by a blood clot or other debris originating proximally from the site of the occlusion. The most common sources of the embolic stroke are cardiogenic embolism (CE) and artery-to-artery embolism from aorta, from carotid or vertebral arteries, or from intracranial arteries. Several clinical characteristics may indicate an embolic stroke. The symptomatology depends on the size, number of emboli and time pattern of embolization. However, the onset of neurological deficit is often sudden, with maximal severity at the beginning of the stroke.[18] Symptoms may fluctuate in intensity as the emboli dissolves or fragmentizes and passes to the distal vessels of smaller calibers. Both simultaneous and successive involvement of multiple arterial territories is characteristic for embolism as the source of emboli often lies proximally to aortic arch.[19] The embolic stroke tends to affect distal parts of the cerebral arterial tree, often appearing as cortical lesions rather than lesions in deeper structures of the brain. Embolic stroke also has a higher tendency of hemorrhagic transformation as a consequence of acute vessel wall damage and disruption. The etiologies of CE are divided into two categories based on the degree of risk for embolism (Table 1).

Table 1. Cardiogenic and aortic sources of embolism

High primary stroke risk	Low or uncertain primary stroke risk
Chronic atrial fibrillation	*Cardiac sources*
Paroxysmal atrial fibrillation	Mitral annular calcification
Left atrial thrombus	Patent foramen ovale
Left ventricular thrombus	Atrial septal aneurysm
Sick sinus syndrome	Atrial septal aneurysm and patent foramen ovale
Atrial flutter	Left ventricular aneurysm without thrombus
Recent myocardial infarction (within one month)	Left atrial spontaneous echo contrast ("smoke")
Mitral stenosis or rheumatic valve disease	Congestive heart failure, ejection fraction <30%
Bioprosthetic and mechanical heart valves	Apical akinesia
Chronic myocardial infarction with low ejection fraction (<28 %)	Wall motion abnormalities (hypokinesia, akinesia, dyskinesia) other than apical akinesia
Dilated cardiomyopathy (left ventricular dilatation with ejection fraction <40% or fractional shortening <25%)	Hypertrophic cardiomyopathy
Non-bacterial thrombotic endocarditis	Left ventricular hypertrophy
Infective endocarditis	Left ventricular hypertrabeculation/ non-compaction cardiomyopathy
Papillary fibroelastoma	*Aortic sources*
Left atrial myxoma	Complex aortic atheroma (protruding >4 mm, or mobile debris, or plaque ulceration)

Adapted from Ay H et al. Ann Neurol 2005

Thrombosis

In contrast to embolism, thrombosis refers to an occlusion occurring on the site of a pathological process in the wall of the affected vessel, such as on top of preexisting atherosclerosis or as a result of arterial dissection. However, both atherosclerotic plaque and arterial dissection may also become a source of distal embolization. The onset of the neurological deficit is often gradual since the occlusion of the affected artery often evolves over time.

Based on the caliber of the affected arteries, two main pathomechanisms are distinguished - small vessel disease (SVD) and large vessel disease (LVD). Large vessel disease mostly refers to large artery atherosclerosis (LAA) within either extracranial or intracranial arteries of a bigger caliber. The terms LVD and LAA are often used interchangeably in relation to the TOAST classification. SVD primarily affects the penetrating arteries arising from the circle of Willis, and from the MCA and the basilar artery (BA) supplying subcortical structures of the brain. SVD is responsible for approximately 25% of all CI. SVD is also one of the most common

causes of dementia. The prevalence of SVD grows rapidly with age reaching almost 100% in patients over 90 years old[20], but varies largely in degree. The pathophysiology of SVD is not entirely understood. However, hypertension, DM, and ageing play an essential role in the pathogenesis. The arterial walls undergo pathological processes including lipohyalinosis and formation of microatheromas and microaneurisms.[21] SVD appears as disseminated white hyperintensities (leukoaraiosis) on fluid-attenuated inversion recovery (FLAIR) MRI. Critical ischemia then manifests as small ischemic lesions appearing as small lacunes. Simultaneous multiple-territory distribution of lacunar stroke is, however, rare as occlusions probably occur independently of each other.[22]

Hypoperfusion

Conditions such as myocardial infarction (MI), pulmonary embolism, severe arrhythmia or cardiac arrest are often accompanied by a reduced or complete failure of cardiac output. Systemic hypoperfusion may lead to an acute reduction of cerebral blood flow followed by cerebral ischemia. ICA stenosis may further aggravate its progress. Hypoperfusion-associated (watershed) stroke usually appears as non-focally distributed lesions along the border-zone of two or three main cerebral arteries.[23]

Prothrombotic blood disorders

Prothrombotic blood disorders are often discussed as a separate pathophysiological entity since both embolism and thrombosis may co-exist. In young stroke patients and patients with so-called cryptogenic stroke, disturbances in blood coagulation should always be taken into consideration. There are many systemic and blood disorders that may promote clot formation and subsequent stroke. A tendency to the hypercoagulable state may be inherited, such as in Factor V Leiden or protein C or S deficiency. However, some inflammatory diseases and malignancies may cause an acquired hypercoagulable state often associated with acute cerebral infarcts in multiple arterial territories (MACI).[24]

Classification

Cerebral infarct (CI) is a heterogeneous disorder that may be caused by over 200 so far known etiologies. There have been proposed several classification systems for CI. The

main purpose is to establish a simple and reproducible clinical tool in daily practice and research. An ideal classification system should be capable of determining the most probable cause and mechanism for the best therapeutic decision-making.

There are two types of classification systems, either causative or phenotypic. The causative system determines the most probable etiology, yet neglecting other competing and less probable etiologies. The phenotypic classification, on the other hand, stratifies alternative etiologies by a degree of probability.[25]

When evaluating the feasibility and quality of a classification system, its reliability must be considered. The reliability shows the reproducibility of the findings performed by either the same (intra-rater reliability) or two different observers (inter-rater reliability). The reliability is expressed by the kappa coefficient (κ), which shows the strengths of agreement between two observers. (Table 2)

Table 2. Observer agreement measure stratification

Kappa	Degree of agreement
≤0.00	Disagreement
0.00-0.20	Slight agreement
0.21-0.40	Fair agreement
0.41-0.60	Moderate agreement
0.61-0.80	Substantial agreement
0.81-1.00	Almost perfect agreement

Adapted from JR Landis & GG Koch, 1977 [26]

The most widely used classification system for CI is the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification representing the causative classification system.[17] TOAST is simple to use but has several drawbacks. It neglects competing etiologies that are less probable. Furthermore, its reliability is not high. While the inter-rater reliability for CE and large artery atherosclerosis (LAA) seems to be quite strong ($\kappa \approx 0.8$), it is rather weak for the SVD and stroke of undetermined etiology (UE) ($\kappa \approx 0.53$ and $\kappa \approx 0.4$, respectively).[27] Based on TOAST criteria, only subcortical lesions with less than 15 mm in diameter accompanied by a lacunar clinical syndrome are classified as SVD. The strict TOAST criteria, based originally on CT findings,

have been challenged for inaccuracy and non-reliability. MRI studies showed that lacunar infarcts may grow in the acute phase and reach over 20 mm in diameter. In patients, where the evaluation of intracranial vessels was not performed sufficiently, subcortical lesions caused by LAA may be categorized as SVD.[28] Only patients with stenosis >50% on the ipsilateral side of the symptomatic lesion are classified as LAA. Therefore, CI accompanied by stenosis <50% and subcortical lesions >15 mm are classified as UE subtype. This also contributes to the fact that around 40% of all patients with CI end up within this category.

Along with the new neuroimaging techniques, TOAST was later on updated to the Stop Stroke Study TOAST system (SSS-TOAST) in order to overcome some of the drawbacks. SSS-TOAST assigns to each causative subtype one of three grades of evidence, “evident”, “probable” or “possible”. The maximum size for a subcortical lesion was increased to 20 mm in order to improve the reliability within the SVD category. Furthermore, subcortical lesions of over 20 mm in size may still be classified as SVD if no other cause is present. Embolic lesions in patients with ipsilateral stenosis <50% with protruding plaque into the vessel lumen are classified as LAA if no other evidence is present. SSS-TOAST also proposed a new sub-category of the undetermined CI subtype, cryptogenic stroke.[29] These thorough changes decreased the proportion of undetermined cause from 40% to only 4% and increased the reliability within this category to κ=0.8. The SSS-TOAST is, however, quite complicated, thus not much used in daily practice. Therefore, a computerized on-line version of SSS-TOAST with few discrete changes known as The Causative Classification of Stroke System (CCS) was introduced in 2007.[30] The web-based platform is freely available. It provides an overview of the etiologies based on the grade of evidence and is quite easy to use.

The ASCO (Atherosclerosis, Small vessel disease, Cardiac source, Other cause) classification represents the first purely phenotypic system.[31] The main advantage of ASCO over TOAST is the inclusion of all potential causes simultaneously assigning corresponding grades of evidence to each of them. This provides a useful overview of all potential risk factors. In 2013, an updated version was introduced known as Atherosclerosis, Small vessel disease, Cardiac source, Other Cause, Dissection

(ASCOD), where dissection became a separate category. [32] This version also redefined significant stenosis by lowering the stenosis degree from 70% to 50%. (Table 3)

Table 3. Classification systems for ischemic stroke

	TOAST	SSS-TOAST	CCS	ASCO	ASCOD
Subtypes	1. LAA 2. CE 3. SVD 4. OD 5. UE	1. LAA 2. CE 3. SVD 4. OD 5. UE 5a. - Cryptogenic embolism - Other cryptogenic - incomplete evaluation 5b. unclassified	1. Supra-aortic LAA 2. CE 3. SVD 4. OD 5. UE 5a - Cryptogenic embolism - Other cryptogenic - incomplete evaluation 5b. unclassified	1. Atherosclerosis 2. SVD 3. CE 4. OD	1. Atherosclerosis 2. SVD 3. CE 4. OD 5. Dissection
Grade of diagnostic certainty	1. Probable 2. Possible	1. Evident 2. Probable 3. Possible	1. Evident 2. Probable 3. Possible	0. Disease absent 1. Potentially causal 2. Causality uncertain 3. Unlikely causal 9. insufficient work-up	0. Disease absent 1. Potentially causal 2. Causality uncertain 3. Unlikely causal 9. insufficient work-up
Max. diameter for lacunar lesion	15 mm	20 mm	20 mm	15 mm	15 mm
LAA diagnose criteria	>50% stenosis in ipsilateral ICA	>50% in ipsilateral ICA (evident) <50% stenosis with protruding atheroma (possible)	>50% stenosis with plaque ulceration or thrombus. <50% stenosis with plaque ulceration and thrombus (evident)	>50% <50% with endoluminal thrombus. Mobile thrombus at aortic arch	>50% <50% with endoluminal thrombus. Mobile thrombus at aortic arch
Aortic atherosclerosis	Not described	Not described	Classified as CE	Classified as LAA	Classified as LAA
Main advantages	- Simple & convenient - Widely used	- Lower prevalence of UE - Better reliability - Grade of evidence	- SSS-TOAST features - Web-based platform - Excellent reliability	- provides overview of non-causative risk factors - ideal for epidemiology	- Same as ASCO - LAA update (lowering of degree of stenosis in both Atherosclerosis)

		- Cryptogenic stroke as a separate entity		- excellent reliability	
Main disadvantages	- High prevalence of UE - Low reliability - Neglects competing causes	- Complex - Complicated to use in daily practice	- Require internet access	- Not widely used - Complicated - Not easy interpretation	- Same as ASCO

Adapted from Kim et al 2013 & Radu et al 2017.

LAA - large artery atherosclerosis; CE - cardiogenic embolism; SVD - small vessel disease; OD - other disease; UE - undetermined etiology; TOAST - Trial of ORG 10172 in Acute Stroke Treatment; SSS-TOAST - Stop Stroke Study TOAST system; CCS - The Causative Classification of Stroke system; ASCO - Atherosclerosis, Small vessel disease, Cardiac source, Other Cause; ASCOD - Atherosclerosis, Small vessel disease, Cardiac source, Other Cause. Dissection; ICA - internal carotid artery

Acute cerebral infarcts in multiple arterial territories (MACI)

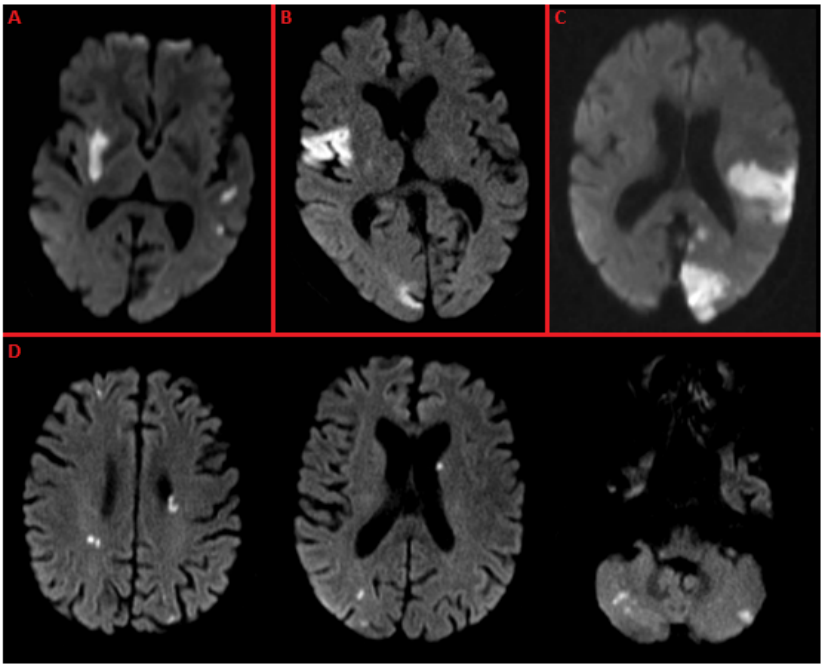
Patients with MACI represent a subgroup of patients with distinct epidemiological and clinical features. Compared to acute cerebral infarct(s) in a single arterial territory (SACI), MACI may give rise to an unusual clinical picture and have a different etiological spectrum.[33] Thus, the diagnostic work-up and the choice of secondary prevention may require a different approach. There have been published several studies aiming at MACI. However, different methodologies and different definitions of MACI have led to contradictory conclusions. Therefore, many epidemiological and clinical aspects remain unclear.

Definition

There is no established definition of MACI used by the stroke society. The cerebral circulation is complex, and every clinician may have a different point of view. However, for simplicity reasons and reliability of the data, a reasonable definition classifies MACI related to the three main arterial territories. There are two anterior territories supplied by the left and right ICA arising from the left and right CCA, respectively. The one posterior territory is supplied by the basilar artery arising from the confluence of the left and right vertebral arteries.[34] ACI must be distributed in at

least two out of the three arterial territories to be defined as MACI. Figure 2 shows four possible topographical distributions of MACI as seen on DWI-MRI.

Figure 2. The combinations of affected arterial territories based on the MACI definition used in the dissertation



A–multiple acute cerebral infarcts distributed in both anterior territories; B-multiple acute cerebral infarcts distributed in the right anterior territory and in the posterior territory; C-multiple acute cerebral infarcts distributed in the left anterior territory and in the posterior territory; D-multiple acute cerebral infarcts distributed in all three territories

Epidemiology

The frequencies of MACI differ between studies and range between 4% and 24%. An overview of studies using MACI as defined in this dissertation is shown in table 4. Slightly different population characteristics and applied methodologies may have had an impact on the final results.

Altieri et al. and Baird et al. reported low frequencies of 5.6% and 3.4%, respectively.[35, 36] These studies may be difficult to interpret since the sample sizes were small and therefore barely representative for the general stroke population.

Another five studies comprising bigger sample sizes showed frequencies in the range of 9.7 % - 14.5 %.[33, 37-40] Three studies of Asian origin reported frequencies between 9.4 - 16%. [41-43] This indicates that the rate among Asians may be similar to the rate among Caucasians.

The stroke group at Charité – Universitätsmedizin Berlin published two studies reporting significantly higher frequencies of MACI (17% and 24%) among consecutively admitted patients with CI.[44, 45] In contrast to other studies, they used 3.0T MRI, which is probably more sensitive to reveal ischemic micro-lesions, normally not visible on 1.5T MRI. The only study aiming at MACI in young stroke patients (age 15-49 years) reported a frequency of 7.5% using a 1.5T MRI.[46]

A simple literature-based pooled analysis comprising 21 studies was recently published.[47] In total, 15056 patients with ACI were enrolled, of which 1914 patients (13%) had MACI. The studies included in the analysis were, however, not specified, and the inclusion criteria slightly differed from those used in this dissertation.

It is not known if gender or age may influence the occurrence of MACI.

Table 4. The frequencies of MACI in selected studies

	Reference	Rate of MACI	MACI (%)	Country	Imaging modality
1.	Altieri 1999	8/142	5.6	CH –Lausanne	1.5T DWI
2.	Baird 2000	2/59	3.4	USA - Boston	1.5T DWI
3.	Roh 2000	31/329	9.4	KR - Seoul	1.5T DWI
4.	Moulin 2000	174/1776	9.8	FR-Besancon	CT/1.5T MRI
5.	Caso 2004	29/182	16	CH - Zurich	1.5T DWI
6.	Cho 2007	67/685	9.8	Hong Kong	1.5T DWI
7.	Braemswig 2013	57/340	17	DE - Berlin	3.0T DWI
8.	Depuydt 2014	80/824	9.7	FR - Paris	1.5T DWI
9.	Chung 2014	432/2702	16	KR - Seoul	1.5T DWI
10.	Sorgun 2016	83/573	14.5	TR - Ankara	1.5T DWI
11.	Sener 2018	126/988	12.8	TR - Izmir	1.5T DWI
12.	Erdur 2019	240/1000	24	DE - Berlin	3.0T DWI
13.	Mustanoja* 2013	41/548	7.5	FI - Helsinki	1.5T DWI
14.	Akhtar 2019**	1914/15056	12	USA - Chicago	1.5T DWI

*MACI - acute cerebral infarct(s) in multiple arterial territories; * Only young patients (15-49 years); ** Pooled analysis of 21 studies*

The importance of cerebrovascular anatomy

In patients with acute cerebral infarct (ACI), the knowledge of vascular and functional brain anatomy is crucial to make a correct diagnosis and initiate acute reperfusion treatment. CI may affect every part of the brain, and the clinical manifestation may therefore be very diverse. In patients with SACI, the neurological deficit usually corresponds to the affected area of the brain. However, patients with MACI may present with unusual clinical manifestation if several independent arterial territories are affected simultaneously.

The blood supply to the brain is maintained by three major arteries, basilar artery (BA) and left and right ICA. However, the cerebral circulation is characterised by considerable anatomical variations which may have clinical significance in regards to MACI definition.[48]

The posterior arterial territory supplied by BA comprises the brain stem including medulla oblongata, pons and structures of the midbrain, cerebellum and occipital lobes of both cerebral hemispheres. The most frequent anatomical variation in the posterior arterial territory is a partial or complete fetal PCA (fPCA) occurring in 20-30% of individuals.[49, 50] fPCA originates from the ipsilateral ICA, and the occipital lobe is then

mostly supplied from the anterior circulation. These patients may experience ACI distributed in anterior territory and ipsilateral occipital lobe, topographically appearing as MACI in both anterior and posterior arterial territory, confusing the MACI definition.

An important anatomical variation in the anterior circulation, which may interfere with the MACI definition, is unpaired (azygos) ACA occurring in approx. 2% of individuals.[51] Left and right ACA or only single ACA arise from one ICA, which supplies both ACA territories. In these individuals, bihemispheric ACI affecting both ACA territories may occur after embolization from the one supplying ICA. MACI in both anterior territories may also be caused by a cross-flow phenomenon where emboli pass to the ipsilateral but also to the contralateral anterior territory over the anterior communicating artery.[52]

Angiographic imaging of the cerebral arterial tree and the examination of cerebral hemodynamics by transcranial duplex ultrasound may clarify the true mechanisms of such CI.

Etiology

A definite and correct etiology is paramount to initiate effective secondary prevention of recurrent CI. The etiological spectrum of MACI may be different compared to SACI. A proximal source of emboli should always be considered in the first line, including cardiac disease and aortic arch atherosclerosis.[47, 53] However, less common etiologies like uncommon cardiac disorders, hypercoagulable states accompanying malignancies or immunological disorders require more focus in the etiological work-up.[54-56]

Some studies have shown that embolism from the heart or aorta is the most common etiology of MACI.[33, 39, 53] High-risk cardiac sources, predominantly paroxysmal or chronic AF, should be investigated first.

Atrial fibrillation

AF represents one of the most common cardiac arrhythmias and is responsible for up to one-third of all cerebral infarcts (CI), frequently distributed in multiple arterial

territories.[44] Thrombogenesis in AF follows the mechanism of Virchow's triad comprising hemodynamic changes within the atrium, followed by endothelial dysfunction and a hypercoagulable state.[57] AF is traditionally categorized as either paroxysmal or chronic. Paroxysmal AF is characterized by periods of arrhythmia lasting less than seven days with periods of normal sinus rhythm in between. However, up to 30% of paroxysmal AF sooner or later transform into the chronic form.[58] Another classification reflects clinical manifestation and categorizes AF as symptomatic or silent based on accompanying symptoms such as palpitations or chest pain. Patients with AF have a five times higher risk of CI. CI may also be the first clinical sign of silent AF.[59] AF-related CI is characterized by a higher tendency for hemorrhagic transformation, early recurrence and generally less favourable outcome in comparison to non-AF related CI.[60] The incidence of AF increases with age and is expected to increase further due to general ageing of the population.

In AF-associated MACI, the ischemic lesions show mostly cortical distribution on brain imaging.[47] Depuyt et al. reported that 49% of MACI were of CE origin of which 64% caused by AF.[33] Patients with MACI on brain imaging with no signs of chronic AF on electrocardiography (ECG) should always undergo thorough cardiologic examination, including echocardiography and prolonged cardiac monitoring. One-third of patients with unknown etiology (UE) of CI have paroxysmal AF. Long-term cardiac monitoring with cardiac loop recorder or other available monitoring devices may significantly reduce the rate of UE-subtype diagnosis. A score using dichotomized variables including age, presence of cardiac diseases and high serum troponin may also guide therapeutic decision-making.[61]

Aortic embolism

The presence of aortic atherosclerotic plaques usually reflects the overall atherosclerotic profile in the patient. As in carotid atherosclerosis, vascular risk factors such as higher age, hypercholesterolemia, hypertension, and smoking are common in these patients.[62] Aortic plaques associated with a higher risk of embolic CI are referred to as complex or unstable. The risk is aggravated by the presence of a mobile superimposed thrombus.[63] An aortic plaque with thickness over 4 mm increases the risk of recurrent CI four times in comparison to those under 1 mm.[64] Apart from

unstable plaque characteristics, and plaque thickness, proximal location in the aortic arch is of high importance for cerebral embolization. The prevalence of complex aortic atheroma in the general population of elderly Caucasian is approximately 8%, of which 0.2% are located in the aortic arch. The prevalence of complex aortic atheroma in patients with CI is 14 to 21%, of which 2.2% of those are located in the aortic arch.[65]

As in other proximal embolic sources, the aortic arch plaque may cause MACI with a typical pattern of multiple small cortical lesions. The morphology and configuration of the aortic plaque seem to be crucial. The presence of mobile components or plaque ulcerations significantly increases the risk of embolization in multiple arterial teritorries.[53, 66]

Type A aortic dissection (located in ascending aorta) represents another, although less common source of aortic emboli. In approximately 6% of all cases, aortic dissection is complicated by CI or TIA following an embolization from the aortic dissection itself, or due to extension of the dissection into the cervico-cerebral arteries.[67] Aortic dissection patients require a fast and correct diagnosis to initiate acute surgical treatment. Unfortunately, typical related symptoms as chest pain or back pain may be masked by concomitant stroke symptoms due to embolization from the site of dissection. Alertness with regard to aortic dissection as the underlying cause of stroke is mandatory as reperfusion therapy by IVT is contraindicated in these patients.

After standard diagnostic work-up, the cause remains unknown in more than one third of these patients. In patients with MACI, where no cardiac source is found, an aortic source of emboli should be ruled out. Angiographic imaging of the aortic arch or transesophageal echocardiography should be considered in further diagnostic work-up.

There are no clear trial data on the secondary prevention of recurrent CI in patients with complex aortic atheroma. The only one, but prematurely ended ARCH trial, concluded that antiplatelet treatment might be superior to anticoagulation. However, the result was not significant.[68]

Endocarditis

Endocarditis is an inflammatory disease affecting the endocardium. It is characterized by formation of protruding lesions, also called vegetations. Depending on their composition, endocarditis is classified as either infective endocarditis (IE) or nonbacterial thrombotic endocarditis (NBTE). The vegetations are predominantly distributed within the aortic and mitral valve. Both IE and NBTE may be a source of embolization to multiple organs, including the brain. It seems that mitral vegetations have a two times higher risk of cerebral embolization compared to vegetations localized within the aortic valve. This is probably linked to the usually more extensive and larger vegetations within the mitral valve. CI occurs as a complication in approximately 10% of patients with IE and in over 30% of patients with NBTE.

The distribution of ischemic lesions in multiple arterial territories is common due to proximity of the source of embolization.[69, 70] Neuroimaging patterns of IE-associated CI may be very heterogeneous in distribution and size. The ischemic lesions are prone to hemorrhagic transformation due to bacterial component of thrombi. NBTE-associated CI has almost uniformly multiple-territory distribution, but hemorrhagic transformation is less frequent.[70]

NBTE known as Libman-Sacks or marantic endocarditis represents a rare form of endocarditis. It is characterized by usually smaller micro-vegetations, consisting of sterile platelet-fibrin thrombi of non-infectious origin. The NBTE is mostly seen as an accompanying complication of other systemic diseases such as systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) but also advanced-stage malignancies. Predominantly adenocarcinomas, including lung, pancreatic or colorectal adenocarcinoma, give a higher risk of developing NBTE. The pathophysiology is not fully understood, but a hypercoagulable state and endothelial damage play probably an important role. The micro-vegetations in NBTE are very friable due to absence of inflammation. Thus, they tend to give recurrent embolization in multiple arterial territories.[56, 71] MACI may be the first sign of on-going malignant processes or of other NBTE-associated diseases.

Even though NBTE is a rare condition, it is probably overrepresented in patients with MACI and should be taken into consideration in the diagnostic work-up. Because of

the small size of vegetations, NBTE is not easy to diagnose by standard transthoracic echocardiography (TTE). There is evidence that transesophageal echocardiography (TEE) is more sensitive for the diagnosis of NBTE then TTE.[72] Another diagnostic tool aiming on the assessment of the effect of secondary prevention and risk of recurrent embolization in patients with endocarditis, is micro-emboli detection.[73]

Several studies showed that intravenous thrombolysis for ACI related to endocarditis is associated with higher rates of ICH and worse outcome.[74, 75] The treatment is in the first line based on management of the underlying disease in both IE and NBTE. However, the approach to secondary prevention differs. Unlike patients with IE, anticoagulation is routinely used in patients with NBTE, although there are no trials on secondary prevention of ischemic stroke in patients with NBTE. However, unfractionated or low-molecular-weight heparin are today the anticoagulants of choice.[76] Vitamin K antagonist is not effective for NBTE and the effect of direct oral anticoagulants (DOAC) is not well documented. The secondary prevention in patients with IE on the other hand is more complex, and anticoagulation must be weighed carefully against the bleeding risk, which is higher than in patients with NBTE. Surgical treatment may be considered in both IE and NBTE under certain indications such as endocarditis-associated heart failure but also to prevent further embolization.

Large artery atherosclerosis

In patients with unilateral ICA, MACI are rarely seen. However, arterial variations such as fPCA or azygos ACA or cross-flow phenomenon may be an explanation for concomitant lesions in the posterior or contralateral anterior arterial territory.[77] Multifocal SACI are, however, frequent due to recurrent embolism from an unstable ICA stenosis.[78] Multiple emboli or fragmentation of bigger emboli are possible mechanisms. These patients often present with hyperhomocysteinemia, probably due to plaque instability. This may facilitate the differential diagnosis.[79] High-grade stenosis increases the risk of developing watershed infarcts in border-zone areas topographically appearing as MACI.[80] Watershed infarcts may be distributed over the ACA, MCA and PCA arterial territory.

Patent foramen ovale

Patent foramen ovale (PFO) is a reminiscence of the fetal communication between the left and right heart atrium, which fails to close postnatally and persists into adulthood. PFO is not rare, it is present in over 25% of the general adult population and the frequency among the patients with cryptogenic CI is 3-5 times higher. PFO hemodynamically represents a right-to-left shunt and is often attributed to paradoxical embolism in patients with cryptogenic stroke, mainly in young stroke patients.[81] MACI may occur among patients with PFO, but there is no strong evidence that multiple-territory pattern is more frequent in comparison to the non-PFO stroke population.[82] It seems that PFO is associated with MACI in young stroke patients and the location of lesions was predominantly described in the posterior circulation.[83, 84]

There was not a strong consensus whether the PFO closure is superior to antiplatelet therapy alone in the prevention of recurrent stroke. However, three clinical trials showed benefit of PFO closure combined with antiplatelet therapy,[85] [86, 87] and this procedure has become a routine in young cryptogenic stroke patients with PFO.

Left ventricular thrombus

Formation of a left ventricular thrombus (LVT) is an important complication of systolic cardiac dysfunction that may follow ST-elevation myocardial infarction (STEMI). The pathophysiology is based on blood stasis in the infarcted area of the heart. The presence of LVT increases the risk of embolic stroke four times, mainly in the first three months after STEMI.[88] As in the case of other CE sources, a multi-territory pattern of ischemic lesions is often reported.[89] Before the era of percutaneous coronary intervention (PCI), the incidence of LVT after STEMI was up to 40%.[90] The introduction of PCI decreased the rate to 2.7% in the general STEMI population and to 7.5% in patients with anterior STEMI.[91] However, LVT still remains an important source of emboli of cardiogenic stroke. Thus, in patients with non-lacunar ischemic stroke with multi-territory distribution, LVT should always be investigated as a possible cause. Anticoagulation with vitamin K antagonist is currently the secondary

prevention of choice in patients with proven LVT. However, the ideal anti-thrombotic regime in these patients is still uncertain.[92]

Since the effect of anticoagulation treatment in patients with embolic stroke of undetermined source (ESUS) is still unclear, the correct diagnosis of LVT is crucial. TEE is a gold standard in the diagnosis of LVT and is more sensitive than TTE. Recent studies have shown that contrast-enhanced cardiac MRI is superior to TEE and may thus substantially facilitate the choice of secondary prophylaxis in patients with ESUS.

Endovascular and vascular interventions

Mechanical thrombectomy (MT) or carotid endarterectomy, carry a risk of periprocedural complications, including thromboembolism. Arterial injury and prothrombotic features of the arterial devices, catheters or contrast agents are often responsible for adverse events.

In MT, embolization may occur both within the downstream of the targeted artery, and within other arterial cerebral territories. The large clinical trials on MT reported embolization to different arterial territories in around 6% of cases.[93] The mechanism of additional embolization in MT is usually caused by fragmentation of the clot during stent retrieval. In some cases, recanalization of these additional occlusions can be achieved by further MT passes or the administration of intra-arterial thrombolysis.[94] Cerebral embolization as a complication following carotid endarterectomy and stenting occurs in 3.3% and 7.3% of patients, respectively. The mechanisms of ischemic stroke are diverse, including hypoperfusion and embolism.[95]

Along with wider use of newer and more accurate brain imaging methods, it is proven that a considerable number of patients undergo asymptomatic (silent) periprocedural embolization, often appearing as embolic micro-lesions.

Left atrial myxoma

Primary cardiac tumor is a very rare cause of stroke. However protruding tumor masses can be a potent source of embolization. Left atrial myxoma is the most common tumor of heart and represents 50-70% of cases. Left atrial myxoma should be considered in the etiological work-up mainly in young stroke patients having cardiac

symptoms such as exertional dyspnea or signs of pulmonary edema. A neurological complication in the form of cerebral embolization occurs in approximately 30% of cases and shows often multiple-territory distribution.[96, 97] Myxoma embolization may also lead to the characteristic formation of multiple intracranial aneurysms within the peripheral branches of intracranial arteries. This phenomenon is probably related to a weakening of the intracranial vessel walls following the infiltration of the vessel wall by spread myxomatous tumor cells.[98] The first choice of treatment is surgical resection of the tumor.

Small vessel disease

The frequency of lacunar MACI among patients presenting with a lacunar syndrome is 16%.[99] It may be difficult to distinguish if the ischemic lesions occurred as simultaneous or as successive events within hours or days. Even though patients with lacunar MACI and SACI often share the same risk factors, there is evidence that in patients with lacunar MACI, a proximal source of emboli often co-exists.[38] Some studies show that lacunar MACI often has another identifiable stroke cause than SVD, including artery-to-artery embolism, concomitant CE or LAA.[38, 99, 100] Simultaneous occlusion caused by multiple microatheroma or lipohyalinosis may be an explanation in some of these patients.[101, 102] However, only histological techniques may distinguish embolic, lacune-shaped lesions from true lacunar lesions. The varying results of studies show that the findings highly depend on the extensiveness of the diagnostic work-up in these patients. More intensified etiological investigation may influence the decision regarding secondary prevention in such patients. Diabetes mellitus and widespread leukoaraiosis are common risk factor in patients with lacunar MACI. These patients also have a higher risk of recurrent stroke and worse functional outcome which should be taken into consideration by the treating physician.[103]

Recurrent and multifocal truly lacunar CI may also be a sign of more rare types of SVD, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL represents a hereditary non-amyloid and non-atherosclerotic SVD caused by NOTCH 3 gene mutation. CADASIL should be considered in young stroke patients presenting with recurrent lacunar MACI, concomitant migraine attacks and cognitive deterioration.[104, 105]

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a multi-organ autoimmune disorder accompanied by the presence of antiphospholipid antibodies (aPL) such as lupus anticoagulant or anticardiolipin antibodies. APS may start either as a primary disorder or as a complication of another autoimmune disease such as systemic lupus erythematosus (SLE). The prevalence of APS is up to five times higher among women and the clinical manifestation usually starts between 30-40 years of age. Major complications of APS are abortions and systemic thromboembolism (Hughes' syndrome or sticky blood syndrome) with a high tendency of arterial embolism. Over 20% of young stroke cases may be associated with APS.[106] The exact pathophysiology of the hypercoagulable state in APS is not completely understood. However, an interaction of aPL with the pathways of coagulation via an impaired function of protein C, platelets and fibrinolysis plays an important role.

The arterial occlusion may be either of embolic or thrombotic origin. APS-associated nonbacterial thrombotic endocarditis (NBTE) usually stands behind the embolic stroke.[107] Thrombosis is most probably associated with activation of platelets and endothelium in the cerebral arteries, thus promoting a hypercoagulable state in the affected vessel. As in other disorders accompanied by hypercoagulable state and NBTE, ischemic lesions often have multi-territory distribution, and the risk of recurrent stroke is high.[24, 108]

There is lack of data and controversy regarding the correct secondary prevention in patients with APS-associated CI. Over 50% of patients experience a recurrent thromboembolic event when treated with aspirin or vitamin K antagonist at INR<3. Only aggressive long-term anticoagulation therapy with vitamin K antagonists at INR>3 seems to be effective secondary prophylaxis. But this therapeutic regime is complicated by a higher risk of bleeding.[109] A catastrophic type of APS is defined by embolization to multiple organs within short time. Here, a high dose steroid treatment, i.v. immunoglobulins or plasma exchange alongside with anticoagulation treatment may be indicated. The monitoring of treatment response may be achieved by microemboli detection, especially in patients presenting with MACI.[73]

Hypereosinophilic syndrome

Another rare etiology of multi-organ thromboembolic event is the hypereosinophilic syndrome. Here, either idiopathic or secondary overproduction of eosinophils, that infiltrate various organs including cerebral vessels, may lead to a local hypercoagulable state. MACI has been reported in connection with this syndrome; however, only as case-reports.[110, 111] The treatment can be complicated depending on the cause of eosinophilia. However, high-dose glucocorticoids seems to be effective in most cases.[112]

Cancer

The pathophysiology of cancer-associated thromboembolism is complex and involves several overlapping mechanisms. The most important mechanism is a hypercoagulable state mediated either by cancer itself or by oncological treatment like chemo- and radiotherapy. The Bergen NORSTROKE registry showed that prevalence of an active cancer among consecutively admitted stroke patients (within the interval of 12 months prior and after the index stroke) is 5%.[113, 114] The frequency of thromboembolic events in cancer patients is estimated to approximately 15%, of which 3% represent CI. However, the number is probably underestimated as cancer-associated CI is underdiagnosed. Patients with active malignancy have a higher risk of a recurrent thromboembolic event of any type, with cumulative rates of 21%, 31% and 37% at 1, 2, and 6 months, respectively.[71]

It seems that predominantly highly aggressive and advanced-stage mucinous adenocarcinomas including lung, pancreas and colorectal cancer are associated with a higher occurrence of thromboembolic events. Some types of adenocarcinoma such as prostate or breast cancer, seem to play a minor role.

The CI may be caused either by in-situ thrombosis or cardiac embolism in relation to NBTE. Prior studies showed that a multi-territory distribution of ischemic lesions is frequent.[54] One study showed that up to 20% of MACI with involvement of all three territories are cancer-related.[115] MACI may be the first symptom of occult cancer. Patients at the same time presenting with worrisome symptoms, such as weight loss, lack of appetite and elevation of biomarkers characteristic for thromboembolic events, should always undergo cancer screening.[54, 115] Very high levels of D-Dimer (≥3 mg/L)

and fibrinogen/fibrin degradation products (FDP) and low level of serum hemoglobin (≤12.0 g/dL) are often seen in patients with cancer-associated CI. These blood tests may serve as a sensitive predictive factor; albeit with low specificity.[116, 117] The cut-off point for differentiation cancer-associated MACI from CE-associated MACI was suggested to be 2 μg/mL of D-Dimer.[118]

In cancer-associated CI, both thrombolysis and thrombectomy may be beneficial after careful consideration of eligibility. The secondary prevention in cancer-associated CI is challenging. Except for the prematurely terminated TEACH-trial, which randomized patients with cancer-associated CI to aspirin and enoxaparin, no other clinical trials have been published to this date.[119] Empiric treatment with low-molecular heparin under the control of the therapeutic range of anti-factor Xa seems to be effective and safe. However, high price and daily subcutaneous administration are major drawbacks. Secondary prevention with DOAC may be effective, but supporting data are not yet available.

Vasculitis

Vasculitis of the central nervous system encompasses a wide range of blood vessel autoinflammatory diseases of either primary or secondary origin. In contrast to the secondary form where disturbance of CNS accompanies a systemic vasculitis, the primary form is limited only to the CNS. The clinical picture may vary; however, cognitive deterioration, headache, and focal neurological deficits are the most characteristic symptoms. The prevalence of vasculitis-associated CI, regardless of primary or secondary origin, is only 0.2% in the general stroke population and therefore a routine screening is not recommended.[120] However, in young stroke patients with ischemic lesions of different ages and distribution in several arterial territories, CNS vasculitis should be considered as differential diagnosis. The lesions are usually distributed in both hemispheres with lesions in cortical as well as subcortical areas.[121] The diagnosis of primary CNS vasculitis is based on angiographic imaging, but CNS biopsy may be needed for final confirmation. Glucocorticoids are usually an effective treatment and may prevent further complications and negative progression.[122] There are several case reports on MACI accompanying secondary

vasculitis such as Takayasu arteritis and Churg-Strauss syndrome. These should be suspected in the context of a systemic disease.[123-125]

Diagnostics

Clinical Manifestation

Patients with MACI may present with unusual clinical manifestation as more than one arterial territory is affected. The examining physician may encounter bilateral neurological deficit or an atypical combination of symptoms usually not seen in patients with SACI. In one prospective cohort study comprising 80 patients diagnosed with MACI, only 24 patients (30%) showed signs of multi-territory clinical manifestation.[33] Presumably, several factors may influence the clinical manifestation of MACI, such as the character of the ischemic lesions.

The role of neuroimaging

The non-contrast computed tomography (CT) is used as standard initial brain imaging in most patients with suspected stroke. The CT is the method of choice for prompt diagnosis of brain hemorrhage or large-volume ACI. Most ACI, however, are not visible on CT during the first several hours. Only chronic white-matter disease or old ischemic lesions may suggest the presence of cerebrovascular disease, however multiple chronic ischemic lesions localized cortically may be suggestive of an active embolic source.

MRI has in the acute setting a much higher sensitivity to identify ACI compared to CT (83% vs. 26%).[126] Its sensitivity increases to 97.5% by use of Diffusion- and Perfusion-Weighted MRI.[127] DWI-MRI has become a cornerstone in the diagnostics of acute ischemic lesions identifiable already within minutes of ischemia which found its use mainly in patients with unknown onset of stroke. Nevertheless, MRI is a time-demanding and expensive examination, and its availability for acute stroke diagnostics is still limited in the majority of hospitals.

MRI is nowadays an essential part of the diagnostic follow-up in stroke patients. Several specific sequences have been introduced in the past two decades, adding additional information on stroke subtype and etiology. Other modalities such as

CT/MR angiography (CTA/MRA) or CT/MR-Perfusion are increasingly implemented in the initial neuroimaging protocols in order to localize an arterial occlusion and to distinguish salvageable brain tissue from the irreversible infarct core.[15, 16] CTA/MRA should always be a part of the stroke protocol in patients with MACI in order to exclude anatomical variations of intracranial arteries which may be responsible for such topographical distribution. CTA/MRA is also a useful method for diagnostics of intracranial stenosis but also less common causes of MACI including vasculitis or Moyamoya disease.

The distribution and pattern of MACI as defined by MRI may be suggestive of the etiology. MACI of both small and large volumes, particularly with cortical distribution, favours proximal embolic sources such as heart or aortic arch. A lacunar pattern of MACI may suggest advanced SVD and simultaneous occlusion of the deep-perforators. Severe leukoaraiosis and multiple microbleeds on FLAIR and susceptibility-weighted imaging (SWI) may support SVD origin. Multiple infarcts within only one arterial sub-territory may suggest an artery-to-artery embolism from the supplying intracranial artery. A combination of multiple cortical and subcortical ischemic lesions within one arterial territory may be caused by fragmentation of the emboli, as often seen in unstable ICA stenosis. Unilateral border-zone (watershed) infarcts are usually associated with stenosis or occlusion of the ipsilateral ICA. Bilateral watershed infarcts rather point towards systemic hypoperfusion.[41, 128]

As in other areas of neuroimaging, the field strength of MRI has an implication on the precision and quality of the findings. In contrast to the routinely used 1.5T MRI, MRI with higher field strengths may reveal additional micro-lesions. Two studies using a 3.0 T MRI scan showed a significantly higher frequency of MACI in their stroke cohorts.[44, 129]

Cardiogenic embolism

AF should always be investigated as a cause of MACI. A normal standard ECG without relevant arrhythmias should be followed by long-term ECG monitoring. Several studies showed that the detection rate of silent (paroxysmal) AF improves with prolonged ECG monitoring. Both 72 hours and continuous ECG monitoring at a stroke unit appear to be superior to standard 24-hours examination.[130, 131] Several devices

capable of even higher detection rates have been introduced. Implantable loop recorders require only a minor surgical procedure and may be used for up to 3 years of continuous monitoring. However, new devices such as chest and thumb-ECG or smartwatches seem to be a less invasive and resource-demanding alternative for AF detection.[132, 133]

Echocardiography plays an important role in the evaluation of structural cardiac sources of emboli. Transthoracic echocardiography (TTE) is sufficient in many patients with heart disease, but transesophogeal echocardiography (TEE) has been shown to be superior to standard TTE. One prospective study showed that 40% of CI/TIA patients with normal findings on TTE showed structural signs associated with cardiac emboli sources on TEE.[134] The prevalence of potential aortic or cardiac sources diagnosed by TEE is high among patients with CI regardless of the vascular distribution. TEE seems to be beneficial in patients with suspected NBTE as a more common cause of MACI.[72] However, MACI alone should not be an indication to perform TEE.[135]

Microemboli detection

Microemboli detection by transcranial Doppler ultrasound is a useful, non-invasive and inexpensive method to identify silent embolization to the cerebral arteries. Silent embolization increases stroke risk and may be a sign of inadequate antithrombotic treatment.[136, 137] MACI often indicates the presence of a highly active source of emboli accompanied by a higher risk of recurrent CI. Microemboli detection should be used more extensively in patients with MACI in order to avoid a negative progression and to assess the effect and possibly adjust the strategy of secondary prevention of recurrent stroke.[73]

Ischemic stroke recurrence

After an ACI, the patient is at high risk of recurrent stroke, readmission for another health issue and death, especially within the first weeks after the index stroke. The highest risk of early recurrence is in patients with stroke due to large artery arteriosclerosis.[138, 139] Initial plaque instability and low immediate effect of the antiplatelet and cholesterol-lowering treatment may play an important role.

Endarterectomy performed early may prevent such events. However, not all patients have an indication for this procedure.[140] CI categorized as other disease TOAST subtype is prone to higher recurrence as well. The explanation may be the rarity of the underlying etiologies as well as hypercoagulable states which may be difficult to get under control.[71, 141] On the other hand, the high recurrence in cardioembolic stroke seems to have decreased in the last years. It is most probably caused by the introduction of highly effective and safer direct oral anticoagulants.[139]

Multi-focal ischemic lesion pattern either within one or several arterial territories is an independent predictor for early recurrent stroke, readmission for another vascular event and death.[129, 142] In patients with MACI, predominantly large artery atherosclerosis and other disease TOAST subtype are associated with a higher risk of early recurrence. One recent study showed that MACI in patients with undetermined etiology TOAST subtype also are associated with higher long-term stroke recurrence.[143] The patients with MACI reported in that study had significantly higher D-Dimer level and occurrence of right-left shunting. This mirrors the importance of the long-term risk of embolism in patients with both cancer and PFO. On the other hand, a sub-analysis of the CHANCE trial, aiming at patients with minor stroke, showed that there is no significant difference in the recurrence between patients with non-lacunar SACI and MACI. Lacunar stroke seems to have a lower risk of recurrence compared to non-lacunar strokes.[144]

There are not sufficient data on short- or long-term clinical or functional outcome of patients with MACI. The same applies for complications. Overall, patients with an index or recurrent MACI may be at a higher risk of recurrent stroke, which may require different approaches both in diagnostic work-up and secondary prevention.

Aims of the dissertation

MACI are not a rare entity in stroke medicine, but few data on MACI has been published. There is still a need to clarify some of the pathophysiological and clinical aspects. The aim of this dissertation is to contribute to this less documented field of stroke medicine by using the Bergen NORSTROKE registry comprising a considerable number of well-described patients with MACI.

Aims:

Paper-I

1. To assess the frequency and the etiological spectrum of MACI based on the TOAST classification.
2. To assess gender and age distribution in patients with MACI.

Paper-II

3. To compare frequencies of LAA- and CE-associated MACI in relation to the time from stroke onset to time of MRI examination.

Paper-III

4. To compare short-term in-hospital complications in patients with MACI and SACI.
5. To compare short-term clinical and functional outcome in patients with MACI and SACI.

Paper-IV

6. To assess the frequency of single- vs, multiple-territory clinical manifestation on admission among the patients with MACI.
7. To assess clinical and radiological aspects associated with single- vs, multiple-territory clinical manifestation.

Methods

The Bergen NORSTROKE registry

The Bergen NORSTROKE registry contains comprehensive information on medical history and baseline and in-hospital clinical characteristics up to discharge of all patients diagnosed with stroke/TIA consecutively admitted to the stroke unite in the Department of Neurology, Haukeland University Hospital, Bergen, Norway. The registry has a prospective design characterized by collecting data determined prior to the start of the registration. For this purpose, a standardized case report form is used for each patient. The inclusion started in 2006 and is still on-going.

Haukeland University Hospital covers a catchment area of almost 300.000 inhabitants. However, young stroke patients under 60 years and patients with large vessel occlusion eligible for MT are transferred from neighboring regional hospitals and are included in the registry as well. Bergen NORSTROKE registry has been approved by local ethics committee REK West.

The first two papers (I-II) published in 2016 are based solely on the data from the Bergen NORSTROKE registry acquired in the time period from 2006 to 2013.[19, 145] The data for the last two papers (III-IV) published in 2019 and 2020 are gathered from the extended version of the Bergen NORSTROKE registry, which is from 2006 to 2017.[22] The paper-IV required additional data on patients with MACI (N=311), which were obtained by reviewing the admission medical records and DWI-MRI findings.

Baseline characteristics

All stroke/TIA patients undergo an initial clinical examination, including National Institutes of Health Stroke Scale (NIHSS) and supplemental neurological assessment, performed by the on-duty neurology resident in the emergency room. The initial brain imaging involves in most of the patients with suspected stroke/TIA, brain native CT or native CT + CTA if indicated. Initial MR or MR + MRA was performed in patients with unknown time of symptom onset such as those who wake up with stroke symptoms (“wake-up stroke protocol”) or those patients where CT was contraindicated

such as pregnant women. Baseline vital signs, ECG and a set of blood tests specific for patients with suspected stroke/TIA were taken in the emergency room.

Medical history and risk factors

Cerebrovascular and cardiovascular medical history, stroke risk factors and other relevant information were obtained during the hospitalization and registered in the case report form.

Diagnostic work-up

Every patient with CI or TIA underwent comprehensive diagnostic work-up including cardiological, neurosonological and radiological assessment indicated as appropriate.

Cardiological assessment

If the initial ECG showed no atrial tachycardia such as AF, atrial flutter or ectopic atrial tachycardia, long-term ECG monitoring lasting 24- / 48- / 72- hours was performed. The structural sources of aortic or cardiac embolism were assessed by TTE or by TEE if indicated.

Neurosonological assessment

Sonographic evaluation of extracranial arteries was regularly performed by either stroke neurologist or trained neurology resident. Details on stenosis grade, dissection, occlusion or other relevant pathologies of extracranial arteries were registered. ICA stenosis was defined as symptomatic if the stenosis >50% is accompanied by ipsilateral symptomatic ACI/TIA. Stenosis >50% with no ipsilateral symptomatic ACI/TIA was defined as an asymptomatic ICA stenosis. Transcranial duplex and microemboli detection were performed if indicated.

Radiological assessment

The majority of patients with stroke/TIA were examined by MRI the same or the next day. The Department of Radiology at Haukeland University Hospital provides several MRI machines of either 1.5 or 3.0 Tesla field strength. The vast majority of patients included in the Bergen NORSTROKE registry were examined by a 1.5T MRI machine

and only a smaller portion had examination by 3.0T MRI machine. Specifications of MRI machines used at Haukeland University Hospital in 2020 are listed in table 5. Both the on-duty neuroradiologist and the stroke neurologist (HN) assessed the MRI scans.

Table 5. Specifications of MRI machines at Haukeland University Hospital

Field strength (T)	**1.5**	**3.0**
MRI scanner	Siemens Healthcare	Siemens Healthcare
Head coil – nummer of channel	8	32
B value (s/mm^2)	0, 500, 1000	0, 500, 1000
Repetition time - TR (ms)	3700	3400
Echo time - TE (ms)	89	54-89
Field of view (mm)	230 x 230	220 x 220
Matrix size	192 x 192	160 x 160
Slices	23	26
Slice thickness (mm)	5 mm with 1 mm gap	4 mm with 1,2 mm gap

MRI – magnetic resonance imaging

Young stroke

Besides the standard diagnostic work-up applied in stroke/TIA patients, young stroke patients under 60 years undergo a more comprehensive diagnostic work-up to exclude rare causes of stroke. Blood tests including tests on thrombophilia, comprehensive neurosonological and cardiological examinations were performed.

Etiology and classification

Based on the diagnostic work-up, the etiology in every patient diagnosed with CI/TIA was classified using TOAST criteria as cardiogenic embolism, large artery atherosclerosis, small vessel disease, other disease or unknown etiology. TOAST subtype unknown etiology (UE) comprises patients with competing etiologies, cryptogenic stroke or incomplete diagnostic work-up.[17]

Based on the clinical manifestation and radiological findings, every CI was also categorized using the Oxfordshire Community Stroke Project (OCSP) classification as total anterior circulation infarct clinical stroke syndrome (TACI), partial anterior circulation infarct clinical stroke syndrome (PACI), lacunar infarct clinical stroke

syndrome (LACI) or posterior circulation infarct clinical stroke syndrome (POCI).[146] Table 6 shows OCSP classification in detail.

Table 6. Oxfordshire Community Stroke Project (OCSP) classification

TACI	PACI	LACI	POCI
Clinical manifestation			
All three of the following: 1-higher cerebral dysfunction (eg. dysphasia, dyscalculia, visuospatial disorder); 2-homonymous hemianopia 3-unilateral weakness: motor and/or sensory deficit in at least two out of the following: face, arm, and leg	Two of the following: 1-higher cerebral dysfunction (eg. dysphasia, dyscalculia, visuospatial disorder); 2-homonymous hemianopia 3-unilateral weakness: motor and/or sensory deficit in at least two out of the following: face, arm, and leg	One of the syndromes: 1-Pure motor stroke 2-pure sensory stroke 3-mixed sensorimotor stroke 4-ataxic hemiparesis 5- Dysarthria/clumsy hand	One of the following: 1-ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit 2-bilateral motor and/or sensory deficit 3-conjugate eye movement disorder (gaze palsy) 4-cerebellar dysfunction (vertigo, nystagmus, ataxia) 5-isolated hemianopia or cortical blindness
Radiological finding			
Large cortical MCA infarcts or >1/2 of the MCA territory + ACA or PCA territory medium sized cortical infarcts (<1/2 of MCA territory) large > 1.5cm subcortical infarcts	Small sized cortical infarcts (<¼ of MCA territory) or any of ACA territory medium sized cortical infarcts (<1/2 of MCA territory) watershed infarcts large > 1.5cm subcortical infarcts	Small <1.5 cm subcortical infarcts	Cortical infarct in PCA territory Brainstem infarct or cerebellar infarct

TACI - total anterior circulation infarct clinical stroke syndrome, PACI - partial anterior circulation infarct clinical stroke syndrome, LACI - lacunar infarct clinical stroke syndrome; POCI - posterior circulation infarct clinical stroke syndrome; ACA – anterior cerebral artery, PCA – posterior cerebral artery; MCA – middle cerebral artery

Stroke severity on admission and short-term outcome

Stroke severity on admission and the in-hospital stroke-related neurological deficit was assessed by NIHSS score. NIHSS represents a scale from 0 to 42, assessing the severity of stroke but NIHSS also gives clues as to the probable topographical location of the ischemic lesion(s).[147] Both validity and reliability have been proven high in clinical trials.[148, 149] After the admission, the NIHSS score was assessed at pre-specified time points up to day 7, or discharge if earlier, to evaluate neurological improvement or deterioration during hospitalization. NIHSS score on admission, the next day and on day 7 or at discharge were assessed by a neurology resident or stroke neurologist.

For the assessment of short-term functional improvement or deterioration, modified Rankin Scale (mRS) was used. MRS is a widely used scale evaluating functional status (0 - no symptoms up to 6 – death) and works as an indicator of the degree of disability/dependence after a neurological event.[150] mRS is used in the majority of clinical trials as a primary outcome measure of an intervention effect. The interval 0-2 is generally considered as a favorable outcome and the interval 3-6 as an unfavorable outcome. The functional status both before the admission and on day 7 or at discharge was assessed by a certified stroke nurse.

Relevant in-hospital complications during the hospitalization, including deep venous thrombosis (DVT), myocardial infarction (MI), recurrent ACI, pulmonary embolism, symptomatic and asymptomatic ICH, heart failure, epileptic seizure, pneumonia, infection of unknown focus, urinary tract infection, urinary retention, urinary incontinence or death were registered.

Definition of MACI

Only patients with acute ischemic lesions revealed by DWI-MRI were included in the four papers. MACI was defined as at least two non-continuous ischemic lesions in at least two arterial cerebral territories. There are two frontal arterial cerebral territories represented by left and right side of the anterior circulation supplied by ACA and MCA originating from ICA. There is one posterior arterial cerebral territory represented by the posterior circulation supplied by posterior inferior cerebellar

arteries, anterior inferior cerebellar arteries, superior cerebellar arteries and PCA originating from BA.[151] Only DWI-MRI lesions appearing as hyperintense signals accompanied by hypointense signals on apparent diffusion coefficient magnetic resonance imaging (ADC-MRI) were considered as acute. Patients with slightly hyperintense DWI-MRI signals or those DWI-MRI signals without corresponding ADC-MRI changes were considered as subacute lesions or artefacts.

The abbreviation "MACI" stands for "Multiple Acute Cerebral Infarcts". However, "acute cerebral infarct(s) in multiple arterial territories" is a more precise description. We decided to keep the abbreviation MACI for its simplicity.

Clinical manifestation and topographical distribution of MACI

The clinical manifestation and topographical characteristics of MACI were assessed by a non-blinded retrospective review of the admission medical records and corresponding DWI-MRI, performed independently by two PhD-fellows in stroke medicine (Vojtech Novotny and Sander Johan Aarli).

Patients with MACI were categorized into 7 groups according to clinical manifestation corresponding to (1) left anterior territory + posterior territory (LAPT), (2) right anterior territory + posterior territory (RAPT), (3) left + right anterior territory (LRAT), (4) all three territories (LRAPT), (5) left anterior territory (LAT), (6) right anterior territory (RAT) or (7) posterior territory (PT).

Based on the combination of the affected arterial territories, the topographical distribution of MACI was categorized into four groups as follows: (1) LAPT, (2) RAPT, (3) LRAT or (4) LRAPT. The number of lesions was categorized as <5, 5-10, >10.

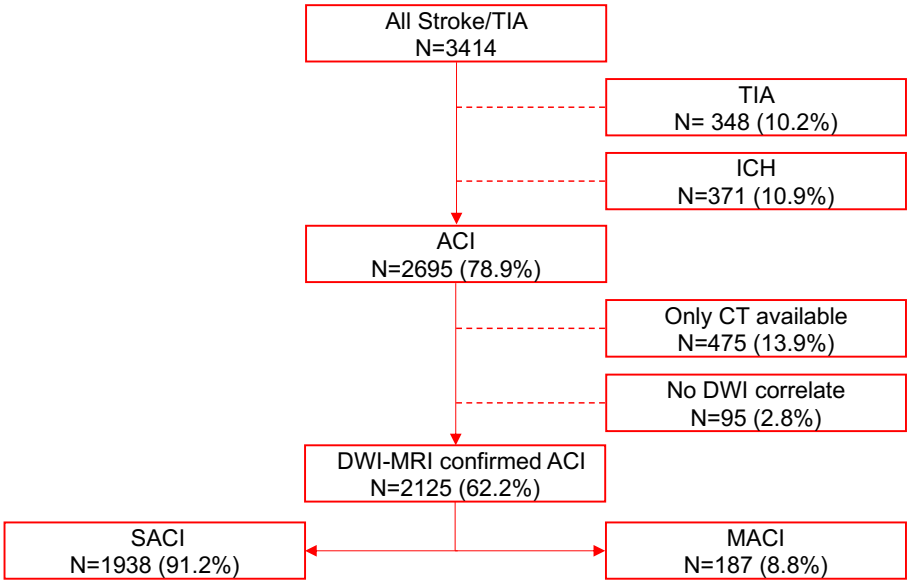
To reach a methodological agreement, both reviewers assessed the first 50 patients simultaneously. Further assessment of the 261 patients was performed independently, and the results were compared. All results which the reviewers agreed on were kept for the final analysis. In case of disagreements, the patients were reassessed in a joint-review, and the consensus was used for final analysis.

Study population

Paper I & II

The first two papers published in 2016[19, 145] are based on The Bergen NORSTROKE registry comprising all stroke/TIA patients consecutively admitted to the stroke unit affiliated to Haukeland University Hospital from February 2006 to October 2013. All patients diagnosed with ICH (N=371) and TIA (N=348) were excluded. Patients diagnosed with ACI where the diagnosis was based only on CT (N=477) or DWI-MRI sequence showed no correlate (N=95) were excluded as well. Out of 2125 patients diagnosed with ACI confirmed by DWI-MRI, 187 (8.8%) had MACI, and 1938 (91.2%) had SACI.

Figure 3. Flowchart of patients included in the Paper-I and Paper-II

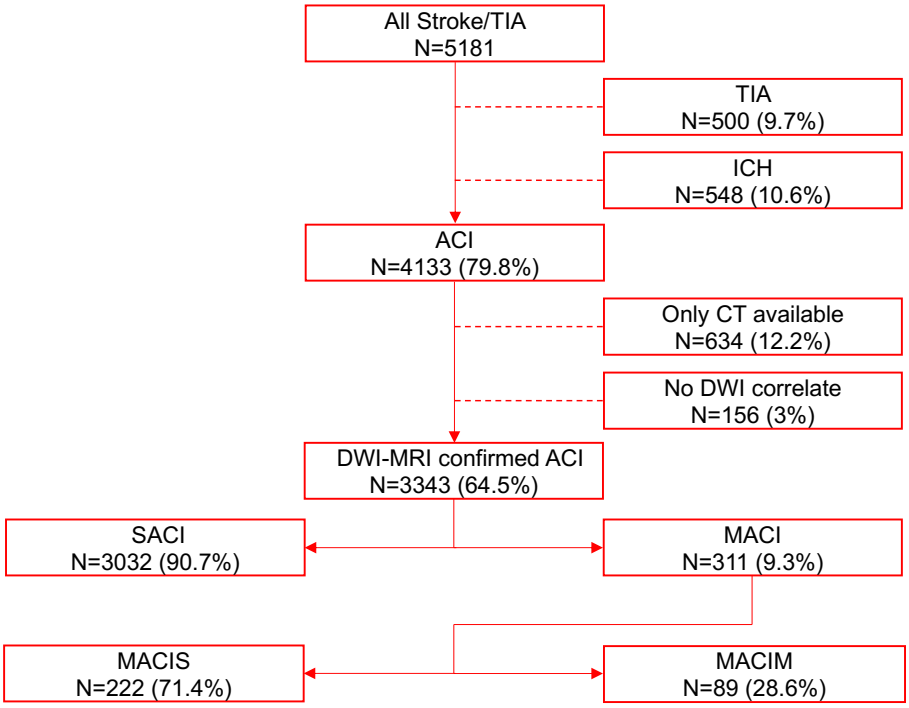


TIA - transient ischemic attack; ICH - intracranial hemorrhage; ACI – acute cerebral infarct; DWI-MRI - diffusion weighted magnetic resonance imaging; MACI – Acute cerebral infarct(s) in multiple arterial territories; SACI - Acute cerebral infarct(s) in a single arterial territory

Paper III & IV

The last two papers published in 2019 and 2020 are based on The Bergen NORSTROKE registry comprising all stroke/TIA patients consecutively admitted to the stroke unit affiliated to Haukeland University Hospital from February 2006 to January 2017.[22] All patients diagnosed with ICH (N=548) or TIA (N=500) were excluded. Patients diagnosed with ACI where the diagnosis was based only on CT (N=634) or DWI-MRI sequence showed no correlate (N=156) were excluded. Out of 3343 patients diagnosed with ACI confirmed by DWI-MRI, 311 (9.3%) had MACI and 3032 (90.7%) had SACI. In the paper-IV, only patients with MACI underwent the final analysis (N=311), of which 89 (28.6%) had acute cerebral infarct(s) in multiple arterial territories with multi-territory clinical manifestation (MACI-M) and 222 (71.4%) had acute cerebral infarct(s) in multiple arterial territories with single-territory clinical manifestation (MACI-S).

Figure 4. Flowchart of patients included in the Paper-III and Paper-IV



TIA - transient ischemic attack; ICH - intracranial hemorrhage; ACI – acute cerebral infarct; DWI-MRI - diffusion weighted magnetic resonance imaging; MACI – Acute cerebral infarct(s) in a multiple arterial territories; SACI - Acute cerebral infarct(s) in a single arterial territory; MACI-M - acute cerebral infarct(s) in multiple arterial territories with multi-territory clinical manifestation; MACI-S - acute cerebral infarct(s) in multiple arterial territories with single-territory clinical manifestation

Statistics

Paper-I, -II, -III and -IV

For the univariate analyses, we used a $\chi 2$ test, t-test or Wilcoxon rank-sum test depending on the type of variable and skewness of the data.

Paper -I, -III and -IV

For the multivariate analyses, we used either logistic regression analysis or linear regression analysis to obtain odds ratio and 95% confidence interval or coefficient and 95% confidence interval, respectively. Statistically non-significant variables from the univariate analyses, however clinically relevant, were included in the multivariate analyses as cofounders (sex, age, mRS before admission, NIHSS on admission, etc.). Independent (exposure) and dependent (outcome) variables were applied as appropriate.

Paper-I

To visualize the relationship between age and occurrence of MACI, the LOWESS (Locally Weighted Scatterplot Smoothing) was used.

Paper-II

Histogram was used to visualize frequency of patients with MACI in relation to the time from the stroke onset to the MRI examination. To express the correlation between time from stroke onset to MRI examination and the frequency of different etiological groups among patients with MACI, we used Pearson's correlation with a coefficient (r) as an indicator of either positive, negative or no correlation. We used linear prediction models together with corresponding confidence intervals to visualize the frequency of MACI in different etiological groups in relation to the time from stroke onset to MRI examination.

Depending on the distribution and skewness of the data, the descriptive statistics, including measures of central tendency and dispersion of the data were expressed by the mean or median and standard deviation or interquartile range, respectively. The level of significance was set to ≤ 0.05. All analyses were performed by using Stata (StataCorp, College Station, Texas, USA); version 14.0 for Paper-I and -II and version 15.0 for Paper-III and -IV.

Results

Paper-I

The final analysis included 2125 patients (78.8%) with ACI confirmed on DWI-MRI. Patients with MACI represented 8.8% of the studied cohort.

Univariate analysis showed that patients with MACI were older (71.7 vs. 68.9 years; P=0.013), more often females (48.7% vs. 39.1%, P=0.011) and had higher mean NIHSS on admission [6.9 (SD=7.5) vs. 4.9 (SD=5.8)] compared to patients with SACI. However, in the multivariate analysis, neither female sex (OR=0.76; 95% CI 0.54 – 1.1; P=0.13) nor higher age (OR=1.0; 95% CI 1.0-1.02; P=0.31) were associated with MACI.

Cardiogenic embolism (35.8 % vs. 28.7%; P=0.042), atrial fibrillation (35.3% vs. 24.8%; P=0.002) and also symptomatic (27.5% vs. 19.1%; P=0.014) and asymptomatic (16.2% vs. 10.5%; P=0.036) ICA stenosis appeared to be associated with MACI. Small vessel disease (3.7% vs. 14.3%; P< 0.001) and lacunar infarcts (15.5% vs. 26.1%; P=0.001) were associated with SACI. The association of cardiogenic embolism and symptomatic ICA stenosis with MACI remained significant in the multivariate analysis with OR of 1.5 (95% CI 1.1 – 2.3; P=0.025) and 1.9 (95% CI 1.2 – 2.8; P=0.003), respectively.

When patients classified within the CE TOAST category were excluded, both symptomatic (35% vs. 25%; P=0.037) and asymptomatic ICA stenosis (20% vs. 13%; P=0.031) remained significantly associated with MACI.

The mortality rate was not higher in patients with MACI compared to those with SACI.

Paper-II

This study was based on a cohort of 2125 patients with ACI confirmed by DWI-MRI, of which 187 (8.8%) had MACI. The etiology based on TOAST criteria among patients with MACI was as follow: CE – 67 (35.6%); LAA – 19 (10%); SVD – 7 (3.7%); OC – 6 (3.2%), UD – 88 (47%). In the MACI group, 24 patients (12.8%) had symptomatic ICA stenosis and 41 (21.9%) had asymptomatic ICA stenosis. The mean

time from stroke onset to MRI examination in the whole cohort was 2.3 (SD=2.6) days, in patients with MACI 2.5 days (SD=2.6) and patients with SACI 2.3 days (SD=2.6).

There was a positive correlation between time from stroke onset to MRI examination and the frequency of LAA-associated MACI (r=0.2; P=0.001), but also the frequency of MACI patients with symptomatic (r=0.14; P=0.01) and asymptomatic ICA stenosis (r=0.21; P=0.006). There was no correlation between time from stroke onset to MRI examination and the frequency of CE-associated MACI (r= -0.02, P=0.61).

In a sub-analysis of 93 patients with MACI in the anterior circulation only (MACI-A), the correlation was stronger for LAA-associated MACI (r=0.27; P=>0.001) as well as for symptomatic (r=0.27; P=>0.001) and asymptomatic ICA stenosis (r=0.28; P=0.001). There was no correlation with CE-associated MACI-A (r=0.5; P=0.33). Among the 93 patients with MACI-A, 25 had ICA stenosis, of which 11 (44%) had symptomatic ICA stenosis and 14 (56%) had a combination of symptomatic and asymptomatic ICA stenosis. In patients with MACI-A and concomitant symptomatic and asymptomatic ICA stenosis (N=14), most of the symptomatic ACI had either mixed (N=6) or a watershed (N=5) pattern on DWI-MRI.

Paper-III

The final analysis comprised 3343 patients with ACI confirmed by DWI-MRI, of whom 311 (9.3%) had MACI.

Univariate analysis showed that that MACI occurred more often in older patients (74.5 vs. 71.1 years; P<0.001) and more often in females (48% vs. 40%; P=0.008). Both median NIHSS score on admission [4 (IQR= 1-9) vs. 2 (IQR=1-5); P<0.001] and median mRS prior to the admission [0 (0-2) vs. 0(0-0); P<0.001] were higher in patients with MACI compared to the patients with SACI. Patients with MACI had a lower mean serum cholesterol (5.0 mmol/l vs. 5.3mmol/l; P=0.014) and LDL on admission (3.1 mmol/l vs. 3.4 mmol/l; P=0.006). Cardiogenic embolism was more common in patients with MACI (53% vs. 28%; P<0.001). On the other hand, both small vessel disease (3% vs. 15%; P<0.001) and unknown etiology (33% vs. 42%;

P=0.004) were more common in patients with SACI. Patients with MACI also had more often AF (39% vs. 26%; P<0.001) and were more often anticoagulated prior to the admission (11.6% vs. 8.3%; P=0.048). Mechanical thrombectomy was more often performed in patients with MACI (10.1 vs. 2.6%; P<0.001). Secondary prevention with anticoagulation was more often started in patients with MACI (59.5% vs. 34.7%; P<0.001), whereas patients with SACI more often started with antiplatelet treatment (67.6% vs. 38.3%; P<0.001) and cholesterol-lowering medication (72.4% vs. 66.9%; P=0.023).

In the final analysis, MACI was associated with both higher NIHSS and mRS at day 7 or discharge if earlier, with adjusted coefficient 0.57 (95% CI=0.15-0.99; P=0.007) and 0.17 (95% CI=0.03-0.32; P=0.018) respectively. MACI was also associated with complication/-s regardless type, DVT and MI with adjusted OR 1.35 (95% CI=1.02-1.79; P=0.035), 6.59 (95% CI=1.4-30.99; P=0.017) and 2.73 (95% CI=1.23-6.02; P=0.013), respectively.

There were 8 patients who got DVT in the first week after the admission, 4 in the MACI group and 4 in the SACI group. All four patients in the MACI group had active cancer, whereas no patient in the SACI group had a history of a cancer (P=0.005). The patients with MACI and MI during the in-hospital stay had more often concomitant AF compared to the patients with SACI and MI (70% vs. 32%: P=0.037).

Paper-IV

Of the 311 patients diagnosed with MACI, 222 (71.4%) had single-territory clinical manifestation (MACI-S).

NIHSS on admission was higher in patients with MACI-M compared to those with MACI-S [5 (IQR=2-11) vs. 3 (IQR=1-8); p=0.036]. Patients with MACI-M were more often categorized as TACI (29.2% vs. 13.5%; P=0.001), whereas patients with MACI-S who were more often categorized as PACI (32.6% vs. 47.3%; P=0.016). The distribution of MACI in the left anterior + posterior territory was more common in patients with MACI-S (20.7% vs. 9%; P=0.014). The distribution of MACI in all three territories was more common in patients with MACI-M (37.1% vs. 18%; P <0.001). Patients having less than five ischemic lesions presented more often with single-territory clinical manifestation (54.5% vs. 40.5%; P=0.025) and those having >10

ischemic lesions presented more often with multi-territory clinical manifestation (36% vs. 19.4%; P=0.002).

After adjustment for NIHSS on admission, sex and age, TACI, involvement of all three territories and >10 ischemic lesions remained significantly associated with MACI-M, with an adjusted OR (aOR) of 3.31 (95% CI = 1.39-7.86; P=0.007), 2.58 (95% CI = 1.49-4.5; P=0.001) and 2.3 (95% CI = 1.32-4.01; P=0.003), respectively. PACI, involvement of the left anterior + posterior territory and <5 ischemic lesions remained significantly associated with MACI-S with an aOR of 0.57 (95% CI = 0.34-0.97; P=0.039), 0.37 (95% CI = 0.16-0.82; P=0.015) and 0.58 (95% CI = 0.35-0.97; P=0.040), respectively.

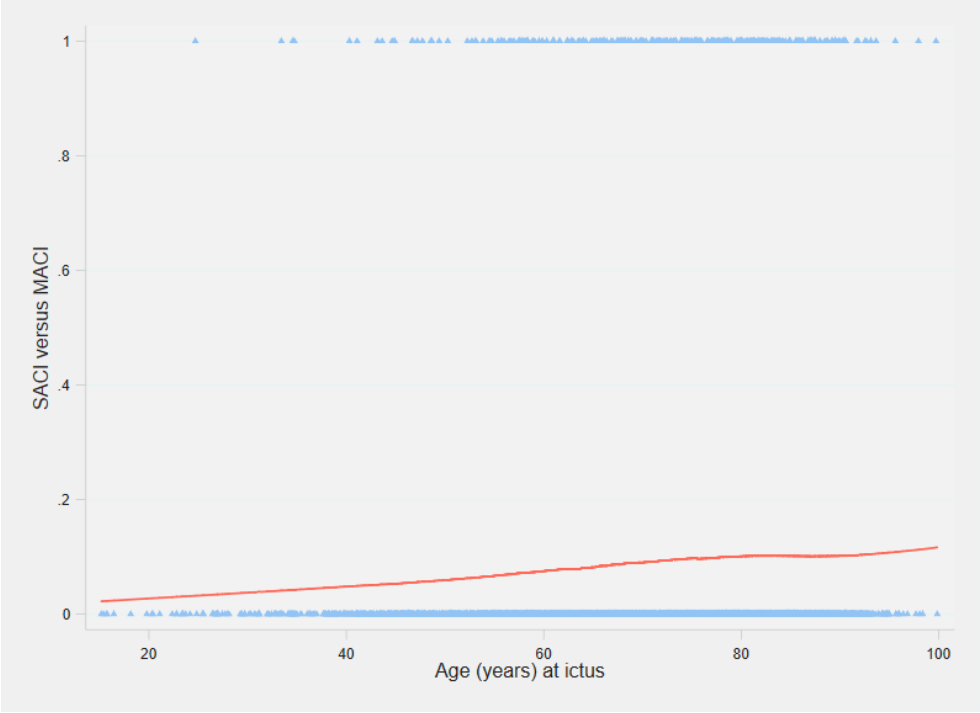
Discussion

Epidemiology

The frequency of MACI in the Bergen NORSTROKE registry is in accordance with other studies applying a comparable methodology. In Paper-I, comprising 2125 patient with DWI-MRI, we found MACI in 8.8%.[145] The extended cohort of 3343 patients in Paper-III showed a slightly higher frequency of 9.3%.[152] Almost all patients included in the studies were examined by 1.5T MRI. This may have underestimated the true frequency. Two studies showed that 3.0 T DWI-MRI may detect additional acute micro-lesions, not seen with 1.5T MRI.[44, 129] On the other hand, a study comparing the accuracy of 1.5T and 3.0T DWI-MRI in diagnosis of ACI within the first 6 hours showed that both sensitivity and specificity were actually lower for 3.0T DWI-MRI and questioned its diagnostic power for the hyperacute ACI.[153] It seems that 3.0T DWI-MRI is less accurate in the hyper-acute stage of ACI despite higher signal-to-noise ratio than in 1.5T DWI-MRI.

A higher number of mechanical thrombectomies (MT) performed in 2014-2017 may explain a slightly higher frequency of MACI in the extended cohort. In the 8 years period from 2006 to 2013, only 44 MT were performed in total, more often in patients with MACI (5.95% vs. 1.72 %; P<0.001). However, in the additional period from 2014 to January 2017, 62 MT were performed in total and the frequency of MT increased to 9.4% in the MACI group compared to 2.6% in the SACI group (p>0.001). We assume that peri-procedural cerebral embolization partly contributes to the increasing number of MACI. Our study shows that females are prone to have MACI relatively more frequently. In the MACI group, females were more often represented than in the SACI group (49% vs. 39%; P=0.011). Even though AF is more prevalent in males,[154] females with AF are at higher risk of stroke compared to males regardless of anticoagulant treatment,[155] which may explain our finding. The overall age in the MACI group was higher than in the SACI group which may be related to higher occurrence of risk factors of CE, including AF, but also due to other disorders linked to hypercoagulable states.[156] Figure 5 shows relatively higher clustering of patients with MACI in the area of higher age (upper X axis).

Figure 5. Age distribution of patients with SACI vs. MACI



Bergen NORTROKE registry (2006-2016);

MACI – Acute cerebral infarct(s) in multiple arterial territories; SACI - Acute cerebral infarct(s) in a single arterial territory

The etiology of MACI

The number of patients with specified cause of ACI increases along with the introduction of new, more advanced diagnostic methods, such as neuroimaging, improved supplementary diagnostic tests and better understanding of stroke pathophysiology.[157, 158] However, over one-quarter of all CI are, based on TOAST criteria, still classified as of undetermined etiology. This may be caused by incomplete investigation, presence of competing etiologies, or truly unidentified cause despite an extensive investigation.[17] The NORSTROKE registry contains information on the TOAST classification. Table 7 shows TOAST etiology among patients with ACI confirmed by DWI-MRI admitted from 2006-2013, but also separately for patients with MACI and SACI.

The role of cardiogenic embolism

Even though the TOAST definition of cardiogenic embolism (CE) states that the evidence of the multiple arterial territory distribution of ischemic lesions supports the clinical diagnosis of CE, many of these patients end up in the category of undetermined etiology (UE).

In Paper-I, 34 patients were diagnosed with UE even though CE was probable, either due to the presence of MACI in all three arterial territories, or due to other factors associated with CE, such as supraventricular tachycardia, palpitations, left bundle branch block or no concomitant ICA stenosis (Table 7). In Paper-III, the symptoms and clinical characteristics highly suggestive of CE were considered determinative. CE was strongly associated with MACI (53% vs. 28%; P<0001) and as a consequence, the UE subtype decreased substantially (42% vs. 32%; P<0.004).[152] This change was accidentally not reported in the methodology section of the Paper-III. Nevertheless, neither CE- nor UE-subtype was included as an adjustment variable to the final analysis. Thus, this change had no implication for the final results.

A recently published study evaluating clinical characteristics of patients with cryptogenic stroke and proven paroxysmal AF showed that bihemispheric distribution of the ischemic lesions was significantly associated with the detection of pAF (30% vs. 5.5%).[159] These data and our results support that the TOAST classification is insufficient for the correct diagnosis among patients with MACI. Possibly, other preferably phenotypic classifications should be used in these patients. Possibly, MACI should be considered as an argument for anticoagulation in patients with cryptogenic stroke.

Table 7. TOAST etiology in the NORSTROKE registry (2006-2013)

TOAST	All ACI N = 2125	MACI (Modified TOAST) N = 187	MACI (Original TOAST) N = 187	SACI N = 1938
CE, N (%)	660 (31.1)	101 (54.0)	67 (35.8)	559 (28.8)
LAA, N (%)	272 (12.8)	19 (10.2)	19 (10.2)	253 (13.1)
SVD, N (%)	285 (13.4)	7 (3.7)	7 (3.7)	278 (14.3)
OD, N (%)	68 (3.2)	6 (3.2)	6 (3.2)	62 (3.2)
UE, N (%)	840 (39.5)	54 (28.9)	88 (47.1)	786 (40.6)

**MACI (Modified TOAST) – etiological spectrum of MACI based on TOAST criteria, where the MACI and other clinical characteristics associated with CE were decisive factors; MACI (Original TOAST) - etiological spectrum of MACI based solely on TOAST criteria; LAA – large artery atherosclerosis; CE – cardiogenic embolism; SVD – small vessel disease;, OD – other disease; UE – undetermined etiology; MACI – Acute cerebral infarct(s) in a multiple arterial territories; SACI - Acute cerebral infarct(s) in a single arterial territory; ACI – acute cerebral infarct*

Our analyses support that CE is probably the leading etiology among patients with MACI. These findings appear to be in line with other studies. Akhtar et al recently published a simple literature-based pooled analysis where they sought to clarify the etiological spectrum among patients with MACI (Table 8). Unfortunately, the authors do not list which studies where included in the analysis and it is probable that the results may be influenced by the inconsistent methodologies.[47] However, this is the biggest pooled analyses on this topic published to this date. The rate of CE was similar to our results in Paper-I (35.8% vs. 37.5%).[145]

Table 8. The etiological spectrum of patients with MACI - pooled analysis

Etiology	Patients with MACI N=1715
Cardiogenic embolism	638 (37.5)
Large artery atherosclerosis	440 (25.7)
Intracranial atherosclerosis	30 (1.8)
Blood disorders and cancer	36 (2.1)
More concomitant etiologies	44 (2.6)
Undetermined	472 (27.6)
Autoimmune diseases	3 (0.2)
Iatrogenic / peri-procedural	2 (0.1)

Adapted from Akhater et al 2019; MACI – Acute cerebral infarct(s) in multiple arterial territories

Atrial fibrillation (AF) probably plays a central role in CE-associated MACI. Among 67 MACI patients with CE, 85% had concomitant AF. On the other hand, 69% of patients with SACI diagnosed with CE had concomitant AF. There is an uncertainty of possible additional patients with paroxysmal AF (pAF), who were not revealed at discharge. There is evidence that up to 30% of all patients with cryptogenic stroke have pAF. Other modalities of long-term ECG monitoring, such as insertable cardiac monitoring (ICM), are superior to conventional follow-up with 24- or 48- hours Holter-monitoring. In our cohort, no patient was followed-up with ICM or other long-term ECG monitoring device. This may have led to underestimation of pAF in our cohort. New, non-invasive devices utilized for long-term ECG monitoring, such as smartwatches may be a widely available and promising approach for the screening of high-risk population, with a possible impact on early primary and secondary prevention.[132]

Other specific causes of CE, such as myocardial infarction or intramural cardiac thrombus, were grouped as CE and not selectively registered in the NORSTROKE database. Therefore, our results cannot provide data on other concrete causes of CE. Most of the patients in the category of CE had mostly cortical lesions on follow-up DWI-MRI. This finding underlines the importance of ischemic lesion patterns in diagnostic considerations (Table 9).

Table 9. DWI-MRI patterns and TOAST classification among patients with MACI

	TOAST					
Stroke pattern	LAA N=25	CE N=164	SVD N=9	OD N=9	UE N=104	MACI N=311
Lacunar, N (%)	1 (4.8)	4 (19.1)	4 (19.1)	1 (4.8)	11 (52.4)	23 (7.4)
Cortical, N (%)	3 (4.2)	50 (70.4)	0 (0)	2 (2.8)	16 (22.5)	71 (22.8)
Subcortical, N (%)	0 (0)	5 (31.3)	0 (0)	0 (0)	11 (68.8)	15 (4.8)
Mixed, N (%)	14 (7.5)	101 (54.0)	5 (2.7)	5 (2.7)	62 (33.2)	187 (60.2)
Watershed, N (%)	7 (46.7)	4 (26.7)	0 (0)	1 (6.7)	3 (20)	15 (4.8)

**The Bergen NORSTROKE registry (2006-2016) – not published*

LAA – large artery atherosclerosis, CE – cardiogenic embolism, SVD – small vessel disease, OD – other disease, UE – undetermined etiology, TOAST - the Trial of ORG 10172 in Acute Stroke Treatment; MACI – Acute cerebral infarct(s) in multiple arterial territories

The role of large artery atherosclerosis

Among patients with MACI, the TOAST diagnosis - large artery atherosclerosis (LAA) had similar occurrence as in patients with SACI (10.2 vs. 13.1).[145] However, the presence of symptomatic ICA stenosis appeared to be significantly associated with MACI in both univariate and multivariate analyses. The LAA subtype includes ICA occlusions but it is often difficult to say if the occlusion is of CE or LAA origin. However, proximal ICA occlusions are more often caused by LAA. Whereas distal ICA occlusions are more likely caused by CE.

Technically, a unilateral symptomatic ICA stenosis hardly causes MACI. So bilateral presence of ICA stenosis seems to be a prerequisite as it is shown in the Paper-II. It is possible that in some of these patients, the anatomic variations of the cerebral arteries, including fetal PCA (fPCA) or azygos ACA contribute. To our knowledge, there are no available data on the exact number of such patients. Reviewing brain imaging in our cohort of MACI patients, we also assessed the presence of the anatomic variations and possible connection to the mechanism of MACI. These data show that 79 out of 311 patients (25.4%) had either bilateral or unilateral fPCA. There were 8 patients (2.6%) where fPCA had configuration corresponding with the distribution MACI. Azygos ACA was present in 14 patients (4.5%), but in only four patients (1.2%), MACI could potentially be attributed to this AV. In only one patient with unilateral ICA occlusion, we could assume that cross-flow mechanism was the mechanism behind MACI. These findings show that such AVs probably are rare contributors to MACI. Other studies have not proven that fPCA may be a risk factor for TIA or CI.[160] An CT- or MR-angiography as a part of the diagnostic work-up, may exclude this less common mechanism of MACI. The MRI pattern of ischemic lesions may also predict the true etiology of MACI. Uni- or bilateral watershed cerebral infarcts may be caused by hypoperfusion either of cardiac origin or due to aggravation of an ipsilateral large artery stenosis, or by embolism from vulnerable, unstable or ruptured atherosclerotic stenosis. In our cohort of MACI patients, 15 (4.8%) patients had watershed infarcts, of which 7 (46.7%) were categorized as LAA (Table 9).

The role of small vessel disease

Based on our results and other studies, small vessel disease (SVD) probably causes a minority of MACI. Only 7 patients (3.7%) had distribution of lacunar infarcts in multiple territories accompanied by risk factors characteristic for SVD (Table 7). In the NORSTROKE registry, patients with lacunar MACI were mostly categorized as UE subtype (52.4%). This indicates that coexistence of etiologies or risk factors suggesting also CE or LAA, may contribute to lacunar MACI in these patients (Table 9).[100] On the other hand, we must distinguish lacunar MACI from multiple lacunar infarcts within only one arterial territory, which may be a sign of a severe generalized SVD.[103]

Except for common risk factors among patients suffering lacunar stroke, such as hypertension, hypercholesterolemia or DM, the extent of leukoaraiosis usually reflects how pronounced ongoing SVD is.[23]

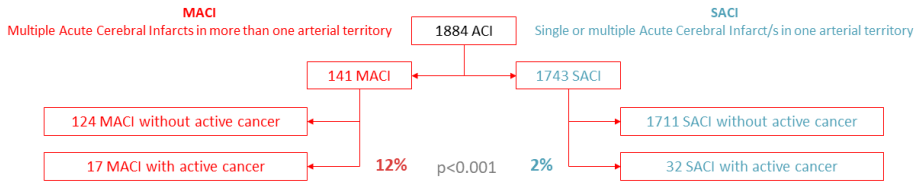
In the NORSTROKE registry, leukoaraiosis seen on MRI was significantly more common among patients with MACI compared to the patients with SACI (67% vs. 56%; P<000.1), which may be also result of the overall older MACI population. Interestingly, patients with MACI who were diagnosed with SVD subtype had similar level of leukoaraiosis compared to patients with SACI who were classified with SVD subtype (65.5% vs. 55.6%; P=0.537). This may again support a multifactorial pathophysiology in lacunar MACI rather than pure SVD in these patients.

The role of rare etiologies

Based on the TOAST classification, rare etiologies are categorized as other diseases (OD) subtype. We found no difference between SACI and MACI (3.2% vs. 3.2%; P=0.97) regarding OD-patients in our cohort. One of the less common etiologies is hypercoagulable state associated with an active cancer (Trousseau syndrome). We performed a sub-analysis using the data from the PhD work of Dr. Aurora Selvik, who reviewed admission records of all stroke patients in the NORSTROKE registry admitted from 2006 to 2013 and extracted all cancer diagnoses.[161] Results were presented at the European Stroke Organization Conference (ESOC) 2018 in Goteborg (Figure 6).[162] We found that the presence of active cancer (cancer diagnosed ±6

months from the index stroke) was significantly more common among patients with MACI compared to patients with SACI (12% vs. 2%; P<001). The MACI patients had a significantly higher median of D-Dimer on admission [7.1 (IQR=2.7-20) vs. 0.9 (IQR=0.5-2.1); P<0.001]. High values of D-Dimer correspond with the fact that most of these patients had mucinous types of cancer, including lung, colon or pancreas cancer, which often are associated with hypercoagulable states.[163] Our findings also indicate that the cancer-associated hypercoagulable state is associated rather with MACI than SACI. It is unknown if some of these patients had nonbacterial thrombotic endocarditis, which often requires TEE for correct diagnosis. It may be difficult to differentiate AF-associated MACI from cancer-associated MACI based on standard diagnostic work-up. One study concluded that patients with cancer-associated MACI often have D-Dimer > 2.0 µg/mL, which remains high also in the subacute phase.[118] We have no further data on other rare etiologies or concomitant diseases potentially associated with hypercoagulable states.

Figure 6. Active cancer in patients with MACI and SACI



**Adapted from the poster Novotny et al. 2018 (ESOC 2018; Gothenburg)*

MACI – Acute cerebral infarct(s) in multiple arterial territories; SACI - Acute cerebral infarct(s) in a single arterial territory

The time-pattern and etiology

As we have shown in Paper-II, cerebral embolization in LAA-associated MACI occurs most probably successively over time. The ischemic lesions may be separated by hours or even days as the blood clots or their fragments are released one by one from the

atherosclerotic plaques. In contrast to this, the ischemic lesions in the CE-associated MACI most likely occur simultaneously as a sudden shower of emboli with no additional embolization the following days after symptom onset. One of the explanations for this phenomenon may be the morphology of atherosclerotic plaque in symptomatic ICA stenoses. Several studies have shown that atherosclerotic plaques in the symptomatic ICA are associated with increased neovascularization, fibrous cap thinning, inflammation, plaque necrosis and rupture.[164, 165] All these factors define instability and vulnerability of the atherosclerotic plaques. Therefore, the plaques are prone to recurrent embolization, mainly during the acute phase, when the plaque is unstable. Ongoing embolization not only leads to a higher total risk of recurrence, but also leads to a higher risk of recurrence within the first 30 days.[139, 166]

In Paper-II, we also conducted a sub-analysis aiming at patients with MACI solely in the anterior circulation and with concomitant symptomatic or asymptomatic ICA stenosis. In the cohort of patients with MACI in the anterior circulation only (N=93), there were 25 patients with ICA stenosis, all of them had symptomatic ICA stenosis on at least one side, and no patient had only asymptomatic ICA stenosis(es). This suggests possible importance of plaque instability but also its bilateral presence in these patients. It is probable that the presence of an unstable plaque bilaterally is a prerequisite for MACI. The morphology and stability of the atherosclerotic plaques may be evaluated non-invasively. Advanced neurosonology, including 3D ultrasound and contrast-enhanced ultrasound imaging may clarify in detail plaque shape and size, but also the degree of intra-plaque neovascularization and hemorrhage.[167, 168] Morphology and neovascularization may also be evaluated by high-resolution contrast-enhanced MRI with higher field strength (Tesla).[169] Microemboli detection has also been shown as an effective and non-invasive approach to evaluate on-going embolization. Silent microembolization after stroke is more common in patients with symptomatic ICA stenosis accompanied by ulcerative plaques.[170, 171] Silent microembolization in the acute phase is also associated with a higher risk of recurrent stroke.[172, 173] These findings may support the theory of successive embolization in LAA-associated MACI, as shown in our results. The presence of microembolization may lead to adjustment or change of inadequate secondary prevention and, thus, preventing recurrent ischemic events in these patients.

Table 10 shows that patients with LAA-associated MACI underwent follow-up MRI later than those with CE-associated MACI. Patients with MACI and concomitant symptomatic or asymptomatic ICA stenosis, regardless of the TOAST category, also underwent MRI later than those with CE-associated MACI. On the other hand, there was no difference between patients with CE- and LAA-associated SACI (P=0.565). It is not clear why MRI was taken later in patients with LAA-associated MACI and we do not have data which can explain this phenomenon directly. It is possible that in patients with LAA-associated MACI, the atherosclerotic plaques are more unstable bilaterally than in those with LAA-associated SACI. These patients might have a minor or transient neurological deficit hours or days before the admission, which was by the patient ignored and a second, major deficit could be the reason for a later admittance relatively to the initial minor neurological event. The evolution of DWI-MRI and ADC-MRI changes is gradual and follows a certain time-course during hyper-acute, acute and chronic stage of CI.[174, 175] However, it is difficult to differentiate the age of the lesions based on one single DWI-MRI. We therefore cannot confirm that all patients categorized as MACI had all their ischemic lesions truly acute in relation to each other in terms of hours.

Table 10. Time from stroke onset to follow-up MRI (days)

Cohort	**CE**	**LAA**	**Symptomatic ICAS**	**Asymtomatic ICAS**
MACI	N=67	N=19	N=41	N=24
median (IQR)	1 (1-2)	2 (1-6)	2 (1-5)	2 (1-7.5)
mean (SD)	1.99 (2.27)	3.74 (3.03)	3.6 (3.96	4.13 (3.8)
	P=0.008			
SACI	N=551	N=246	N=275	N=152
median (IQR)	1 (1-3)	1 (1-3)	1 (1-3)	1 (1-3)
mean (SD)	2.21 (2.62)	2.39 (2.77)	2.32 (2.8)	2.59 (2.84)
	P=0.565			

Comparison of time (days) from stroke onset to MRI within CE and LAA subgroup as well as in patients with either symptomatic ICAS or asymptomatic ICAS regardless of TOAST classification

MACI – Acute cerebral infarct(s) in multiple arterial territories; SACI - Acute cerebral infarct(s) in a single arterial territory; CE – cardiogenic embolism; LAA – large arthery atherosclerosis; ICAS –

internal carotid artery stenosis; MRI – magnetic resonance imaging; IQR – interquartile range; SD – standard deviation

Clinical manifestation may be misleading

The brain is extremely complex and knowledge of its topographical function is paramount to set a correct diagnosis in an acute setting. This mainly applies to the neurological disorders craving prompt therapeutic decision-making. Stroke is the field of acute neurology comprising the highest number of such patients. In suspected CI without visible vascular occlusion on vascular imaging, the clinician must rely solely on her/his diagnostic skill and experience in order to initiate prompt IVT and to exclude other differential diagnoses. Patients with MACI are characterized by involvement of at least two distinct arterial territories simultaneously. Therefore, the patients may present with unusual clinical manifestation than in patients with SACI. One may expect a higher frequency of bilateral neurological deficits or bi- / unilateral neurological deficits in combination with the symptoms from functional areas supplied by the posterior circulation. However, the ischemic lesions in MACI are often heterogeneous in size, number and distribution. These factors together with coexisting comorbidities may influence the final clinical manifestation. A standard initial neurological assessment is usually performed by NIHSS, which represents a widely used assessment scale of clinical severity of a stroke.[147] NIHSS has high reliability and validity. It may predict the clinical outcome and has been used in numerous clinical trials for acute stroke.[176] However, some aspects of NIHSS has been challenged for its inaccuracy. Several studies showed that NIHSS favors the left, in most cases, dominant hemisphere, over the right, usually non-dominant, despite similar lesion volumes.[177, 178] An analysis of a large German hospital-based registry comprising 20.097 stroke patients showed an unequal distribution of left- and right hemisphere stroke (56% vs. 44%, P<0.0001).[179] These differences applied for CI, but not for ICH. The difference also diminished with increasing severity of the stroke, as the probability of symptom recognition then is higher, regardless of the side of the stroke. The fact that there was no difference between left and right-sided ICH also corresponds with generally more severe neurological deficit independently of the affected side. Right hemisphere lesions are associated with neglect and thus decreased awareness of the symptoms also by the patient. Similarly decreased recognition of

such symptoms may also apply for the first-line physician. Two studies reported around 15% higher occurrence of silent strokes in the right hemisphere.[180, 181] It is therefore not by chance that patients with ACI in the left hemisphere are more frequently treated with tPA, and also more frequently admitted within the first 3 hours after symptom onset.[182]

From a clinical point of view, MACI are interesting model to study. Based on the admission records, only 89 out of 311 patients with MACI (28.8%) admitted to Haukeland University Hospital presented with clinical manifestation corresponding to the involvement of more than one arterial territory. Looking separately at patients with MACI in only the anterior circulation (N=133), left-hemisphere symptoms were more often described in the admission records (43.6 vs. 28.6%). Our analyses showed that a lesion in the left arterial territory is associated with single-territory clinical manifestation (OR=0.37, 95% CI=0.16-0.82). This again emphasizes an underestimation of right-hemisphere stroke symptoms. The left-hemisphere symptoms give more prominent and more recognizable neurological deficits and may shadow the right-hemisphere symptoms. A paresis in the dominant extremity or aphasia may easily pull the attention of both patient and examining physician from other, sometimes hardly recognizable forms of cognitive deficit, as apraxia or neglect.

Neglect may be unrecognized by both patient and examining physician. However, NIHSS itself underestimates the clinical manifestation from the right-hemisphere. It is possible to assign only 2 points to the neglect compared to 7 points to the deficit in the language.

Interestingly, an involvement of all three arterial territories (N=73) seemed increased the recognition of the right-hemisphere symptoms. It is unclear if concomitant symptoms originating from the functional areas supplied by posterior circulation may increase attention towards the right-hemisphere symptoms.

Another drawback of NIHSS is its limitation in recognition of stroke in the posterior circulation compared to the anterior one.[183] The issue mainly is an underestimation of posterior stroke severity. Sato et al. showed that patients with CI in the posterior circulation have a higher probability of unfavorable outcome at three months despite relatively low NIHSS compared to the CI in the anterior circulation. The proposed

NIHSS cut-off predicting favorable outcome in posterior circulation CI was therefore estimated to ≤4-5 compared to ≤8 for anterior circulation CI. [183, 184] Our study showed that in patients with MACI and involvement of the posterior circulation, symptoms from the posterior circulation were recognized almost uniformly in 50% of cases. It may be sometimes challenging to distinguish if the ischemic lesion lies in the anterior or posterior circulation since the symptomatology may be overlapping. In general, symptoms from posterior circulation are less often recognized and follow-up neuroimaging is essential for final confirmation and accurate localization of the lesions.[185] Our findings indicate that without MRI, majority of MACI would be barely diagnosed based on the initial clinical manifestation only.

The burden of MACI

In general, patients with TIA or CI are at a higher short- and long-term risk for complications and readmission during stroke recovery.[186-188] Infections and recurrent vascular events are the most common complications. An increased presence of comorbidities in these patients may further worsen the outcome. We analyzed patients with MACI as a separate entity and compared the course of in-hospital stay to patients with SACI.

In the Bergen NORSTROKE registry, the overall frequency of patients experiencing one or more in-hospital complications, as defined in Paper-III, was 36.1%. Other studies have reported frequencies of in-hospital complications in a range from 25.2% to 59%. [189-192] The frequency and types of these complications are also strongly related to stroke subtype, severity and localization.[193] However, different methodologies and different sets of studied complications make comparison difficult.

Table 11 shows the distribution of in-hospital complications in the two groups. Patients in the MACI group experienced more complications in total (51 % vs. 36%; P<0.001). Based on univariate analyses, several complications appeared to be more frequent in the MACI group, including deep venous thrombosis (DVT), myocardial infarction (MI), symptomatic intracranial hemorrhage, epileptic seizure, pneumonia, urinary tract infection, urinary retention and urinary incontinence. However, in the

multivariate analysis, only DVT, MI and any complication remained significantly more frequent in the MACI group.[22]

Table 11. Comparison of in-hospital complications between MACI and SACI

Complications	**MACI** N=311	**SACI** N=3032	p-value
Any complication, N (%)	159 (51.1)	1049 (35.6)	<0.001
Deep venous thrombosis, N (%)	4 (1.3)	4 (0.1)	<0.001
Cerebral infarction, N (%)	1 (0.3)	15 (0.5)	0.672
Myocardial infarction, N (%)	10 (3.2)	28 (0.9)	<0.001
Pulmonary embolism, N (%)	3 (1.0)	11 (0.4)	0.118
Symptomatic ICH, N (%)	7 (2.3)	14 (0.5)	<0.001
Heart failure, N (%)	6 (1.9)	26 (0.9)	0.065
Epileptic seizure, N (%)	15 (4.8)	85 (2.8)	0.047
Pneumonia, N (%)	37 (11.9)	202 (6.7)	0.001
Infection with unknown focus, N (%)	7 (2.3)	31 (1.0)	0.052
Urinary tract infection, N (%)	53 (17.0)	357 (11.8)	0.007
Urinary retention, N (%)	78 (25.1)	529 (17.4)	0.001
Urinary incontinence, N (%)	50 (16.3)	304 (10.7)	0.003
Depression, N (%)	19 (6.1)	161 (5.3)	0.552
Death, N (%)	5 (1.6)	21 (0.7)	0.080

MACI – Acute cerebral infarct(s) in multiple arterial territories; SACI - Acute cerebral infarct(s) in a single arterial territory; ICH – intracranial hemorrhage

DVT during in the first seven days of in-hospital stay was registered in 8 out of 3343 (0.24%) patients regardless of the lesion distribution. This rate is in line with other studies.[191] However, four of these patients had MACI (P=0.017). We hypothesized that concomitant comorbidity might contribute to the higher occurrence of DVT in the MACI group. It is well known that some malignancies are associated with a hypercoagulable state (Trousseau syndrome). This syndrome is associated with a higher risk for thromboembolism in general, including CI or venous thromboembolism.[194] Our data, and also other studies, show a higher occurrence of MACI among the cancer patients[115, 162] and the same applies for pulmonary embolism and DVT.[195, 196] We therefore performed a sub-analysis on concomitant cancer in patients experiencing DVT (supplement of Paper-III). All four patients having MACI and DVT during hospitalization also had active cancer. One of these patients had

cancer accompanied by a catastrophic antiphospholipid syndrome. These patients have often resistant hypercoagulable states, which makes the secondary prevention of recurrent embolism challenging or ineffective. The four patients in the SACI group experiencing DVT had no cancer but experienced a more severe stroke than patients with MACI and DVT, as confirmed by the higher median NIHSS on admission (13 [IQR=7-16.5] vs. 1 [IQR=0-4]). It is possible that in these patients, the DVT was mainly associated with reduced post-stroke mobility during the first days of hospitalization. The confidence interval for DVT in the analysis was rather wide, and this is related to the small sample size. However, these findings suggest that concomitant DVT and MACI should always work as a warning sign and cancer screening should be considered in these patients.

MI was more frequent in the MACI group (3.2% vs. 0.9%). An explanation may be a higher occurrence of atrial fibrillation (AF). AF is associated with an increased risk of MI independent of common coronary heart disease risk factors.[197] We therefore performed a sub-analysis of patients experiencing MI during hospitalization who had or were diagnosed with concomitant AF (supplement of Paper-III). We found that 70% of patients with MACI and MI had concomitant AF, in contrast to only 32% in the SACI group. In other studies, the risk of MI after stroke is 2.3% per year (95% CI, 1.6 to 2.9).[198] In our registry, more than 3% of MACI patients experienced MI in the first week after the index stroke. The relationship between MI and AF is not clear. It is possible that AF is not a direct risk factor for MI, but rather a marker for existing coronary heart disease. Pure coronary embolism related to AF is considered rare. It is attributed to the mutual constitution between coronary arteries and aorta. Up to 12% of MI is caused by coronary embolism, of which 24% are attributed to AF.[199] Another explanation may be a type 2 MI caused by a non-coronary trigger in the absence of acute plaque disruption. Some patients with AF may experience poorly controlled ventricular response followed by oxygen supply-demand mismatch and consequently myocardial ischemia.[197, 200]

Our findings indicate that both DVT and MI most likely are related to the underlying malignancy or AF/heart disease respectively. On the other hand, the complications among the patients with MACI, which appeared to be more frequent in the univariate

analysis, may be mainly related to higher age, worse functional status before the index stroke, or stroke severity itself.

Death within the first seven days of in-hospital stay did not differ significantly between MACI and SACI patients. This result may, however, be biased. Some patients died within 24 hours after admission before the MRI scan was taken. Moreover, in some patients with poor prognosis, MRI was not performed. These patients (N=634) were examined only with CT scan and were therefore not included in the analysis. An autopsy was not performed in the vast majority of our patients. Thus, the frequency of additional MACI patients is unknown. It is possible that this group comprised a considerable number of patients with MACI.

All of these factors may have contributed to the overall worse early clinical and functional outcome (Table 12). Our study confirms that MACI should be seen as a "red flag" not only in the diagnostic work-up but also in the follow-up during hospitalization.

Table 12. NIHSS and mRS on admission and at day 7 / discharge.

	MACI (N=311)	SACI (N=3032)	P-value
NIHSS on admission	4 (1-9)	2 (2-5)	<0.0001
NIHSS at discharge	2 (1-7)	1 (0-4)	<0.0001
mRS prior admission	0 (0-2)	0 (0-0)	0.008
mRS at discharge	3 (1-4)	2 (1-3)	<0.001

NIHSS- National Institutes of Health Stroke Scale; mRS - Modified Rankin Scale

Impact of MACI on treatment

There are no particular limitations in acute reperfusion therapy for patients with MACI. Our findings show no significant difference in the frequency of intravenous thrombolysis (IVT) between patients with MACI and SACI (23.5 vs. 19.5; P=0.09). Patients with MACI received, however, more often mechanical thrombectomy (MT) (10.1% vs. 2.6; p=<0.001) (Supplement Paper-III). Overall more severe stroke in the MACI group may be related to a higher occurrence of large vessel oclusions (LVO). Patients with MACI who received IVT had a higher median NIHSS on admission compared to the patients with SACI (8 [IQR=4-14] vs. 5 [IQR=3-11] P=0.007). A

similar trend applies for MACI patients who underwent MT (17 [IQR=10-20] vs. 13.5 [IQR=6.5-19.5; P=0.185]. The severity of stroke probably represents a critical factor in therapeutic decision-making in regard to acute reperfusion therapy.

As shown in the supplement of Paper-III, the patients with MACI were more often anticoagulated prior to the index stroke. This corresponds with the higher frequency of known paroxysmal and chronical AF before admission. This pattern is also reflected in the secondary prevention introduced during hospitalization or after discharge. Almost twice as many patients in the MACI group were discharged with anticoagulation compared to those having SACI (59.5% vs. 34.7%; <0.001), whereas antiplatelet and lipid-lowering therapy more often was introduced in patients with SACI. The etiological spectrum of MACI discussed in this dissertation is the explanation.

Higher occurrence of rare forms of CE among patients with MACI, such as Trousseau syndrome, may require a different approach both in regards to acute reperfusion therapy and to secondary prevention.

Strengths and limitations

The Bergen NORSTROKE registry represents prospective study comprising a large number of well-described stroke patients, of which the majority was examined by MRI. To our knowledge, there have not been published any studies with a comparable number of patients with DWI-MRI confirmed MACI.

There are, however, several limitations to this study. Not all stroke patients underwent complete investigation. Even though our results show that cardiogenic embolism, predominantly atrial fibrillation, is the major cause of MACI, this etiology may be underestimated. If standard ECG or Holter-monitoring did not reveal AF, further investigation was not performed. Long-term cardiac monitoring would probably reveal more cases of AF or relevant arrhythmias, predominantly in patients with MACI. It is possible that more extensive echocardiographic examination would reveal a higher number of cardiac emboli sources as well. It applies, for example, to nonbacterial thrombotic endocarditis, which often requires confirmation by TEE. The TOAST classification has several drawbacks in the form of over- or underestimation of some

TOAST categories. Following the strict TOAST criteria, many patients often end up in the undetermined etiology subtype.

One of the limitations in Paper-III and Paper-IV is the lack of data on lesion volumes which could influence the results in both papers. This issue was pointed out in the two comments to the paper-III.[201, 202] The importance of lesion volume may, however, be misleading in case of MACI. It is possible that some patients with MACI had worse outcome despite low lesion volume. A concomitant lesion in vital or important functional brain areas such as brain stem or capsula interna may be an example.[203]

Conclusions and implications

Patients with MACI represent a substantial portion of the stroke population which every stroke physician encounter in clinical practice. However, few studies have been published on this topic. With our four papers, we contribute to clarify some etiological, clinical and diagnostic aspects of this specific group of stroke patients.

I. We confirmed that MACI are not a rare phenomenon and represents approximately 10% of ischemic stroke patients consecutively admitted to our stroke unit. We may also conclude that cardiogenic embolism subtype is the major TOAST category among MACI and AF the primary etiology. However, presence of symptomatic ICA stenosis appeared to be associated with MACI and is probably an additional risk factor. In these patients, bilateral atherosclerotic plaque instability is probably a prerequisite. In a substantial part of MACI classified as unknown etiology subtype, the cardiogenic embolism (CE) subtype was highly probable due to distribution of the lesions in all three territories, absence of ICA stenosis and concomitant clinical characteristics suggesting CE instead. This finding shows that TOAST classification may underestimate CE-subtype among MACI to a large extent. Other rare etiologies of stroke, such as cancer, should always be considered in these patients. MACI occurs relatively more often in females, which may be related to a higher risk of CI in females having atrial fibrillation. The frequency of MACI increases with age, which is in line with an increasing occurrence of comorbidities, such as atrial

fibrillation or atherosclerosis. Patients with MACI have higher NIHSS on admission, indicating more severe strokes in this stroke group.

II. We showed that the time from clinical onset to the first MRI imaging may shed light on the etiology of MACI. We found a positive correlation between the time from the stroke onset to DWI-MRI and the frequency of LAA-associated MACI. We also found a positive correlation in patients having asymptomatic and symptomatic ICA stenosis regardless of TOAST classification. The same patterns apply for MACI limited to only anterior circulation. There was no correlation between the time from stroke onset to DWI-MRI and the frequency of CE-associated MACI. Our results indicate that emboli originating from ICA stenosis are probably loosened successively in step-wise time pattern. This may be related to the unstable character of atherosclerotic plaques bilaterally in the acute phase after the stroke onset. CTA or MRA should be performed in all patients with MACI to exclude arterial variation associated mechanism. On the other hand, emboli from the heart are probably loosened rather concurrently as a shower of emboli. The single episode is probably not followed by any additional embolization in the nearest days after the stroke. We therefor suggest that microemboli detection should be considered in LAA-associated MACI to assess the effectiveness of secondary prevention of stroke recurrence.

III. We found that during the first seven days of the in-hospital stay, patients with MACI, do worse than those with SACI. Deep venous thrombosis (DVT) and myocardial infarction (MI) occur more often in the MACI group. This may be related to the concomitant comorbidities or etiology of the MACI itself. All MACI patients experiencing DVT also had cancer diagnosed within 6 months from the index stroke. Thus, on-going Trousseau syndrome may be a plausible explanation for thromboembolism. The association between MACI and MI may be explained by the higher frequency of AF, which has been shown as a risk factor for MI. Both short-term clinical and functional outcome appeared to be worse in the MACI group. Higher frequency of complications, more severe stroke, higher age or worse functional status before the admission among the patients diagnosed

with MACI may explain these findings. We believe that tight early follow-up and extensive diagnostic work-up in these patients may reduce some of these complications and prevent negative progression.

IV. We showed that more than 70% of patients diagnosed with MACI on DWI-MRI present with a single-territory clinical manifestation (MACI-S). MACI-S was associated with less than five ischemic lesions in total, involvement of the left arterial territory and partial anterior circulation infarct clinical stroke syndrome (PACI) as defined by the OCSP classification. Multi-territory clinical manifestation was associated with more than 10 ischemic lesions in total, involvement of all three territories and total anterior circulation infarct clinical stroke syndrome (TACI) as defined by the OCSP classification. We assume that the overweight of MACI-S may be explained by several factors. First, NIHSS fails to sufficiently recognize clinical manifestation from the right anterior and posterior territory. Second, some of the acute ischemic lesions might be clinically silent and right hemisphere symptoms may be overshadowed by more striking symptoms from the left hemisphere. Our findings emphasize the importance of DWI-MRI imaging for the final diagnosis of MACI in the acute phase, facilitating the further diagnostic and therapeutic decision-making process in these patients.

We believe that MACI should be seen as a “red flag” in stroke medicine. Our results showed that MACI are not rare and differ from SACI in many clinical aspects, including etiology, pathophysiology, clinical manifestation and early outcome. Thus, patients with MACI require a different diagnostic and therapeutic approaches. We believe that this dissertation and associated papers will contribute with additional and useful knowledge which may be applied in the daily practice.

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Errata

Paper I

Abstract Missing word: “relatively more often females” instead of “more often females”

Paper II

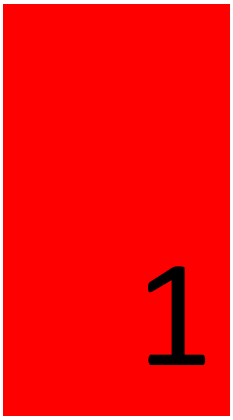
Figure 2 Incorrect description: “fraction of patients with acute cerebral infarcts in multiple arterial territories” instead of “fraction of patients with recurrent cerebral infarcts”

Methodology section (Page 2): “We analyzed the data…” instead of “We retrospectively analyzed the data…”

Paper III

Introduction section: “We hypothesized that ischemic stroke comprising MACI may worsen early recovery” instead of “We hypothesized that ischemic stroke independently of lesions’ volume, comprising MACI may worsen early recovery”

Methodology section: “February 2006 to January 2017” instead of “October 2006 to January 2017”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Acute cerebral infarcts in multiple arterial territories associated with cardioembolism

Novotny V, Thomassen L, Waje-Andreassen U, Naess H. Acute cerebral infarcts in multiple arterial territories associated with cardioembolism.
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Objectives – It is generally believed that cardioembolism is the main cause of multiple acute cerebral infarcts (MACI). However, there are surprisingly few DWI studies and results are conflicting. Based on a large prospective study we hypothesized that MACI are associated with cardioembolism. *Materials and methods* – We studied 2697 patients with acute cerebral infarcts between February 2006 and October 2013 who were prospectively registered in The Bergen NORSTROKE Registry. Among them, 2220 (82.3%) patients underwent magnetic resonance imaging (MRI) and 2125 (96%) of these 2220 patients had DWI lesions. Only patients with DWI lesions were included. MACI were defined as at least two DWI lesions in at least two different arterial territories. *Results* – MACI were detected in 187/2125 (8.8%) patients with DWI lesions. MACI patients were older and more often females. MACI were associated with cardioembolism ($P = 0.042$), especially atrial fibrillation ($P = 0.002$). Other associations were symptomatic internal carotid artery (ICA) stenosis ($P = 0.014$), asymptomatic ICA stenosis ($P = 0.036$), and higher NIHSS score on admission ($P < 0.001$). Among patients with no cardioembolism, 34 (35%) with MACI had symptomatic ICA stenosis versus 268 (25.0%) with non-MACI ($P = 0.037$); 20 (20%) with MACI had asymptomatic ICA stenosis versus 134 (13%) with non-MACI ($P = 0.031$). In the logistic regression analysis, cardiac embolism and symptomatic ICA stenosis were independently associated with MACI. *Conclusions* – Acute cerebral infarcts in more than one arterial territory occur among almost 10% of the patients and are associated with cardioembolism.

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Key words: acute cerebral infarcts; cardioembolism; DWI

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Introduction

The etiology of cerebral infarcts must be determined to prevent recurrence. Diffusion weighted imaging (DWI) is sensitive to acute ischemic lesions and valuable as to etiologic considerations (1, 2). For visualization of ischemic lesions within the first hour after the onset of symptoms, DWI is the optimal modality. Furthermore, it allows differentiation between acute and chronic lesions in most cases (3, 4). Some patients have multiple acute cerebral infarcts (MACI) occurring in more than one arterial territory. This suggests that MACI represent embolic mechanism and stroke neurologists generally believe that cardioembolism (CE) is often the main cause besides other potential sources of embolism, for example, from the aorta, major extracranial and intracranial vessels, fetal type of PCA or due to cross-flow mechanism, coagulation disturbances, hyperhomocysteinemia, etc. (3, 5, 6). However, the number of DWI-based studies supporting this concept is surprisingly low, and previous results are conflicting (7). Furthermore, most studies have used different methods and have been retrospective with too small sample sizes (7, 8).

TOAST classification divides cardiac sources into high-risk and medium-risk groups according

to the probability of cardioembolic stroke. Evidence of previous transitory ischemic attack (TIA) or stroke in more than one vascular territory or systemic embolism supports a cardiogenic mechanism (9). The mechanisms behind multiple acute lesions in a single territory must be distinguished from those which occur in more than one territory. Most multiple brain infarcts in a single territory are probably caused by early fragmentation of one thrombus or embolus, whereas MACI are probably caused by CE or ICA stenosis (3, 10). We present the data on MACI in a prospective study including a large number of patients. We hypothesized that MACI are associated with CE.

Materials and methods

All consecutive patients with acute ischemic stroke (the index stroke) admitted to the Neurovascular center, Department of Neurology, Haukeland University Hospital between February 2006 and October 2013 were prospectively registered in The Bergen NORSTROKE Registry. Ischemic stroke was defined in accordance with the Baltimore-Washington Cooperative Young Stroke Study Criteria comprising neurological deficits lasting more than 24 hours because of ischemic lesions or TIA where computer tomography (CT) or MRI showed infarcts related to the clinical findings (11). In this study, only patients with DWI lesions were included.

CT was performed as soon as possible after admission to the hospital. It was the routine of our department to refer all patients with cerebral infarction to MRI unless there were contrary reasons such as pacemaker, none-consenting, or unstable patient. DWI was performed as part of a routine MRI protocol for stroke patients on 1.5 Tesla Siemens Magnetom (Symphony). The DWI-sequence used was ep2d_diff_3scan_trace, with the following specifications of parameters: field of view (FOV) 230 mm, slice thickness 5 mm, TR 3200 ms, TE 94 ms. All CT and MRI scans were reviewed by a neurologist (HN) with long CT and MRI experience.

The National Institutes of Health Stroke Scale (NIHSS) was used to assess stroke severity on admission. Investigations included cerebral MRI and CT, Holter monitoring, echocardiography, and carotid duplex sonography. Isolated acute ischemic lesions on DWI imaging were defined as lacunar infarcts if <1.5 cm and located subcortical or in the brainstem (9). All other DWI lesions were defined as non-lacunar possibly embolic infarcts (12). ICA stenosis was defined as stenosis >50% or occlusion based on duplex sonography (13). Among patients with MACI, most patients had neurologic deficits from only one of the affected arterial territories. If the patient had symptomatic ICA stenosis associated with ipsilateral non-lacunar infarction, asymptomatic infarction in another territory and no high- or medium-risk cardiac source, then atherosclerosis was considered to be the cause.

Traditional risk factors were defined according to a predefined protocol and included angina pectoris, myocardial infarcts, intermittent claudication, hypertension, diabetes mellitus, and smoking (14, 15). Current smoking was defined as smoking at least one cigarette per day. Diabetes mellitus was considered present if the patient was on glucose-lowering diet or medication. Hypertension, angina pectoris, myocardial infarcts, and peripheral artery disease were considered present if diagnosed by a physician any time before stroke onset. In addition, atrial fibrillation was registered. Atrial fibrillation required electrocardiography (ECG) confirmation any time prior to stroke onset or during hospital stay and was categorized as paroxysmal atrial fibrillation or chronic atrial fibrillation (16, 17). Etiology was determined by the Trial of Org 10172 in Acute Stroke Treatment classification (TOAST) and classified as large-artery atherosclerosis, cardioembolism, small vessel disease, other, and unknown. CE was defined as a sudden arterial occlusion due to embolus released from heart because of high- or medium-risk cardiac source. Large-artery atherosclerosis had to be excluded as a probable cause (9).

MACI in different arterial territories were defined as at least two DWI lesions in at least two different arterial territories (right or left anterior or posterior cerebral circulations) (18, 19). The arterial territories in the anterior circulation included anterior cerebral artery (ACA), the middle cerebral artery (MCA), the leptomeningeal branches of the ACA, MCA, the anterior choroidal artery (AchA), the perforating branches of the ICA, AC
A, MCA, and the AchA. In the posterior circulation, the vascular territories were vertebral arteries, basilar artery, the superior cerebellar artery, the anterior inferior cerebellar artery, the posterior inferior cerebellar artery, and the posterior cerebral artery (PCA) (20).

Chi-square test was used for categorical variables. For continuous variables, we used Student's t-test and Mann–Whitney U-test as appropriate. Stepwise forward logistic regression analyses were performed based on variables in Table 1 as detailed in the Results. Lowess

Table 1 Demographics of patients with acute cerebral infarctions in one or two or more arterial territories among 2125 patients in the Bergen Stroke study

	Two or three territories $N = 187$	One territory $N = 1938$	P
Age, years (SD*)	71.7 (14.0)	68.9 (14.7)	0.013
Female, n (%)	91 (48.7)	758 (39.1)	0.011
Male	96 (51.3)	1180 (60.9)	
TOAST			
Large-artery atherosclerosis	19 (10.2)	253 (13.1)	0.26
Cardiac embolism	67 (35.8)	557 (28.7)	0.042
Small vessel disease	7 (3.7)	277 (14.3)	<0.001
Other cause	6 (3.2)	61 (3.2)	0.97
Unknown cause	88 (47.1)	783 (40.4)	0.084
Prior cerebral infarction	34 (18.2)	297 (15.3)	0.30
Myocardial infarction	25 (13.4)	251 (13.0)	0.89
Angina pectoris	20 (10.8)	216 (11.2)	0.86
Hypertension	105 (56.5)	989 (51.3)	0.18
Diabetes mellitus	29 (15.6)	272 (14.2)	0.60
Atrial fibrillation	66 (35.3)	481 (24.8)	0.002
Smoking	48 (27.9)	504 (27.3)	0.86
NIHSS* score on admittance (SD)	6.9 (7.5)	4.9 (5.8)	<0.001
Symptomatic ICA stenosis	41 (27.5)	283 (19.1)	0.014
Asymptomatic ICA stenosis	24 (16.2)	154 (10.5)	0.036
Lacunar infarctions	29 (15.5)	506 (26.1)	0.001
None-lacunar infarctions	158 (84.5)	1432 (73.9)	
Old infarcts on MRI	72 (38.5)	630 (32.5)	0.098

*SD, standard deviation, NIHSS, The National Institutes of Health Stroke Scale.

smoother curve was obtained for the relative frequencies of MACI in relation to age. STATA 14.0 (StataCorp, College Station, Texas, USA) was used for analyses.

The study was approved by the local ethics committee (REK Vest).

Results

In total, 2697 patients had acute cerebral infarcts. MRI including DWI imaging was performed in 2220 (82%) patients, and among these, 2125 (96%) had DWI lesions. MACI were detected in 187 (8.8%) patients. In total, 1058 patients (49.8%) underwent Holter monitoring and paroxysmal atrial fibrillation was detected in 155 patients (14.7%). Among patients with MACI, 23 (12.4%) had known paroxysmal atrial fibrillation and 18 (9.8%) had known chronic atrial fibrillation prior to the index stroke.

Table 1 shows demographics of MACI and non-MACI patients. MACI patients were older ($P = 0.013$) and more often females ($P = 0.011$). MACI were associated with CE ($P = 0.042$), atrial fibrillation ($P = 0.002$), symptomatic ICA stenosis ($P = 0.014$), asymptomatic ICA stenosis ($P = 0.036$), and higher NIHSS score on admission ($P < 0.001$).

Among patients with no CE according to TOAST criteria, 34 (35%) with MACI had symptomatic ICA stenosis versus 268 (25.0%) with non-MACI ($P = 0.037$), and 20 (20%) with MACI had asymptomatic ICA stenosis versus 134 (13%) with non-MACI ($P = 0.031$).

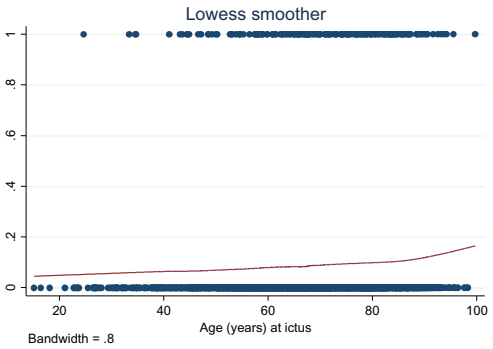

Figure 1. Relative frequencies of acute infarction in one (0) versus more than one (1) arterial territory according to age

Figure 1 shows the relative frequency of MACI according to age based on lower smoother function.

Table 2 shows the results of the final logistic regression analysis with MACI versus non-MACI as dependent variable and using independent variables from Table 1 in a stepwise forward procedure. Age and sex were kept as independent variables in all analyses. MACI were independently associated with CE and symptomatic ICA stenosis.

Table 2 Logistic regression with acute infarction in more than one arterial territory versus one territory as dependent variable

	Odds ratio	95% confidence interval	P-value
Male	0.76	0.54–1.1	0.13
Age	1.00	1.00–1.02	0.31
Symptomatic ICA* stenosis	1.9	1.2–2.8	0.003
Cardiac embolism	1.5	1.1–2.3	0.025

*ICA, internal carotid artery.

Table 3 Mortality rates 7 days after stroke onset for different subtypes compared to all other subtypes of stroke

	No. of deaths	P-value	OR
Cardioembolism	44 (4.9)	0.001	2.085
Atherosclerosis	4 (1.3)	0.034	0.352
Small vessel disease	0 (0)	<0.001	1
Unknown	33 (3.1)	0.78	0.940
Atrial fibrillation	45 (5.7)	<0.001	
MACI*	2 (1.1)	0.60	

*MACI, Multiple Acute Cerebral Infarcts.

Among 34 patients with MACI and unknown etiology according to the TOAST criteria, CE was considered probable due to MACI in three arterial territories, supraventricular tachycardia, palpitations likely to represent atrial fibrillation, left bundle branch block, and no ICA stenosis.

We did not have data on the presence or not of fetal posterior cerebral artery. We therefore did subanalysis excluding 16 patients with DWI lesions in both the anterior circulation and the posterior circulation limited to the supply of the posterior cerebral artery (temporal lobe, occipital lobe, and thalamus). These analyses still showed MACI to be associated with atrial fibrillation ($P = 0.002$) and CE ($P = 0.042$).

Discussion

We confirm that acute cerebral infarcts in more than one arterial territory are associated with CE. Although intuitively not surprising, some studies have been conflicting. Two South Korean studies including 685 and 329 patients did not find an association with CE (21, 22). Nevertheless, it should be emphasized that the incidence of CE is lower in South Korea (23). We should also consider racial differences in the distribution of extracranial and intracranial stenotic lesions which can influence results of Asian studies. There is higher prevalence of intracranial arterial disease in Asians in contrast to Caucasians where the atherosclerosis of the larger extracranial arteries is more prevalent (24).

There are few studies regarding the etiology standing behind small multiple lacunar infarcts sometimes referred as a subtype of MACI (4). One prospective study concluded that embolic mechanisms were not a likely explanation for the occurrence of multiple acute lacunar infarcts in most patients, because definite embolic source was found only in one patient of 10 patients with MACI. Diffuse cerebral microvascular abnormalities such as atherosclerosis or lipohyalinosis were suggested as probable causes (25). According to our results, small vessel disease causes only 3.7% of all MACI. One possible explanation is that lacunar infarctions sometime occur temporally close. Another possibility is that some lacunar infarctions are caused by CE or large-artery atherosclerosis and not small vessel disease. Takahashi et al. (2) reported that multiple lacunar infarcts are more likely caused by CE and large-artery atherosclerosis in accordance with the present study.

We found acute cerebral infarcts in more than one arterial territory in 8.8% of the patients. This is similar to two recent studies (9.8 and 9.7%) (7, 21). Other studies have reported higher frequencies, but different inclusion criteria make the comparison difficult (7). Many studies have included patients with several DWI lesions in the same arterial territory. However, these lesions are probably caused by one thrombus or emboli undergoing early fragmentation in most patients (10). In our opinion, the mechanisms behind multiple DWI lesions in one arterial territory and multiple DWI lesions in more than one arterial territory should be analyzed separately as they may be different in most cases.

On multivariate analyses, we found that multiple DWI lesions in more than one arterial territory were associated with symptomatic ICA stenosis independent of CE. Whether the cause of symptomatic ICA stenosis including occlusion is due to CE or large-artery disease (including atherosclerosis) is sometimes difficult to determine. Some studies have been unable to differ between large-artery atherosclerosis and CE as to association with acute infarcts in more than one arterial territory, and this needs more explorations in the future studies (21). Clinical presentation of stroke and medical history can possibly help in distinguishing between CE and other subtypes of stroke. The presence of certain predictive factors such as sudden onset of stroke to maximal deficit up to 5 min, decreased level of consciousness at onset, spectacular shrinking deficit syndrome, Wernicke/global aphasia without hemiparesis, Wallenberg's syndrome, valvular heart disease, and onset of symptoms after a Valsalva-provoking activity predict CE origin. In contrast, subacute onset of stroke, chronic obstructive pulmonary disease, hyperlipidemia, hypertension, TIA, ischemic heart disease, and DM are potential predictors of large atherosclerosis source of MACI. In addition, lacunar stroke signs exclude CE origin in most cases (26, 27).

Anatomical variations of cerebral arteries should be also considered. PCA originates directly from the ICA in up to 25%, which represents the fetal type. Due to this anatomic variant, ICA disease may cause MACI in both the anterior and posterior circulation simultaneously (22). Another variation can possibly occur, unpaired ACA also called azygos artery supplying both hemispheres. The incidence of azygos ACA ranges from 0 to 5%, and its occlusion can result in bilateral infarct (28). Furthermore, we have to consider the cross-flow mechanism when single carotid artery lesion can cause bihemispheric infarcts via intracranial cross-flow through the anterior communicating

artery (5). Vascular imaging of the cerebral vessels is therefore necessary.

Interestingly, among patients with unknown etiology according to the TOAST criteria, CE was considered possible in a substantial fraction. This suggests that the TOAST criteria fail to diagnose CE in many patients with infarcts in more than one arterial territory even after extensive investigations. Anticoagulation is highly effective for the prevention of recurrent cerebral infarcts among patients with atrial fibrillation (29). Compatible with others (27), mortality among our patients indicates that atrial fibrillation is associated with severe stroke (Table 3). Our findings suggest that anticoagulation should be considered among patients with MACI and unknown etiology.

Strengths of our study include prospective design, high frequency of MRI investigations, and a large number of patients. However, there are some limitations. Some patients did not undergo full investigations and we probably underdiagnosed atrial fibrillation because we did not perform long-term ECG monitoring. A recent study showed that long-term ECG monitoring with insertable cardiac monitor is superior to conventional follow-up for detecting atrial fibrillation at 6 and 12 months after cryptogenic cerebral infraction (30). More extensive investigations might have disclosed the etiology among more patients. In conclusion, acute cerebral infarcts in more than one arterial territory occur among almost 10% of the patients and are associated with CE.

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Conflict of interests

None.

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