A REAl-life study on short-term Dual Antiplatelet treatment in Patients with ischemic stroke or Transient ischemic attack

(READAPT)

Protocol version 1.0

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PROTOCOL SYNOPSIS

Title:	A REAl-life study on short-term Dual Antiplatelet treatment in Patients with ischemic stroke or Transient ischemic attack (READAPT)
Objectives:	Aim of the present study is to evaluate the benefits and harms of dual antiplatelet treatment in patients fulfilling different possible definitions of minor or moderate acute ischemic stroke or high risk transient ischemic attack (TIA) and to evaluate risk and benefits in subgroups of patients which were not addressed in the randomized clinical trials.
Study design and setting:	Observational multicenter Italian study including centers affiliated to the Italian Stroke Organization.
Population:	Patients with ischemic stroke or transient ischemic attack aged at least 18 years.
Key inclusion criteria:	Consecutive patients with mild or moderate acute ischemic stroke or high-risk TIA treated with a short course of dual antiplatelet treatment.
Key exclusion criterion:	Patients with acute ischemic stroke or TIA who receive dual antiplatelet treatment because of vascular stenting, acute coronary syndrome, or any other indication not related to the acute cerebrovascular event.
End points:	The main considered endpoints will be occurrence of total stroke, ischemic stroke, TIA, death, disability, intracerebral bleeding, systemic bleeding. Treatment adherence will also be evaluated.
Recruitment period:	Planned study duration is of 2 years (24 months).
Follow-up:	Patients will be followed-up for 90 days with in-person visits or telephone calls.
Statistical analyses:	We will evaluate occurrence of outcome events in the overall cohort and will perform sensitivity analyses by groups which are considered relevant according to the clinical perspective (i.e. type of event, time to dual antiplatelet treatment [DAPT], type of DAPT, DAPT duration, clinical severity of the index event and its acute treatment).

STUDY PROTOCOL

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

Recent data from randomized controlled trials (RCTs) indicate that short-term dual antiplatelet therapy (DAPT) with aspirin and clopidogrel or aspirin and ticagrelor for 21-30 days may provide benefits over treatment with a single antiplatelet agent in patients with mild or moderate ischemic stroke or high-risk transient ischemic attack (TIA)[1-4]. Also a recent Cochrane metanalysis including data from 15 RCTs confirmed the benefit of DAPT in reducing stroke recurrence, which outweigh the harm of the treatment [5].

Three RCTs (CHANCE, FASTER, POINT) tested the combination of aspirin and clopidogrel versus aspirin and placebo (Table).[1-3] Only patients with mild ischemic stroke and high-risk TIA were included in those trials. Minor ischemic stroke was defined as a National Institutes of Health Stroke Scale (NIHSS) score of 3 or less in the POINT, CHANCE and FASTER trials. High-risk TIA was defined as an $ABCD_2$ score of 4 or more in CHANCE and POINT trials,[1,3] while in the FASTER trial, TIA patients needed to have either weakness or speech disturbance as part of the symptom complex with a duration of at least 5 minutes to qualify for inclusion in the study.[2] More recently, one RCT (THALES) tested aspirin and ticagrelor versus aspirin and placebo in people with mild or moderate ischemic stroke, i.e. NIHSS score of 5 or less, or high-risk TIA defined as $ABCD^2$ score of 6 or more [4] (Table 1).

It is not established if findings of RCTs can be replicated in real-life settings. In fact, to be included in the trials, patients had to meet strict inclusion and exclusion criteria which are not always fulfilled by patients, who in real-life receive DAPT. Patients with low-risk TIA or only possible TIA were not included in any of the identified RCTs. Moreover, definition of mild ischemic stroke was inconsistent among the RCTs, and patients eligible for revascularization procedures were excluded, as well as patients with events attributed to procedures such as carotid endarterectomy.

2. STUDY OBJECTIVES

The aim of the present study is to evaluate the benefits and harms of dual antiplatelet treatment in patients with mild-to-moderate acute ischemic stroke or high-risk TIA in a real-life setting. The study will aim to evaluate if findings of the RCTs can be replicated and to explore subgroup of patients who were not included in the trials for whom information was unclear. Additionally, this study will evaluate adherence to the prescribed treatment in a real-life setting.

3. METHODS

3.1 Study design

The study is a prospective observational multicenter Italian study.

3.2 Study setting

The study will involve patients from 126 Neurology departments and Stroke Units located in Italy and affiliated to the Italian Stroke Organization (ISO).

All Centers affiliated to the ISO were contacted. The list of participating Centers is reported in **Appendix 1**.

The University of L'Aquila and the Neurology department of SS Filippo e Nicola hospital in Avezzano will have the role of coordinating center.

Further centers could join the project depending on study needs. Participation of any new center must be approved by the Institutional Review Board (IRB) of the coordinating center. A communication to the IRB of all the participating centers will be also sent.

3.3 Study population

The study will include consecutive patients referring to the selected Centers who fulfill the criteria to participate in the study.

3.4 Inclusion criteria

The study will include all subjects who meet all the following inclusion criteria:

1. Patients with mild or moderate non-cardioembolic ischemic stroke or high-risk TIA treated with a short course of DAPT (usually 21-30 days but up to 90-day at the physician's discretion) for the acute event;
2. Male or female aged at least 18 years;
3. Providing signed and dated informed consent form;
4. Willing to comply with all study procedures and to be available for the duration of the study.

As one the major study aim is to evaluate DAPT in the real-life setting, the protocol will not adopt predefined criteria to define mild-to-moderate ischemic stroke or high-risk TIA. Data on ischemic stroke severity as defined by the NIHSS and on TIA-related stroke risk as defined by the $ABCD^2$ score will be collected to stratify patients and perform subgroup analyses.

For the same reason we did not adopt any pre-defined inclusion criteria for initiation of DAPT after the acute event as one of the objectives of the study is to describe timing from acute event to initiation of the acute treatment and provide data for efficacy and safety stratified for subgroups.

Moreover, we will not adopt stringent criteria referring to duration of DAPT but we will try to maximize adherence to guidelines or treatment paradigm of the RCTs.[1-6] Conventional duration of DAPT is from 21 to 90 days.

We also recognize that at the time of starting the study, ticagrelor will be probably not approved in Italy for stroke prevention and thus patients treated with ticagrelor will not be included in the study. Anyhow, the protocol was drafted to allow the inclusion of patients treated with ticagrelor if the drug will receive the approval before study completion.

3.5 Exclusion criteria

Subjects presenting with the following characteristics will not be included in the study:

1. Patients receiving DAPTs after endovascular procedures with stenting;
2. Patients who are randomized in any interventional RCTs on stroke prevention;
3. Presence of any condition which at the physician judgement may preclude reliability of the collected information;

3.6 Variables of interest

The study will collect information on patients' characteristics, vascular risk factors, pre-event treatment, stroke severity (as measured by the NIHSS), $ABCD^2$ score, carotid or intracranial stenosis, pre- and post-event disability (as measured by the modified Rankin Scale [mRS] score), time from symptom onset to initiation of DAPT, type of DAPT with loading and daily dosage, duration of DAPT, neuroimaging characteristics, findings at examinations to ascertain the cause of the event, treatment in the acute phase (thrombolysis/thrombectomy), treatment at discharge, outcome and adverse events occurring during the follow-up.

A detailed list of the variables of interest which will be collected for the present study is reported in the **Appendix 2** which displays the baseline case report form (CRF) of the study.

3.7 Recruitment

Each participating center will be requested to include in the study all consecutive patients (hospitalized or non-hospitalized) who will meet inclusion criteria for the study. We anticipate that the study will mostly include patients who will be hospitalized for the index event. Inclusion of non-hospitalized patients managed in the emergency department of dedicated TIA outpatient clinics will be allowed and encouraged.

3.8 Study duration

Recruitment period will last two years from the approval of the Institutional Review Board of the coordinating center. Follow-up will last for 90 days for each included patient.

3.9 Follow-up

A single follow-up visit will be scheduled for each patient at 90±5 days from symptom onset. Follow-up visits may be in-person or via a telephone call depending on the center practice. Scheduled telephone calls will be performed by trained research staff or health care staff at the local clinic. Consent to be contacted for a telephone interview is included in the consent form subscribed before inclusion in the study.

At the follow-up visit the local PI or the co-investigators will fill-in the control visit data collection form. The detailed list of variables of interest for the follow-up visit can be found in the follow-up CRF shown in **Appendix 3**.

3.10 Study Outcomes

The primary efficacy outcome will be a composite of new stroke events (ischemic or hemorrhagic) or death at 90 days.

The primary safety outcome will be any moderate-to-severe bleeding event.

Key secondary efficacy outcomes will include ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, myocardial infarction, vascular death, and any hospitalization. Key secondary outcome will also include disability as measured by the mRS and adherence to DAPT and other stroke preventive agents.

Secondary safety outcome will include minor bleeding events.

Outcomes will be adjudicated at each center by the local Principal Investigator (PI). Adjudication of outcomes will be based on review of medical charts.

3.11 Study procedures

The study is observational and no change in diagnostic and treatments procedures will be made. Patients will be treated according to the doctor's decisions and in line with the available guidelines and current good clinical practice.

Data will be collected locally by physicians and other health care professionals involved in patient care. At each visit, a paper copy of collected data for each included patient will have to be stored at local Centers. The paper copy will contain demographic information, along with a patient ID that will be unique for each patient and will be created upon insertion of the data in the e-CRF. The record ID of the patient will be requested in the e-CRF at follow-up visits. Only local Centers will know the identity of included patients. In the e-CRF patients will be identified by their ID.

4. STATISTICAL ANALYSIS

Statistical analyses will be performed by the statistical data manager under the advice of the SC.

All analyses will be performed according to the intention-to-treat principle in all patients died within 90 days or completing the 90-day follow-up.

Descriptive statistics will be used to report baseline information.

We will analyze the time from event to the first occurrence of primary and secondary outcome events with the use of a Cox proportional hazards model. We will use two statistical models; Model 1 will be unadjusted, while Model 2 will be adjusted for age, arterial hypertension, diabetes mellitus, cigarette smoking, and baseline mRS score. P values for interaction will be calculated according to the following subgroups: type of event (ischemic stroke vs TIA), time to DAPT (≤24 hours vs >24 hours from symptom onset), type of DAPT (aspirin+clopidogrel vs aspirin+ticagrelor), DAPT duration (≤21 vs >21 days and ≤30 vs >30 days), NIHSS score at onset (≤3 vs >3 and ≤5 vs >5), revascularization procedure (i.v. thrombolysis and/or mechanical thrombectomy vs no interventions). Hazard ratios with 95% confidence intervals will be reported. Should multiple events of the same type occur, the time to the first event will be used in the model. Data from patients who had no events during the study will be censored at the time of study termination or death.

Assuming a 95% confidence interval, we estimate that a sample size of 347 subjects would be required to detect a 6% proportion of primary outcome occurrence with a two-sided 5% margin of error. The 6% proportion was taken from the THALES trial.[4]

Tests will be two-sided, and a P value of 0.05 will be considered to indicate statistical significance. All statistical analyses will be performed with the use of SPSS software.

5. ETHICS

5.1 Ethical approval

The study will be firstly approved by the Institutional Review Board of the coordinating center and then submitted to local Ethic Committee (EC) or IRB of all the participating centers.

All study procedures will start after EC or IRB approval. Additionally, any other necessary approvals required by sites will be obtained prior to initiation of the study at each site.

Each center will be in charge of storing its own Ethical Documentation.

5.2 Patient Information Sheet and patient informed consent

The patient information sheet and informed consent have to be approved at each study site. A master patient information sheet and informed consent form will be provided to all participating centers in Italian language. Each Center will be in charge adapt to local procedures.

The research staff will seek consent from any eligible patient for enrolment into the study. At the time of the first visit an explanation of the study, a patient information sheet, and an informed consent form will be provided. Adult patients able to understand the study information must personally sign the informed consent form before being included in the study. In the presence of aphasia or any other condition impairing the ability to provide an informed consent, the consent will be requested to the patients' legal representatives or to a proxy.

Signed informed consent forms will be stored locally upon the responsibility of the local PI, who will be responsible for providing them upon request of authorized auditors and authorities.

5.3 Privacy of data

The CRF includes anonymized data which will not allow to identify or contact the patient. Only the recruiting center will be aware of the patient identity.

5.4 Withdrawal from participation

Included patients may request to have their information deleted from the study at any time. Included patients do not have to disclose their reasons for withdrawal of consent. The local PI will inform the study manager and include a record of end of study participation.

5.5 Modifications of the study protocol

Any modification of the registry protocol, including substantial changes in collected information, will require a formal amendment to the protocol.

5.6 Risk analysis

The study is observational and does not change the usual clinical practice. The study does not put patients at any specific risk related to study procedures.

5.7 Premature termination of the study

This study may be suspended or prematurely terminated for predictable and unpredictable causes. Premature termination of the study can be decided by the SC. Circumstances that may warrant termination include, but are not limited to:

- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.

- Determination of futility.

If the study is prematurely terminated or suspended, the local PI will promptly inform the EC and will provide the reason(s) for suspension or termination.

6. DATA SECURITY, MANAGEMENT, QUALITY, AND PROPERTY

6.1 Data collection and storage

Data will be collected using the REDcap software. Detailed information on security of the system can be found at https://projectredcap.org.

The local PI or the co-investigators will be able to upload patient data through a single form specifically created for the study, which will include a user-friendly drop-down menu.

Anonymized data are stored on a secured server upon the responsibility of University of L'Aquila. The data are automatically backed-up once a week.

Data will not be shared with unauthorized persons.

6.2 Quality management

The database incorporates automated inputs to prevent errors.

Plausibility of the entered data will be checked. After data from each CRF is entered into the registry, data will be manually verified by the study manager and the statistical data manger and data queries will be resolved with the study site. Cases with missing data or unresolved queries will be rejected to ensure only the highest quality data are retained in the registry.

Data from centers not ensuring consecutive recruitment of patients or adequate follow-up will not be included in the final data base.

6.3 Property of data

Aggregated data belong to the ISO.

6.4 Governance of data

Local PIs will have unrestricted access to the data of their patients. The study SC, the study manager, and the statistical data manager will have access to the whole database.

Data from the study can be shared upon reasonable request and for scientific purposes only after the approval of all the members of the SC.

7. STUDY MANAGEMENT

The study has a SC who is responsible of the study design and the whole project. The study will have a study manager and a statistical data manager.

The study manager will create and manage the electronic CRF. Upon the course of the study, the study manager will check the quality of the data entered into the database and contact centers sending queries to solve possible problems. The study manager will issue a periodic newsletter for study participants reporting progresses of the study and will provide reminds to participating centers for follow-up visits.

The statistical data manager will be in charge of exporting data from the server and of providing preliminary reports. The statistical data manager will perform all the statistical analyses under the guide of the SC.

7.1 Local study staff

Each center will be led by a local PI. The local PI will select the local co-investigators. Participation of the local co-investigators has to be approved by the local EC or IRB. The local PI will inform the SC and the study manager of the personnel involved in the study and of any change that may occur over time. The study manager will store a list of all the investigators contributing to the study and will update this list as needed.

7.2 Staff training

The study manager will perform a specific training upon request from the involved clinical site before starting enrollment. The training will be done remotely. During the training all the study procedures will be explained to the local PI and coinvestigators and CRF will be explained in detail.

8. FUNDINGS AND STUDY COSTS

This is a no-profit study. Local PIs and co-investigators will not have to pay any fee to participate in the project and will not be compensated. All procedures will be covered through the standard of care insurance or public health system covering the patients' medical care. Participants will receive no payment for participation in this study.

The present study may receive funding by application to research agencies or private parties. Any funding shall be approved by the SC and managed through the ISO office or University Departments.

9. DATA SHARING AND PUBLICATIONS

9.1 Scientific publications

Data from this study will lead to aggregated reports which will be published in Scientific Journals and presented at national and international conferences.

The publication plan is decided by the SC. Proposals of publications can also be received by the local PIs. Any proposal of data analysis and publication derived from this study has to be approved by the SC. Each proposal must report a clear aim and a detailed statistical analysis plan.

For each approved publication the SC will designate one leading (first author of the paper) and one guarantee author (last author of the paper). The leading author will be in charge of drafting the manuscript, of organizing the statistical analyses, and coordinating the study group. The guarantee author will support the leading author in writing the manuscript, in revising the text and in all the procedures which will be necessary to finalize the project.

9.2 Authorship

To meet authorship criteria, local investigators shall include all consecutive patients meeting study criteria and provide the complete follow-up data for each included and consenting patient. Investigators from centers with poor data quality which will not be included in the analysis will not meet authorship criteria.

Maximal effort will be done to include the local investigators of the participating centers as study contributors in all the publications derived from the study. When Journals will put a limit in the number of contributing authors, selection for authorship will be done by giving priority to one investigator per center as first criterion and to the centers including higher number of patients as second criterion. In any case, all local PIs and co-investigators will receive group

authorship in every publication derived from this study; in this case “on behalf of the Italian Stroke Organization” will be used as the preferred terminology to assign group authorship.

9.3 Costs of publications

The SC may ask to the ISO to cover the publication fees for articles published in open-access journals. Other funding to cover publication costs can be searched. Any funding should be approved by the study SC. Funding can be used also to cover possible costs for medical writing of statistical analyses.

Avezzano, 24 December 2020

Professor Simona Sacco

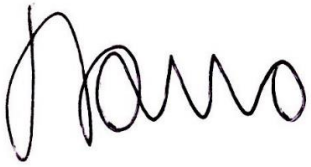

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Table 1. Randomized Clinical Trials on short-term Dual Antiplatelets Treatments in patients with ischemic stroke or Transient Ischemic attack.

Trial	Age range	Time-window	Population	Main exclusion criteria	Treatment regimen	Dual antiplatelet treatment duration
CHANCE [1]	≥40 years	≤24 h	-Ischemic stroke with NIHSS ≤ 3 - High-risk TIA ($ABCD^2$ ≥4)	TIA with isolated sensory symptoms (i.e., numbness), isolated visual changes, or isolated dizziness or vertigo; thrombolysis for the event; pre-morbid mRS≥2; anticipated use of NSAIDs; use of anticoagulants within 10 days before randomization; planned or probable revascularization; TIA or minor stroke caused by procedure	Aspirin: loading dose 75-300 mg followed by 75 mg daily Clopidogrel: loading dose of 300 mg followed by 75 mg daily aspirin on days 22 through 90.	21 days
FASTER[2]	≥40 years	≤24 h (efforts to have a relevant proportion of patients starting treatment ≤ 12 h)	-Ischemic stroke with NIHSS ≤ 3 -TIA (defined by weakness or speech disturbance, dysarthria or dysphasia, for greater than 5 min)	Acute coronary syndrome, pre-morbid mRS≥3, event secondary to a procedure (ie, carotid stenting)	Aspirin: loading dose of 162 mg (if patients were naïve to aspirin) followed by 81 mg daily Clopidogrel: 300 mg loading dose followed by 75 mg daily	90 days
POINT[3]	≥18 years	≤12 h	-Ischemic stroke with NIHSS ≤ 3 -High-risk TIA ($ABCD^2$ ≥4)	Candidates for thrombolysis, endovascular therapy, or endarterectomy; use of NSAIDs for more than 7 days during the trial period	Aspirin: 50- 325 mg daily Clopidogrel: 600-mg loading dose followed by 75 mg daily.	90 days
THALES[4]	≥40 years	≤24 h within onset or from the last time seen well	-Ischemic stroke with NIHSS ≤5 -TIA with $ABCD^2$≥6 or symptomatic intracranial or extracranial arterial stenosis (≥50% narrowing in the diameter of the lumen of an artery that could account for the TIA)	Intravenous or intraarterial thrombolysis or mechanical thrombectomy; history of atrial fibrillation or ventricular aneurysm or a suspicion of a cardioembolic cause of the TIA or stroke, planned carotid endarterectomy; major surgery within 30 days before randomization	Aspirin: loading dose of 300- 325 mg followed by 75-100 mg daily Ticagrelor: 180 mg loading dose followed by 90 mg daily	30 days

Abbreviations in the table: modified Rankin scale (mRS); National Institutes of Health Stroke Scale (NIHSS); Transient ischemic attack (TIA); Non-steroidal antinflammatory drugs (NSAIDs)

Appendix 1: Center List

Center	City (district)	Principal investigator	Contact
Unità di trattamento neurovascolare, Azienda Ospedaliero Universitaria Policlinico Umberto I	Roma (RM)	Danilo Toni	danilo.toni@uniroma1.it
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Neurologia, Ospedale SS Annunziata	Sulmona (AQ)	Mario Di Napoli	mariodinapoli@katamail.com
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Appendix 1: Center List

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Neurologia e Stroke Unit e Neurofisiopatologia, AOUP Paolo Giaccone	Palermo (PA)	Paolo Aridon	paolo.aridon@unipa.it
Neurologia e Stroke Unit, Azienda Ospedaliero Universitaria Maggiore della Carità	Novara (NO)	Roberto Tarletti	robertotarletti@yahoo.it
Neurologia e Stroke Unit, ASUR Marche AV2 Jesi	Jesi (AN)	Emanuele Medici	emanuelemedici@yahoo.it
Neurologia, Ospedale Vito Fazi	Lecce (LE)	Leonardo Barbarini	clasi33@libero.it
Stroke Unit, Azienda Ospedaliero Universitaria Sant'Andrea	Roma (RM)	Mario Beccia	beccia.mario@gmail.com
Neurologia e Stroke Unit, Ospedale Guzzardi di Vittoria	Vittoria (RG)	Antonello Giordano	antonello.giordano@asp.rg.it
Neuro Vascolare, Ospedale Maria Vittoria	Torino (T0)	Fabio Melis	fabio.melis@aslcittaditorino.it
Neurologia e Stroke Unit Ospedale San Bortolo	Vicenza (VI)	Francesco Perini	francesco.perini@aulss8.veneto.it
Stroke Unit, Azienda Ospedaliera San Camillo	Roma (RM)	Sabrina Anticoli	santicoli@scamilloforlanini.rm.it
Stroke Unit, Azienda Ospedaliera "San Carlo" di Potenza	Potenza (PZ)	Antonio Matera	matera.a@tiscali.it
Neurologia e Stroke Unit, ASST Settelaghi	Varese (VA)	Federico Carimati	federico.carimati@asst-settelaghi.it
Neurologia, ASUR Area Vasta 4 (ex ZT11)	Fermo (FM)	Patrizio Cardinali	patrizio.cardinali@sanita.marche.it
Stroke Unit, Azienda Ospedaliera Universitaria Careggi	Firenze (FI)	Patrizia Nencini	nencinip@aou-careggi.toscana.it
Neurologia Ospedale Sant'Andrea, Azienda Sanitaria Locale n. 5 "Spezzino" La Spezia	La Spezia (SP)	Elisa Giorli	Elisa.giorli@me.com

Appendix 1: Center List

Neurologia e Stroke Unit, Ospedale Regionale "U. Parini"	Aosta (AO)	Guido Giardini	ggiardini@ausl.vda.it
Neurologia Vascolare, Azienda Ospedaliera Spedali Civili	Brescia (BS)	Mauro Magoni	mago1959@hotmail.com
Stroke Unit, Istituto Clinico Città Studi	Milano (MI)	Carlo Sebastiano Tadeo	carlosebastiano.tadeo@ic-cittastudi.it
Neurologia e Stroke Unit, Ospedale Santa Maria delle Croci	Ravenna (RA)	Pietro Querzani	pietro.querzani@auslromagna.it
Stroke Unit, Azienda Ospedale Università	Padova (PD)	Claudio Baracchini	claudiobaracchini@gmail.com
Neurologia, Ospedale San Donato, Azienda USL Toscana Sud Est, Arezzo e Val D'Arno	Arezzo (AR)	Giovanni Linoli	giovanni.linoli@uslsudest.toscana.it
Neurologia, Ospedale della Murgia Fabio Perinei SS 96	Altamura-Gravina (BA)	Bonaventura Ardito	bonaventura.ardito@asl.bari.it
Neurologia e Stroke Unit, Ospedale di Desio ASST Monza	Desio (MB)	Ignazio Santilli	i.santilli@asst-monza.it
Neurologia Terapia Sub-Intensiva Stroke Unit, Azienda ospedaliera Santa Maria di Terni	Terni (TR)	Carlo Colosimo	c.colosimo@aospterni.it
Medicina e Chirurgia d'Accettazione e d'Urgenza Azienda USL 6 Livorno	Livorno (LI)	Paolo Pennati	paolo.pennati@uslnordovest.toscana.it
Stroke Unit, Ospedale San Giacomo	Novi Ligure (AL)	Eugenia Rota	eugenia.rota.md@gmail.com
Neurologia, Casa sollievo della sofferenza	San Giovanni Rotondo (FG)	Pietro Di Viesti	pietro.diviesti@gmail.com
Neurologia e Stroke Unit Ospedale di Legnano	Legnano (MI)	Francesco Muscia	francesco.muscia@asst-ovestmi.it
Neurologia, Ospedale Fatebenefratelli	Roma (RM)	Francesco Passarelli	francescopassarelli54@gmail.com
Neurologia,Ospedale San Bassiano	Bassano del Grappa (VI)	Alessandro Burlina	alessandro.burlina@aulss7.veneto.it
Neurologia, San Filippo Neri	Roma (RM)	Cinzia Roberti	cinziaroberti02@gmail.com
Neurologia, Ospedale F Renzetti	Lanciano (CH)	Maurizio Maddestra	maurizio.maddestra@asl2abruzzo.it
Clinica neurologica e di riabilitazione, Azienda sanitaria universitaria integrata	Udine (UD)	Gian Luigi Gigli	gianluigi.gigli@asufc.sanita.fvg.it

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Stroke Unit, Azienda Ospedaliera "Bianchi-Melacrino-Morelli"	Reggio Calabria (RC)	Luciano Arcudi	larcudi@libero.it
Stroke Unit, Ospedale San Martino di Belluno ULSS 1	Belluno (BL)	Sandro Zambito Marsala	sandro.zambito@aulss1.veneto.it
Neurologia, Azienda Ospedaliera Cannizzaro	Catania (CT)	Maria Giovanna Pennisi	mariagiovannapennisi@virgilio.it
Neurologia, AUSL Piacenza,	Piacenza (PC)	Donata Guidetti	d.guidetti@ausl.pc.it
Clinica Neurologica e Stroke Unit Ospedali Riuniti Ancona	Ancona (AN)	Giovanna Viticchi	viticchi.g@gmail.com
Neurologia Azienda Ospedaliera-Universitaria di Ferrara	Ferrara (FE)	Alessandro De Vito	aledevito@hotmail.com
Neurologia INRCA-IRCCS Ospedale "U Sestili"	Ancona (AN)	Giuseppe Pelliccioni	g.pelliccioni@inrca.it
Neurologia e Stroke Unit, Ospedale Umberto I	Siracusa (SR)	Enzo Sanzaro	e.sanzaro@asp.sr.it
Neurologia, Ospedale Sant'Andrea	Vercelli (VC)	Cristoforo Comi	cristoforo.comi@med.uniupo.it
Neurologia e Stroke Unit, Policlinico Tor Vergata	Roma (RM)	Marina Diomedi	marina.diomedi@uniroma2.it
Stroke Unit, Ospedale Valduce	Como (CO)	Nicoletta Checcarelli	nicolettache@yahoo.com
Neurologia e Stroke Unit, Ospedale Civile E. Agnelli	Pinerolo (TO)	Carmelo Roberto Labate	crlabate@aslto3.piemonte.it
Neurologia e Stroke Unit, Ospedale San Giuseppe	Milano (MI)	Paola Santalucia	p_santalucia@hotmail.com
Neurologia e Stroke Unit dell'Ospedale Maggiore, IRCCS Istituto delle Scienze Neurologiche di Bologna	Bologna (BO)	Andrea Zini	a.zini@ausl.bologna.it
Neurologia, Presidio Ospedaliero Mirano-Dolo	Venezia (VE)	Luigi Bartolomei	luigi.bartolomei@aulss3.veneto.it
Stroke Unit, Ospedale Civile "S.Agostino-Estense", Azienda Ospedaliera Universitaria di Modena	Modena (MO)	Guido Bigliardi	bigliardi.guido@aou.mo.it

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Stroke Unit, Azienda Ospedaliera Universitaria Gaetano Martino	Messina (ME)	Rosa Musolino	rosa.musolino@unime.it
Neurologia, Ospedale Cà Foncello	Treviso (TV)	Simone Tonello	tonello74@gmail.com
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Neurologia, Ospedale San Giacomo	Castel Franco Veneto (TV)	Bruno Marini	bruno.marini@aulss2.veneto.it
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Neurologia, Azienda Ospedaliera Nazionale SS Biagio e Cesare Arrigo	Alessandria (AL)	Luigi Ruiz	lruiz@ospedale.al.it
Stroke Unit, Fidenza AUSL PR	Fidenza (PR)	Doriana Medici	dmedici@ausl.pr.it
Stroke Unit, Ospedale del Mare	Napoli (NA)	Maria Pia Mazzaferro	mariapia.mazzaferro@libero.it
Stroke Unit, Azienda ospedaliera universitaria San Luigi Gonzaga	Orbassano (TO)	Roberto Ferri	r.ferri@sanluigi.piemonte.it
Neurologia e Stroke Unit, Ospedale San Giovanni Bosco	Torino (TO)	Roberto Cavallo	roberto.cavallo@aslcittaditorino.it
Neurologia e Stroke Unit, IRCCS Istituto Auxologico Italiano, Ospedale San Luca	Milano (MI)	Laura Adobbati	laura.adobbati@auxologico.it

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Stroke Unit, Ospedale Buccheri La Ferla	Palermo (PA)	Aurelio Piazza	aurelio.piazza@email.it
Neurologia, Azienda Cardio-toraco-neuro-vascolare USL Toscana sud est	Grosseto (GR)	Roberto Marconi	roberto2.marconi@uslsudest.toscana.it
Neurologia, Fondazione Istituto G. Giglio di Cefalù	Cefalù (PA)	Luigi Grimaldi	luigi.grimaldi@hsrgiglio.it
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Neurologia Mirano ULSS 3 Serenissima	Mirano (VE)	Maela Masato	maelamasa@gmail.com
Neurologia, Ospedale Sant'Orsola	Bologna (BO)	Marina Guarino	maria.guarino@aosp.bo.it
Neurologia, Azienda Ospedaliera San Pio	Benevento (BN)	Marco Sparaco	marcosparaco@alice.it
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Neurologia e Stroke, Unit ASST Ospedale Maggiore di Crema	Crema (CR)	Luigi Caputi	luigi.caputi@asst-crema.it
Stroke Unit, Ospedale Santa Croce	Moncalieri (TO)	Marco De Mattei	demattei.marco@aslto5.piemonte.it
Neurologia, Ospedale F Renzetti	Rimini (RN)	Enrico Maria Lotti	enricomaria.lotti@auslromagna.it

Appendix 1: Center List

Neurologia e Stroke Unit, Azienda Sanitaria Provinciale Trapani	Trapani (TP)	Luigi Sicurella	luigi.sicurella@libero.it
Neurologia e Stroke Unit, Ospedale S Elia	Caltanissetta (CL)	Maria Giovanna Randisi	giovannarandisi@gmail.com

Baseline CRF

Please fill in the survey to record baseline characteristic of your patient.

Please notice that patients, who early discontinue the dual antiplatelet treatment SHOULD be included.

Please refer to this link for the study protocol, CRF instructions and more useful tools:https://drive.google.com/drive/folders/1vdMcXNSho0lFpv2AcZ1f8ArnrJPNoG33?usp=sharing

1. DEMOGRAPHICS

Center and patient's code (please note the code on patient's documents, it will be necessary for the follow-up CRF)	_____ (Please insert the XXX code of the center followed by patient's number 000)
Was the patient hospitalized?	◯ Yes ◯ No
Duration of the hospitalization (days)	_____
Gender	◯ Male ◯ Female
Race	◯ White ◯ Black ◯ Asian ◯ Other
Date of birth	_____
Height (cm)	_____
Weight (kg)	_____
Body Mass Index (kg/m^2)	_____ (This field is automatically calculated)

2. RISK FACTORS, COMORBIDITIES AND MEDICAL HISTORY

Current or previous cigarette smoker	◯ Yes ◯ No
Smoking status	◯ Current ◯ Former
Arterial hypertension	◯ Yes ◯ No
Diabetes mellitus	◯ Yes ◯ No
Hypercholesterolemia	◯ Yes ◯ No
Hypertriglyceridemia	◯ Yes ◯ No
History of cancer	◯ Yes-current ◯ Yes-past * ◯ No (* absence of disease in the past 5 years, otherwise consider the option "current")
Type of cancer	◯ Gastrointestinal cancer ◯ Lung cancer ◯ Prostate cancer ◯ Breast/ovarian cancer ◯ Hematopoietic/lymphoid cancer ◯ Skin cancer ◯ Other
Previous history of ischemic stroke or TIA	◯ Yes ◯ No
Type of previous ischemic event	◯ Ischemic stroke ◯ TIA
Previous history of intracerebral hemorrhage	◯ Yes ◯ No
Location of previous intracerebral hemorrhage	◯ Lobar ◯ Non-lobar ◯ Uncertain (For the classification please refer to https://discovery.ucl.ac.uk/id/eprint/1535936/1/Werring_Th
History of myocardial infarction	◯ Yes ◯ No

History of angina	◯ Yes ◯ No
Congestive heart failure	◯ Yes ◯ No
Valvular heart disease	◯ Yes ◯ No
Peripheral artery disease	◯ Yes ◯ No
Vascular disease (prior myocardial infarction, peripheral vascular disease or aortic plaque)	_____ (This field is automatically calculated)

3. PREVIOUS OR CONCOMITANT MEDICATIONS

Was the patient taking aspirin before the event?	◯ Yes ◯ No
Was the patient taking clopidogrel before the event?	◯ Yes ◯ No
Was the patient taking ticagrelor before the event?	◯ Yes ◯ No
Was the patient taking a statin before the event?	◯ Yes ◯ No
Was the patient taking any antihypertensive before the event?	◯ Yes ◯ No
Was the patient taking any antidiabetic treatment before the event?	◯ Yes ◯ No
modified Rankin Scale score before the event	_____

4. INDEX EVENT

Date of the event	_____
Was the event related to a procedure (event occurring after endarterectomy, coronary stenting, or any other procedure)?	◯ Yes ◯ No
Systolic blood pressure (mmHg)	_____
Diastolic blood pressure (mmHg)	_____

Symptoms duration	◯ >24 h ◯ < 24 h
Presence of a lesion in CT or MRI scan consistent with symptoms	◯ Yes ◯ No
NIHSS score at onset or before any acute procedure	_____ (In case of TIA please report 0)
Was the patient treated with intravenous thrombolysis?	◯ Yes ◯ No
Was the patient treated with endovascular treatment?	◯ Yes ◯ No
Was the patient treated with carotid endoarterectomy?	◯ Yes ◯ No
Days from onset to carotid endoarterectomy	_____
Hemorragic infarction	◯ Yes asymptomatic ◯ Yes symptomatic (sICH) ◯ No ◯ Unknown (sICH defined according to SITS-MOST: Parenchymal hematoma H2 or Parenchymal hematoma r2 on imaging 22 to 36 hours after treatment, or earlier if scanned because of clinical deterioration, combined with a neurologic deterioration of ≥4 NIHSS points or leading to death within 24 hours (Neurology 2015;85:2098-2106))
Classification of hemorragic infarction	☐ HI1: Scattered small petechiae, no mass effect ☐ HI2: Confluent petechiae, no mass effect ☐ PH1: Hematoma within infarcted tissue, occupying < 30%, no substantive mass effect ☐ PH2: Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect ☐ PH remote from infarcted brain tissue ☐ Intraventricular hemorrhage ☐ Subarachnoid hemorrhage ☐ Subdural hemorrhage (PH= parenchymal hematoma; HI=Hemorragic infarction REFERENCE: Stroke. 2015;46:2981-2986.)
Date of hemorragic infarction	_____
Days to hemorragic infarction	_____ (This field is automatically calculated)
NIHSS score at 24 h from onset	_____

modified Rankin scale at discharge	_____

4.1. CLINICAL PRESENTATION

Symptoms of the event (select all that apply)	☐ Motor weakness ☐ Aphasia ☐ Dysarthia ☐ Sensory disturbance ☐ Visual field defect ☐ Diplopia ☐ Vertigo ☐ Loss of balance ☐ Monocular visual loss ☐ Other
Symptom location	◯ Unknown ◯ Right hemisphere or eye ◯ Left hemisphere or eye ◯ Posterior circulation ◯ Multiple vascular districts
Age	_____ (This field is automatically calculated)
Age ≥60 years	_____ (This field is automatically calculated)
Age 65-74 years	_____ (This field is automatically calculated)
Age ≥75 years	_____ (This field is automatically calculated)
BP ≥140/90 mmHg	◯ Yes ◯ No (Initial BP. Either SBP ≥ 140 or DBP ≥ 90)
Clinical features of the TIA	◯ Unilateral weakness ◯ Speech disturbances without weakness ◯ Other symptoms
Duration of TIA symptoms	◯ < 10 minutes ◯ 10-59 minutes ◯ ≥60 minutes
$ABCD_2$ score	_____ (This field is automatically calculated)
CHA_2DS_2-VASc	_____ (This field is automatically calculated)

4.2 EXAMINATIONS

Examinations performed (select all that apply)	☐ ECG ☐ Epiaortic doppler ultrasonography ☐ CT extracranial angiography ☐ MRI extracranial angiography ☐ Transcranial doppler ☐ CT intracranial angiography ☐ MRI intracranial angiography ☐ Angiography ☐ Transthoracic echocardiogram ☐ Transthoracic echocardiogram with bubble study ☐ Transesophageal echocardiogram ☐ Transesophageal echocardiogram with bubble study ☐ Immunologic screening ☐ Coagulation screening
Brain CT	◯ Yes ◯ No
Brain CT timing	◯ Acute (within 24h from onset) only ◯ Follow-up (24h or more from onset) only ◯ Both acute and follow-up
CT markers of small vessel disease	☐ Leukoaraiosis ☐ Prior lacunar infarcts (asymptomatic) ☐ None (REFERENCE: Neurol 2020;94:e439-e452)
Leukoaraiosis severity (anterior regions)	◯ No lucency ◯ Lucency restricted to region adjoining ventricles ◯ Lucency covering entire region from lateral ventricle to cortex (REFERENCE: Neurol 2020;94:e439-e452)
Leukoaraiosis severity (posterior regions)	◯ No lucency ◯ Lucency restricted to region adjoining ventricles ◯ Lucency covering entire region from lateral ventricle to cortex (REFERENCE: Neurol 2020;94:e439-e452)
Leukoaraiosis score	_____ (This field is automatically calculated)
Ischemic lesion volume at brain CT (ml)	_____ (Estimated on the brain CT performed after the acute phase by the ABC/2 method. Reference can be found here: https://radiopaedia.org/articles/abc2. Please report "0" if lesion is absent.)
Brain MRI	◯ Yes ◯ No
Number of acute lesions at brain MRI	◯ None ◯ One ◯ Two ◯ More than two

Were the lesions in the same vascular territory?	◯ Yes ◯ No
MRI markers of small vessel disease (select all that apply)	☐ White matter hyperintensity ☐ Lacune ☐ Perivascular space ☐ Cerebral microbleeds ☐ Brain atrophy ☐ Cortical superficial siderosis ☐ None (REFERENCE: Lancet Neurol 2013 Aug;12(8):822-38)
Fazekas scale for white matter lesions (periventricular white matter)	◯ No white matter lesions (grade 0) ◯ "Caps" or pencil-thin lining (grade 1) ◯ Smooth "halo" (grade 2) ◯ Irregular periventricular signal extending into the deep white matter (grade 3) (REFERENCE: https://radiopaedia.org/articles/fazekas-scale-for-white-mat
Fazekas scale for white matter lesions (deep white matter)	◯ No white matter lesions (grade 0) ◯ Punctate foci (grade 1) ◯ Beginning confluence (grade 2) ◯ Large confluent areas (grade 3) (REFERENCE: https://radiopaedia.org/articles/fazekas-scale-for-white-mat
Ischemic lesion volume at brain MRI (ml)	_____ (Estimated by the ABC/2 method. If multiple acute lesions, consider the larger one. Reference can be found here: https://radiopaedia.org/articles/abc2. Please report "0" if lesion is absent.)
Electrocardiography monitoring	◯ Yes ◯ No
Duration of electrocardiography monitoring	◯ < 24 hours ◯ 24 hours-7 days ◯ 7-30 days ◯ >30 days

5. CAUSE OF THE EVENT

Presence of right carotid stenosis/occlusion	◯ Yes ◯ No ◯ Unknown (not performed examinations to explore extracranial arteries)
Degree of right carotid stenosis	◯ 1-30% ◯ 31-49% ◯ 50-69% ◯ 70-99% ◯ Occlusion

Presence of left carotid stenosis/occlusion	◯ Yes ◯ No ◯ Unknown (not performed examinations to explore extracranial arteries)
Degree of left carotid stenosis	◯ 1-30% ◯ 31-49% ◯ 50-69% ◯ 70-99% ◯ Occlusion
Presence of vertebrobasilar stenosis/occlusion	◯ Yes ◯ No
Vertebrobasilar stenosis/occlusion	☐ Right vertebral artery ☐ Left vertebral artery ☐ Basilar artery
Presence of intracranial stenosis?	◯ Yes ◯ No ◯ Unknown (not performed examinations to explore intracranial arteries)
Symptomatic intracranial stenosis (i.e. consistent with symptoms of index event)?	◯ Yes ◯ No
Presence of aortic arch plaque?	◯ Yes ◯ No ◯ Unknown
Presence of patent foramen ovale (PFO)?	◯ Yes ◯ No ◯ Unknown (PFO identified through transthoracic, transesophageal echocardiography or transcranial doppler with bubble study)
Other anatomic features associated with PFO	☐ Atrial septal aneurysm ☐ Hypertrophy of the interatrial septum ☐ Presence of the Eustachian valve ☐ Aortic root dilation ☐ Other
Severity of the shunt	◯ 1-10 MES small shunt ◯ > 10 MES medium shunt ◯ > 10 MES with "curtain effect," large shunt
Cause of the event	◯ Large vessel stroke ◯ Lacunar stroke ◯ Stroke or TIA due to other defined cause ◯ Stroke or TIA of undetermined cause (In case of PFO check "stroke of undetermined cause")
Other determined cause:	◯ dissection ◯ vasculitis ◯ hypercoagulable state ◯ other

Undetermined cause:	◯ more than one probable cause ◯ negative evaluation ◯ incomplete evaluation
Does the event fulfill the characteristics of ESUS?	◯ Yes ◯ No ◯ Not applicable (required examinations not performed) (DEFINITION: Non-lacunar ischemic stroke; absence of atherosclerosis causing >50% stenosis in arteries supplying ischemic area; no major risk cardioembolic source, no other specific cause of stroke identified. REQUIRED EXAMINATIONS: imaging of the brain, intra- and extracranial vessels, 12-lead ECG, ≥24h cardiac monitoring, and precordial echocardiography. REFERENCE: Lancet Neurol 2014;13:429-438.)

6. ANTIPLATELET TREATMENT

Type of dual antiplatelet treatment	◯ clopidrogrel and aspirin ◯ ticagrelor and aspirin
Timing of initiation of dual antiplatelet treatment	◯ < 12 h ◯ 12-24 h ◯ 25-48 h ◯ >48 h
Did the patient receive a loading dose of aspirin?	◯ Yes ◯ No
Did the patient receive a clopidogrel loading dose?	◯ Yes ◯ No
Did the patient receive a ticagrelor loading dose?	◯ Yes ◯ No

Follow-up CRF

Please complete the survey below adding the follow-up data of your patients.

Thank you!

Please refer to this link for the study protocol, CRF instructions and more useful tools:https://drive.google.com/drive/folders/1vdMcXNSho0lFpv2AcZ1f8ArnrJPNoG33?usp=sharing

Center and patient's code (please insert the code reported on the baseline CRF)	_____ (Please insert the XXX code of the center followed by patient's number 000)
Lost to follow-up?	◯ Yes ◯ No

1. ANTIPLATELET TREATMENT DURATION

Date of dual antiplatelet treatment start	_____
Was the patient compliant with the prescribed dose and duration of dual antiplateletet?	◯ Yes ◯ No
Did the patient early discontinue the treatment with dual antiplatelet?	◯ Yes ◯ No
Which was the antiplatelet discontinued? (Select all that apply)	☐ Cardioaspirin ☐ Ticagrelor/clopidogrel
Reason for early dual antiplatelet discontinuation	◯ Adverse events ◯ Lack of compliance ◯ Diagnosis of atrial fibrillation or other condition requiring anticoagulant treatment ◯ Other
Adverse event leading to discontinuation	◯ Allergic reaction ◯ Bleeding
Duration of treatment with dual antiplatelet (days)	_____
Antiplatelet prescribed after DAPT cessation	◯ Aspirin ◯ Clopidogrel ◯ Ticagrelor ◯ None

2. VISIT DETAILS, COMPLIANCE TO TREATMENTS AND OTHER THERAPEUTIC PROCEDURES

Date of follow-up visit

_____

Type of visit

◯ On site
◯ Remote

	Yes	No	N/A (not prescribed)
Compliance to antihypertensives	◯	◯	◯
Compliance to statins	◯	◯	◯
Compliance to antidiabetics	◯	◯	◯

Did the patient undergo endarterectomy?

◯ Yes
◯ No
◯ N/A (not applicable)

Did the patient undergo PFO closure?

◯ Yes
◯ No
◯ N/A (not applicable)

3. OUTCOMES

Ischemic stroke or TIA

◯ Yes
◯ No

Symptoms duration

◯ >24 h
◯ < 24 h

Presence of a lesion in CT or MRI scan consistent with symptoms?

◯ Yes
◯ No

Date of ischemic event

_____

Days to ischemic event

_____
(This field is automatically calculated)

Symptom location

◯ Unknown
◯ Right hemisphere or eye
◯ Left hemisphere or eye
◯ Posterior circulation
◯ Multiple vascular districts

NIHSS score of ischemic stroke at onset

_____
(In case of TIA please report 0)

Clical features of TIA

◯ Unilateral weakness
◯ Speech disturbances without weakness
◯ Other symptoms

Duration of TIA symptoms

◯ < 10 minutes
◯ 10-59 minutes
◯ ≥60 minutes

Cause of the ischemic stroke or TIA	◯ Large vessel stroke ◯ Lacunar stroke ◯ Cardioembolism ◯ Stroke or TIA due to other defined cause ◯ Stroke or TIA of undetermined cause
Other determined cause of the ischemic stroke or TIA	◯ dissection ◯ vasculitis ◯ hypercoagulable state ◯ other
Undetermined cause	◯ more than one probable cause ◯ negative evaluation ◯ incomplete evaluation
Does the ischemic stroke fulfill the characteristics of ESUS?	◯ Yes ◯ No ◯ Not applicable (required examinations not performed) (DEFINITION: Non-lacunar ischemic stroke; absence of atherosclerosis causing >50% stenosis in arteries supplying ischemic area; no major risk cardioembolic source, no other specific cause of stroke identified. REQUIRED EXAMINATIONS: imaging of the brain, intra- and extracranial vessels, 12-lead ECG, ≥24h cardiac monitoring, and precordial echocardiography. REFERENCE: Lancet Neurol 2014;13:429-438.)
Intracerebral hemorrage	◯ Yes ◯ No
Date of intracerebral hemorrhage	_____
Days to intracerebral hemorrhage	_____ (This field is automatically calculated)
NIHSS score of intracerebral hemorrhage at onset	_____
Intracerebral hemorrhage location	◯ Lobar ◯ Non-lobar ◯ Uncertain (For the classification please refer to https://discovery.ucl.ac.uk/id/eprint/1535936/1/Werring_Th

Intracerebral hemorrhage cause	◯ Probable amyloid angiopathy (lobar location AND age >55 years) ◯ Hypertensive angiopathy (SBP>160mmHg OR DBP>100mmHg OR history of antihypertensive medication) ◯ Other/Unknown (Hypertensive patients aged >55 years and with lobar ICH are included in the "Probable amyloid angiopathy" category)
Subarachnoid hemorrage	◯ Yes ◯ No
Date of subarachnoid hemorrhage	_____
Days to subarachnoid hemorrhage	_____ (This field is automatically calculated)
Other intracranial bleeding	◯ Yes ◯ No (Intracranial bleeding is an hemorrage within the cranial vault regardless the etiology)
Type of intracranial bleeding	◯ Subdural hematoma ◯ Epidural hematoma ◯ Other (Intracranial bleeding is an hemorrage within the cranial vault regardless the etiology)
Date of intracranial bleeding	_____ (Intracranial bleeding is an hemorrage within the cranial vault regardless the etiology)
Days to intracranial bleeding	_____ (This field is automatically calculated)
Myocardial infarction	◯ Yes ◯ No
Date of myocardial infarction	_____
Days to myocardial infarction	_____ (This field is automatically calculated)
Vascular death (i.e. death due to stroke (ischemic or hemorrhagic), systemic hemorrhage, myocardial infarction, congestive heart failure, pulmonary embolism, sudden death, or arrhythmia)	◯ Yes ◯ No
Date of vascular death	_____

Days to vascular death

_____
(This field is automatically calculated)

Non-vascular death (i.e. death occurring for any cause different from those of the previous variable)

◯ Yes
◯ No

Date of non-vascular death

_____

Days to non-vascular death

_____
(This field is automatically calculated)

Any hospitalization

◯ Yes
◯ No

Date of hospitalization

_____

Days to hospitalization

_____
(This field is automatically calculated)

Severe bleeding (i.e. fatal hemorrage or hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention)

◯ Yes
◯ No

Date of severe bleeding

_____

Days to severe intracranial bleeding

_____
(This field is automatically calculated)

Moderate bleeding (i.e. bleeding that required transfusion of blood but did not lead to hemodynamic compromise requiring intervention)

◯ Yes
◯ No

Date of moderate bleeding

_____

Days to moderate bleeding

_____
(This field is automatically calculated)

Minor bleeding (i.e. any bleeding not requiring blood transfusion and not leading to hemodynamic compromise)

◯ Yes
◯ No

Date of minor bleeding

_____

Days to minor bleeding

_____
(This field is automatically calculated)

modified Rankin Scale score at 90 days

_____