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Stroke and its consequences: protocol and pilot data of the observational Berlin Long-term Observation of Vascular Events (BeLOVE) stroke stratum

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ABSTRACT

Introduction Following a cerebrovascular event, the associated risks for further major adverse cerebro- and cardiovascular events and death (MACE) and important aspects of cognitive, mental and patient-reported outcomes are currently not understood, particularly long-term. Here, we present the study design of the ongoing Berlin Long-term Observation of Vascular Events (BeLOVE) stroke stratum and report data of the first study phase.

Methods and analysis BeLOVE is a prospective, longitudinal, observational, hospital-based cohort study. Its stroke stratum enrols adult patients with acute ischaemic stroke, transient ischaemic attack (TIA) or non-traumatic intracerebral haemorrhage. Patients undergo deep phenotyping including cerebral and cardiac MRI, ECG, echocardiography and bio-sampling including multi-omics analyses. Regular, standardised follow-ups take place annually over a period of up to 10 years and record the frequency of MACE as the primary outcome.
Secondary outcomes include the frequency, progression and interactions of functional impairments, namely post-stroke cognition, pain, depression, seizures and their relationship to quality of life.
The first study phase included 758 patients (median 69 years, 37% female). At 2-year follow-up, the cumulative incidence (95% CI) of the composite primary endpoint MACE was 0.107 (0.085 to 0.132) and that of first ischaemic stroke, first myocardial infarction and death were 0.066 (0.049 to 0.086), 0.015 (0.008 to 0.026) and 0.040 (0.027 to 0.056), respectively.

Ethics and dissemination Each participant will provide informed written consent during the acute in-hospital phase. Data will be available for research purposes via a written request to the data use and access committee.

Trial registration number German Clinical Trials Register: http://www.drks.de/DRKS00023323 on 4 November 2020.

WHAT IS ALREADY KNOWN ON THE TOPIC

⇒ After stroke, patients have a significantly increased risk of further vascular events, reduced functional independence and cognitive impairment.
⇒ Stroke may even affect the function of other organs, for example, by altering upstream control centres of many regulatory circuits.
⇒ Better prognostic models are warranted to identify high-risk individuals and to develop tailored individual secondary prevention strategies.

WHAT THIS STUDY ADDS

⇒ The BeLOVE (Berlin Long-term Observation of Vascular Events) stroke stratum will improve the prediction and mechanistic understanding of the course of cerebrovascular disease in multiple domains.

HOW THIS STUDY MIGHT AFFECT RESEARCH OR PRACTICE

⇒ The BeLOVE stroke stratum will enhance research by shifting focus from a single-organ disease to a disease-overarching understanding of brain-body-brain loops.

INTRODUCTION

After an ischaemic or haemorrhagic stroke, patients have a significantly increased risk of further cerebrovascular and cardiovascular events including deaths.[1 2] Furthermore, many patients suffer from reduced functional independence, cognitive impairment, post-stroke pain, post-stroke depression and seizures.[3–6] These complications heavily influence the quality of life of patients who had a stroke.[5] Moreover, there is an interaction between these complications, with a complex impact on recovery and mortality. Moreover, ischaemic brain injury can directly affect the function of other organs, for example, by altering upstream control centres of many regulatory circuits. Examples include the stroke-heart syndrome and stroke-induced immunosuppression, which in turn worsen prognosis.[7 8]

Importantly, individual risk varies considerably and depends on numerous factors such as stroke severity, brain lesion location, concomitant diseases, the genome and social factors, among others.[9 10] Many pathophysiological aspects of post-stroke outcomes and complications are not well understood. Therefore, better prognostic models are warranted to identify high-risk individuals and to develop tailored individual secondary prevention strategies.[11] The results of prospective, standardised studies will help to better forecast, prevent and treat post-stroke complications.

The overall goal of the Berlin Long-term Observation of Vascular Events (BeLOVE) study is to improve short- and long-term prediction and disease-overarching mechanistic understanding of disease progression in patients with various cardiovascular and cerebrovascular high-risk conditions.[12] We here present the scientific concept of the stroke stratum of BeLOVE, as well as the baseline characteristics and the 2-year follow-up on frequency of cerebrovascular and cardiovascular events of the first study phase.

METHODS AND ANALYSIS

Study design

The stroke population described here is part of the BeLOVE study that additionally includes patients with acute coronary syndrome, acute heart failure and very high-risk chronic cardiovascular conditions.[12] As such, the BeLOVE-stroke stratum is a prospective cohort study conducted at all three campuses of the Charité, Universitätsmedizin Berlin, Germany (Charité Campus Mitte, Charité Virchow Klinikum and Charité Campus Benjamin Franklin). All patients admitted to the Department of Neurology with suspected stroke or transient ischaemic attack (TIA) at one of these sites are screened for eligibility. After study inclusion, the first study visit is carried out 0–7 days after the index event, while the participants are still hospitalised. Information on demographic and clinical variables, living situation, health-related behaviour, functional status pre-stroke, concomitant diseases and concomitant medication, laboratory variables and data on acute treatment are collected during the acute in-hospital stay. In addition, blood samples for bio-banking (serum, plasma, EDTA, citrate) as well as urine are collected and deep-frozen. Samples serve to analyse multi-omics (proteomics and metabolomics), carry out genome-wide association studies, clonal haematopoiesis of indeterminate potential (CHIP) mutation analysis and immunophenotyping.

At day 30 (±14) and day 60 (±14) after the event, telephone follow-ups inquire on vital status and complications. At day 90 (±14), comprehensive ('deep') phenotyping is performed. While the participation in all study visits is intended, joining either this visit or the very first visit after 0–7 days is the minimal prerequisite for study participation. Phenotyping includes a structured face-to-face interview to record new clinical events including major adverse cerebrovascular and cardiovascular events and seizures. The composite primary endpoint MACE includes new ischaemic or haemorrhagic stroke, acute myocardial infarction, hospital admission for worsening or new heart failure and vascular deaths.

Moreover, the degree of disability is assessed using the Modified Rankin Scale (mRS).[13] Patients receive ECG, echocardiography and ocular coherence tomography. Patients receive standardised cardiac and cerebral MRI. Cerebral MRI (3 Tesla) is performed to delineate infarct lesion location, assess severity of cerebral small vessel disease and map symptom networks using brain lesion data stemming from structural MRI. EEG is performed in a subset of participants. The overall level of fitness or frailty is scored using the Clinical Frailty Scale (CSHA-CFS).[14] Cognitive performance is assessed using the Montreal Cognitive Assessment (MoCA) and Cambridge Neuropsychological Test Automated Battery (CANTAB).[15 16] Cognitive impairment is defined as −1.5 SD (compared with normative test score) in one of the following tests: Paired Associates Learning (PAL) for memory, Rapid Visual Information Processing (RVP) for attention and Spatial Working Memory (SWM) for executive function.

Depressive symptoms are captured using the Patient Health Questionnaire-8 (PHQ-8).[17] Patient-reported Outcome Measures (PROMs) are collected using the generic Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29) profile,[18] the generic EuroQol 5-Dimensions-5-Level (EQ-5D-5L)[19] and the disease-specific Stroke-Specific Quality of Life (SSQoL) questionnaire.[20] PROMIS-29 assesses seven domains (Physical Function, Fatigue, Pain, Sleep, Social Activity, Depression, Anxiety). Raw measures for each subdomain are translated into T-scores. SSQoL assesses 12 domains (Mobility, Energy, Upper Extremity Function, Mood, Self-Care, Work, Social Roles, Family Roles, Vision, Language, Thinking, Personality). Means of domain scores and overall sum score will be reported. EQ-5D-5L index values will be derived from the German value set.[21]

Symptom scores include the National Institutes of Health Stroke Scale (NIHSS) for stroke severity and type of symptoms,[13] the New York Heart Association (NYHA) classification for symptoms and severity of heart failure and the painDETECT for screening of neuropathic pain.[22]

Biosampling includes Olink Target96 and mass spectrometry for proteomics, MxP Quant 500 XL for metabolomics and serves for genome-wide association studies and clonal haematopoiesis.

Multiple additional measures, for example, for physical, cardiovascular and metabolic function, are carried out as has been described before.[12]

After the extensive phenotyping at day 90, structured telephone interviews are performed every 6 months to collect data on new clinical events (MACE in particular), functional (mRS) and cognitive outcome (Telephone MoCA)[23] as well as PROMs.[18] The schedule of the measures is presented in table 1. Follow-up occurs up to 10 years.

BeLOVE was initiated on 18 July 2017. The first study phase ended on 31 December 2020. Here, demographic data of the first study phase and the 2-year follow-up on the frequency of cerebrovascular and cardiovascular events is presented.

Recruitment of the stroke subcohort was terminated on 31 December 2025 and a total of N=1584 participants were included in the stroke stratum.

Inclusion and exclusion criteria

BeLOVE includes patients of both sexes, aged 18 years or older with ischaemic stroke, intracerebral haemorrhage (ICH) or TIA.

Ischaemic stroke is defined as an acute-onset neurological deficit lasting >24 hours or less than 24 hours with an acute lesion on neuroimaging (MRI or CT) corresponding to ischaemia. Patients who do not receive cerebral MR imaging during hospital stay (but only CT) may be included if symptom duration is >24 hours or if acute monocular vision impairment with evidence for retinal central artery occlusion occurred. Patients with a symptom duration >24 hours who do not show evidence of an ischaemic or haemorrhagic lesion on cerebral MRI cannot be included.

Non-traumatic intracerebral haemorrhage is defined as an acute-onset neurological deficit and evidence for fresh intracerebral haemorrhage on neuroimaging (MRI or CT).

TIA is defined as an acute-onset neurological deficit with clinical restitution within 24 hours without proof of an acute ischaemic or haemorrhagic lesion on imaging and verification of the diagnosis by a neurologist or ABCD2 score ≥3.[10] TIA includes the diagnosis of amaurosis fugax.

Patients must give written informed consent before study participation.

Patients cannot participate if they are pregnant or breastfeeding, do not have health insurance or a reduced life expectancy (<6 months) due to a non-cardiovascular cause. The BeLOVE stroke stratum does not include patients with active cancer or a history of organ transplantation.

Endpoint assessment and adjudication of outcomes

Endpoint assessment and adjudication procedures have been published in detail.[12] In brief, the primary endpoint, namely subsequent first MACE (ischaemic or haemorrhagic stroke, myocardial infarction, hospitalisation for heart failure or vascular death) as well as multiple secondary endpoints (including all deaths and any hospitalisation) are assessed at 30, 60 and 90 days and every 6 months thereafter up to 10 years according to a standard operating procedure, supervised by an endpoint adjudication committee. Assessment is based on all clinical information available (patients' history, clinical assessments, discharge letters, test results). Death is categorised as cardiovascular, non-cardiovascular or unknown. For patients lost to contact, the citizen registration office as well as the respective family doctor are contacted. In case of death, any available information concerning the cause of death including the latest medical reports, death certificates and information by family doctors and proxies are obtained. Events have to display signs and symptoms; clinically covert findings (eg, so called silent strokes) do not qualify as primary outcome (detailed definition given as supplement).

This project is conducted with data and samples from BeLOVE cohort study. The BeLOVE study is substantially funded by the Berlin Institute of Health at Charité (BIH).

Study data were collected and managed using REDCap electronic data capture tools hosted at Charité – Universitätsmedizin Berlin. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.[24 25]

Patient and public involvement

The general concepts, overall research question and the study design were developed without patient involvement. However, all patients will be interviewed about their motivation to participate in the study during the inclusion visit; reasons for study participation and patient's motivation will be used to improve processes serving to inform and retain patient's participation. Patients are also informed about clinically relevant findings within the framework of incidental findings management. Furthermore, patients' representative involvement is planned as part of the

Table 1 Visit participation and performance of selected examinations in the BeLOVE stroke stratum

	Recruitment*	Acute phenotyping	Deep phenotyping	Telephone visits	
Visit schedule: time after the index cerebrovascular event	Acute phase	Day 0–7	Day 90, and after 2 years, 4 years, 6 years, 8 years, 10 years	Long visit: after 1 year, 3 years, 5 years, 7 years, 9 years and as a substitute for any 'missed' deep phenotyping visits	Short visit: every 6 months after a long telephone visit or deep phenotyping visit
Measures/examinations					
Sociodemographics		x	x	x	
Behavioural risk factors		x	x	x	
Medical history/clinical course	x	x	x	x	
Current medication		x	x	x	
Imaging					
Cranial MRI	x		x		
Cardiac MRI			x		
2D-echocardiography	x		x		
ECG	x		x		
Biosampling					
Blood, standard parameters		x	x		
Blood, proteomics: Olink Target 96; mass spectrometry		x	x		
Blood, metabolomics: MxP Quant 500 XL (biocrates)		x	x		
Blood, GWAS		x‡			
Blood, immunophenotyping		x§			
Blood, CHIP		x‡			
Urine		x	x		
Stool					
Functional status and physical symptoms					
mRS	x		x	x	
NIHSS	x		x		
NYHA classification for heart failure		x	x	x	
Frailty Scale			x		
FFS			x		

Continued

Table 1 Continued

	Recruitment*	Acute phenotyping	Deep phenotyping	Telephone visits	
painDETECT Questionnaire			x		
PROM					
PROMIS-29 profile†		x	x	x	
PHQ-8			x		
SSQoL		x	x	x	
EQ5DL-5		x	x	x	
MOCA		x	x	x	
CANTAB			x		
Clinical outcomes, that is,			x	x	x
Ischaemic stroke			x	x	x
Haemorrhagic stroke			x	x	x
Myocardial infarction			x	x	x
Hospital admission due to heart failure			x	x	x
Death			x	x	x

The deep phenotyping at day 90 visit, which is optionally repeated up to every second year for up to 10 years per participant is an on-site visit with deep phenotyping but may be performed as long telephone visit, if participants cannot join an on-site visit. Participation in at least acute phenotyping or deep phenotyping at day 90 is mandatory for all participants. Long telephone visits are performed every full year (eg,1 year, 3 years) after the index cerebrovascular event and measure new clinical events (endpoints) and patient-reported outcomes (PROMS). Long telephone visits can also be carried out instead of deep phenotyping visits. Short telephone visits to measure new clinical events are carried out 6 months after a long telephone visit or deep phenotyping visit.

*Examinations given in the recruitment column represent data taken from the clinical context if available.
†PROMIS-29 contains several subdomains including physical function, social activity, pain, sleep, fatigue, depression, anxiety.
‡GWAS and CHIP analysis were performed from blood samples obtained either at acute or at day 90 deep phenotyping.
§Immunophenotyping was performed in a subset of participants; exams marked[§]are carried out during full year but not 0.5 year telephone visits.
CANTAB, Cambridge Neuropsychological Test Automated Battery; CHIP, clonal haematopoiesis of indeterminate potential; EQ5DL-5, EuroQol 5-Dimensions-5-Level; FFS, Fatigue Severity Scale; GWAS, genome-wide association studies; MoCA, Montreal Cognitive Assessment; mRS, Modified Rankin Scale; NIHSS, National Institutes of Health Stroke Severity Scale; NYHA, New York Heart Association; PHQ-8, Patient Health Questionnaire-8; PROM, Patient-Reported Outcome Measures; PROMIS–29, Patient-Reported Outcomes Measurement Information System-29; SSQoL, Stroke-Specific Quality of Life.

data and sample use process. We will develop further patient participation strategies in close cooperation with BIH-QUEST (BIH Center for Transforming Biomedical Research).

Ethics and dissemination

Each participant will provide informed written consent during the acute in-hospital phase. Data will be available for research purposes via a written request to the data use and access committee.

Statistics

Descriptive results in this manuscript are presented as absolute and relative frequencies, mean and SD, or as median and IQR.

Cumulative incidence functions (CIFs) with 95% CIs were used to estimate the 2-year occurrence of (1) the first MACE in the presence of non-vascular death as the competing risk; (2) the first myocardial infarction, first hospitalisation for heart failure and first stroke with all-cause death as the competing risk; and (3) death to any cause. CIFs were estimated using the Aalen-Johansen estimator with complementary log-log transformation for CIs.[26 27] All analyses were performed using R V.4.2.2.[28]

For future analysis, associations between exposures and clinical events will be examined through time-to-event analyses using appropriate regression models, for example, Cox proportional regression models, with time since index stroke as the underlying time variable with adjustment for potential confounders. Effect estimates and corresponding CIs will be reported where possible and appropriate, as is recommended by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[29]

RESULTS

Between mid-2017 until the end of 2020, a total of 758 participants were recruited into the first study phase of the stroke stratum (37% female, median age 69 years (59–78), 22% atrial fibrillation).

The majority of patients had an ischaemic stroke (574/758; 75.7%), about one in six participants had a TIA (125/758; 16.5%) and 1 in 25 had an ICH (30/758; 4.0%). In addition, 20 out of 758 (2.6%) patients had a retinal stroke and 9 out of 758 (1.2%) retinal TIA, respectively. Demographic and clinical data, risk factors at baseline, frequency and results of diagnostic tests are shown in table 2.

During the 2-year follow-up of the patients of the first study phase, a composite major adverse vascular event had occurred in 73 patients (cumulative incidence 0.107 (0.085–0.132). Strokes accounted for the largest share of the composite endpoint (n=46, 60%). The type of MACE-defining event is shown in figure 1.

The most common secondary endpoint was ischaemic stroke (n=46; cumulative incidence 0.066 (0.049–0.086). The second most frequent event was all-cause death, which occurred in 27 patients (cumulative incidence 0.040 (0.027–0.056). Twelve patients were hospitalised due to heart failure (cumulative incidence 0.018 (0.010–0.030), 10 had a myocardial infarction (cumulative incidence 0.015 (0.008–0.026), and 2 patients had haemorrhagic stroke (cumulative incidence 0.003 (0.001–0.010). Of the 27 patients who died, 4 (15%) were adjudicated as vascular death (table 3).

DISCUSSION

The BeLOVE stroke stratum included n=1584 participants so far. As outlined, BeLOVE collects detailed data on various aspects of stroke aftermaths enabling the analysis of the inherent risks for major adverse cerebrovascular and cardiovascular events (MACE) and seizures, and important aspects of functional, cognitive, mental and patient-reported outcomes employing long-term follow-up up to 10 years.

The cohort of the first study phase comprised more than 750 patients with mild to moderate stroke and TIA. Median age, stroke severity and distribution of vascular risk factors compare well to other cohort studies requiring informed consent, suggesting good comparability.[2 30 31]

During the 2-year follow-up, the composite endpoint MACE was detected in 10% of participants.

The most common secondary outcome event was ischaemic stroke, followed by all cause death, hospitalisation for heart failure and myocardial infarction. Only two patients had a haemorrhagic stroke. The incidences are well in line with previous cohort studies of mild to moderate stroke requiring informed consent.[2 30 31]

Due to the study design, which required informed consent and the ability to join an extensive study visit after 3 months, aphasic, frail and moribund patients are underrepresented. On the other hand, the cohort comes with a high rate of cerebral MRI, securing correct diagnosis and enabling detailed studies on stroke location and size allowing novel imaging analysis techniques such as lesion symptom and network mapping.[32 33] Such analyses are planned with respect to post-stroke cognitive decline, depression, pain, gait impairment and seizures.

Cognitive impairment is increasingly recognised as one of the most important secondary health outcomes after stroke with major implications on post-stroke functioning and quality of life.[3 4] Of note, dementia after stroke is associated with a higher rate of stroke recurrence, poor functional outcome and higher mortality.[34] In the BeLOVE stroke stratum, neuropsychological testing uses the reliable and validated CANTAB battery measuring even subtle cognitive deficits.[16] CANTAB allows a differentiated evaluation as it includes tests on general memory and learning, working memory and executive function, attention and reaction time as well as semantic/verbal memory and decision-making and response control.[16]

Table 2 Baseline characteristics at enrolment of patients recruited during the first study phase

Data category, type		Stroke stratum, total (n=758)	Ischaemic stroke subgroup (n=573)
Demographic data			
Age	Median (IQR)	69 (59, 78)	69 (58, 78)
Sex	n (%)	Male 476 (63) Female 282 (37)	Male 372 (65) Female 201 (35)
School education >11 years	n (%)	279 (41) [74]	212 (41) [59]
Baseline risk factors	n (% available) [n missing]		
Hypercholesterolaemia	n (%) [n]	700 (93) [7]	530 (93) [4]
Arterial hypertension	n (%) [n]	604 (80)	456 (80)
Smoking, current or former	n (%) [n]	483 (66) [22]	373 (67) [19]
Smoking, current	n (%) [n]	156 (21) [30]	131 (24) [23]
Diabetes	n (%) [n]	171 (23)	128 (22)
Atrial fibrillation	n (%) [n]	167 (22)	128 (22)
History of ischaemic stroke	n (%) [n]	140 (19)	112 (20)
Coronary artery disease	n (%) [n]	119 (16)	87 (15)
History of TIA	n (%) [n]	81 (11)	44 (8)
History of carotid artery intervention	n (%) [n]	56 (8) [64]	41 (8) [52]
Peripheral artery disease	n (%) [n]	43 (6)	34 (6)
Index event, hospitalisation			
Length of hospitalisation (days)	Median (IQR)	4 (3, 6)	4 (3, 7)
mRS score at admission	Median (IQR)	1 (0, 3)	2 (1, 3)
Patients with mRS 0–2 at admission	n (%)	525 (69)	363 (63)
Blood glucose at admission (mg/dL)	Median (IQR)	117 (104, 139) [38]	117 (105, 140) [28]
Blood pressure, systolic at admission (mm Hg)	Mean (SD)	159 (26) [43]	160 (26) [31]
Blood pressure, diastolic at admission (mm Hg)	Mean (SD)	88 (18) [48]	89 (18) [36]
MoCA at baseline	Median (IQR)	24 (22, 27) [366]	24 (22, 27) [274]
Index event, symptoms			
Symptoms at admission			
Paresis	n (%)	341 (45)	306 (53)
Aphasia	n (%)	87 (12)	71 (12)
Dysarthria	n (%)	162 (21)	144 (25)
Other	n (%)	365 (48)	297 (52)
No symptoms	n (%)	127 (17)	47 (8)
NIHSS at admission	Median (IQR)		2 (1, 4)
· NIHSS at admission >5	n (%)		85 (15)
NIHSS at admission >10	n (%)		
ABCD[2]	Median (IQR)		5 (4, 6) (29)
Ischaemic stroke, neuroimaging			
MRI performed	n (%)		500 (87)
CCT performed	n (%)		441 (77)
Fresh ischaemia detected	n (%)		520 (91)
Anterior vascular territory	n (%)		243 (47)

Continued

Table 2 Continued

Data category, type		Stroke stratum, total (n=758)	Ischaemic stroke subgroup (n=573)
Posterior vascular territory	n (%)		195 (38)
Anterior *and* posterior vascular territories	n (%)		78 (15)
Ischaemic stroke, diagnostic workup	n (% available)		
Vascular imaging, type			
Duplex sonography	n (%)		526 (92)
MR angiography	n (%)		450 (79)
CT angiography	n (%)		221 (39)
Vascular imaging, result			
Extracranial macroangiopathy			
Atherosclerosis, non-stenosis	n (%)		382 (67)
Stenosis ≥50%*	n (%)		43 (8)
Carotid artery occlusion	n (%)		18 (3)
Vertebral artery occlusion	n (%)		14 (2)
Intracranial macroangiopathy			
Intracranial art. stenosis	n (%)		160 (28)
Intracranial art. occlusion	n (%)		86 (15)
Intracranial aneurysm	n (%)		21 (4)
Echocardiography, performed	n (%)		333 (58)
TEE	n (%)		205 (62)
TTE	n (%)		85 (26)
TEE+TTE	n (%)		43 (13)
Echocardiography, result			
Aortic plaque	n (%)		141 (42)
Patent foramen ovale	n (%)		72 (22)
Atrial septum aneurysm	n (%)		11 (3)
Intracardial thrombus	n (%)		6 (2)
Ischaemic stroke, aetiology (TOAST)	n (% available) [n available]		
Macroangiopathic	n (%)		80 (14)
Microangiopathic	n (%)		66 (12)
Cardioembolic	n (%)		133 (23)
Other aetiology	n (%)		18 (3)
Undetermined	n (%)		276 (48)
Ischaemic stroke, therapy	n (% available)		
Systemic thrombolysis	n (%)		153 (27)
Mechanical recanalisation	n (%)		44 (8)
Carotid artery intervention	n (%)		20 (4)

Continued

Table 2 Continued

Data category, type	Stroke stratum, total (n=758)	Ischaemic stroke subgroup (n=573)

Data on *Baseline Risk Factors* are based on a data export from 14 November 2025 on self-reported history which was largely validated by reviewing medical records or medical records only. Coronary artery disease includes reported coronary artery disease, coronary artery interventions and history of myocardial infarction. Besides the reported history, additional information was considered for the definition of some conditions: Hypercholesterolaemia was additionally defined by a measured LDL-cholesterol ≥100 mg/dL or current intake of statins. Arterial hypertension was additionally defined by intake of antihypertensive drugs. Diabetes was additionally defined by intake of antidiabetic medication, a measured HbA1c ≥6,5% or a fasting glucose ≥200 mg/dL. Atrial fibrillation (AF) includes patients with a prior history of AF as well as those for which a new AF diagnosis was made during acute stroke treatment.
Parameters are indicated as absolute numbers and in percent of available datasets. In the case of missing data, missing numbers are presented in [ ].
CCT, Cranial Computed Tomography; HbA1c, Haemoglobin A1c; LDL, low-densitiy lipoprotein; MoCA, Montreal Cognitive Assessment; mRS, Modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TEE, transoesophageal echochardiogramme; TIA, transient ischaemic attack; TOAST, Classification according to Trial of Org 10172 in Acute Stroke Treatment; TTE, transthoracic echochardiogramme.

Depression is a prevalent and debilitating condition among stroke survivors, yet an association with a specific stroke location is questionable. One potential of the BeLOVE stroke stratum is to enable connectivity-based analyses like lesion network mapping.[35]

Just as depression hinders recovery after stroke and impairs quality of life, so too does pain.[5] BeLOVE's advantage lies in its ability to differentiate between post-stroke pain (eg, assessed using PROMIS-29) and central neuropathic pain (eg, identified using painDETECT) as a subtype of post-stroke pain.

Post-stroke seizures are associated with an increased risk of death, functional disability, impaired cognitive functioning and lower disease-specific quality of life.[36] Notably, post-stroke seizures are associated with a 2.5 times increased risk of post-stroke dementia.[6] Importantly, BeLOVE also addresses epileptogenicity of cerebral small vessel disease and of influence of antiseizure medication.[36 37]

Other interesting areas of research covered by BeLOVE stroke stratum are the effect of stroke on the heart (ie, the so-called stroke heart syndrome) and on the immune system.[7 8] The deep phenotyping improves knowledge on the prognostic relevance of different cardiac biomarkers in stroke, identifies blood-based proteomic and transcriptomic signatures underlying post-stroke cardiac injury patterns, determines the frequency and relevance of overt and covert heart disease in patients who had a stroke and assesses the interplay of acute and chronic brain lesions and stroke-specific changes

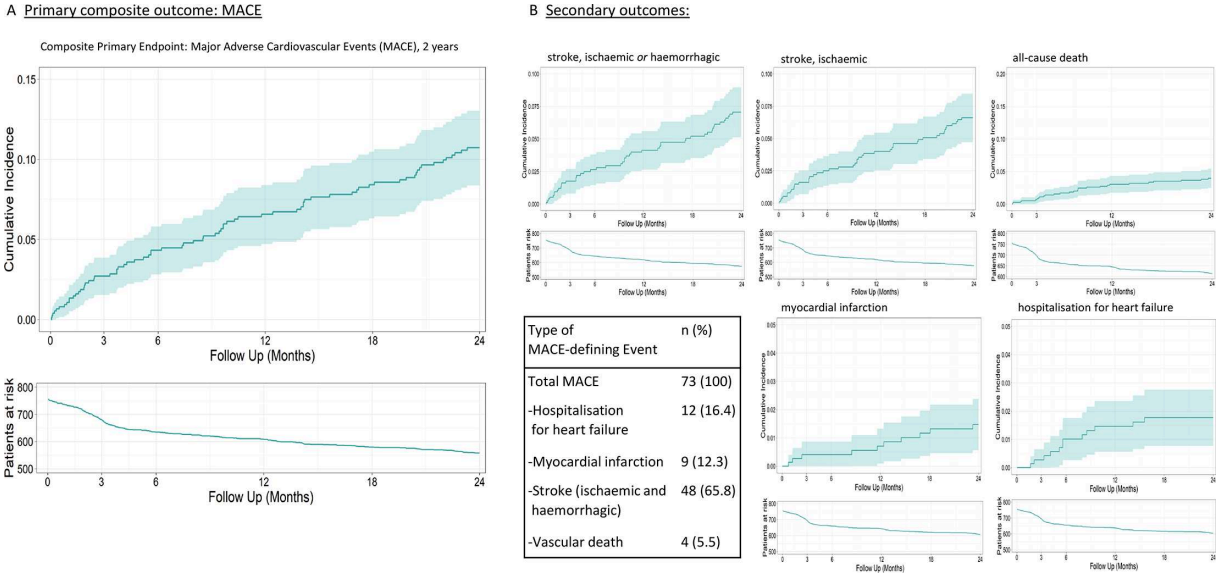

Figure 1 Cumulative incidence function (CIF) plots (A) for the first major adverse cardiovascular event (MACE) in the presence of non-vascular death as the competing event. MACE is the composite primary endpoint defined by first occurrence of stroke or myocardial infarction or hospitalisation for heart failure or vascular death after study inclusion. Numbers and proportions of the different types of events that defined MACE are given in the table. (B) CIF for the secondary endpoints: any first stroke, first ischaemic stroke, total all-cause deaths, first myocardial infarction and first hospitalisation for heart failure up to 2 years after study inclusion. All-cause death was the competing event present for the secondary outcomes stroke, myocardial infarction and hospitalisation for heart failure. All data reported here are based on a database export from 19 November 2025.

Table 3 Numbers and cumulative incidence at 2-year follow-up

	Number at 2-year follow-up	Cumulative incidence (95% CI)
MACE (composite endpoint)	73	0.107 (0.085 to 0.132)
Secondary endpoints		
Ischaemic stroke	45	0.066 (0.049 to 0.086)
Haemorrhagic stroke	2	0.003 (0.001 to 0.010)
Myocardial infarction	10	0.015 (0.008 to 0.026)
Hospitalisation for heart failure	12	0.018 (0.010 to 0.030)
All cause death	27	0.040 (0.027 to 0.056)

At the beginning of the observation, 758 patients were at risk. For MACE, 558 participants remained at risk after 2 years. Within that period, 18 died of a non-vascular cause (competing event) and 108 were censored (largely due to drop out following withdrawal of consent) without being affected by MACE.
MACE, major adverse cardiovascular event.

in brain networks on the occurrence of the stroke-heart syndrome.

Immunodepression after stroke results in bacterial infections such as stroke-associated pneumonia and dysfunction of the gut microbiome, which contributes to neuroinflammation in the acute and chronic course of stroke via systemic inflammation. Importantly, epidemiological data indicate that post-stroke infections significantly increase the risk of post-stroke cognitive impairment.[8 38] BeLOVE characterises the underlying signalling cascades of these brain-body-brain loops.

Strengths and limitations

The prerequisite of capability and willingness to participate in the study inevitably introduces selection bias towards healthier patients for BeLOVE. One of BeLOVE's strengths, however, is the collection of PROMs, an outcome that has been neglected in many previous studies to date.[39] BeLOVE collects data on generic (PROMIS-29, EQ-5D-5L) and disease-specific instruments (SSQoL). A further strength of the BeLOVE protocol is the mostly standardised data collection through the use of Common Data Elements (CDEs). This allows for the comparison and combination of BeLOVE with other cohorts (www.nlm.nih.gov/cde). The selection of phenotyping methods not captured by CDEs is the result of scientific exchange and interpersonal communication with various cardiovascular and population-based studies, such as the population-based Framingham Heart Study[40] and the German National Cohort Study (GNC).[41]

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