TITLE

Gapless **E**CG-**M**onitoring for **S**troke **P**revention by **A**trial **F**ibrillation detection **(GEMS-PAF-randomized trial) –** A multi-centre, randomized controlled outcome trial.

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1. LIST OF ABBREVIATIONS (in alphabetical order)

- Atrial fibrillation (AF)
- Austrian Agency for health and Food Safety (AGES)
- Case report form (CRF)
- Clinical Investigation Plan (CIP)
- Confidence intervals (CI)
- Coordination center for clinical studies, Medical University of Vienna (KKS)
- Cranial computed tomography (CCT)
- Cryptogenic Stroke and Underlying Atrial Fibrillation trial (CRYSTAL-AF)
- Electrocardiogram (ECG)
- Ethics Committee (EC)
- Ethylene-Diamine-Tetra-Acetic acid (EDTA)
- Gapless ECG-Monitoring in Stroke at high risk for Atrial Fibrillation (GEMS-AF)
- Hazard ratios (HR)
- High sensitivity troponin T (hsTNT)
- ILR (implantable loop recorder)
- Institutional Review Board (IRB)
- Intention-to-treat (ITT)
- Ischemic stroke (IS)
- Magnetic resonance imaging (MRI)
- Medical Device Law (MPG, Medizinproduktegesetz)
- Mid-regional atrial natriuretic peptide (mrANP)
- N-terminal pro Brain Natriuretic Peptide (nt-proBNP)
- Source Data Verification" (SDV)
- Standard operating procedure (SOP)
- RCT (randomized controlled trial)
- Transient ischemic attack (TIA)
- Transesophageal echocardiography (TEE)
- Transthoracic echocardiography (TTE)

2. CLINICAL INVESTIGATION PLAN SUMMARY AND ABSTRACT

Title

Gapless **E**CG-**M**onitoring and **S**troke **P**revention by **A**trial **F**ibrillation detection **(GEMS-PAF-randomized trial) –** A multi-centre, randomized controlled outcome trial.

Purpose

To prove, whether early implantation of an implantable loop recorder (ILR) during stroke-unit-admission, without disruption of ECG monitoring time, (i.e. "gapless") compared to conventional ECG monitoring results in a lower rate of re-stroke due to a higher detection rate of paroxysmal atrial fibrillation (AF) which will be proven by control cerebral magnetic resonance imaging (cMRI) after 12 months.

Study population

Consecutive patients with ischemic stroke/ transient ischemic attack admitted to the stroke-unit of one of the participating study-centers.

Study design

Multicentre, randomized, controlled trial. Patients will be randomly assigned into either gapless ECG-monitoring (Group 1: implantation of an implantable loop recorder directly after ECG-monitoring during stroke unit admission), or standard ECG-monitoring (Group 2: use of 24-72h-Holter ECG during hospital admission and/or after discharge in the ambulatory setting according to the post-stroke follow-up protocols of the treating stroke center). For analysis of the primary and secondary endpoints patients will receive a control cerebral magnetic resonance imaging (cMRI) after 12 months.

Primary endpoint

Prevention of re-stroke by detection of paroxysmal AF and (silent) stroke in cMRI after 12 months.

Secondary endpoints

- Time to first detection of AF (AF burden, total number of AF episodes)
- Any fatal/non-fatal cardioembolic events, fatal/non-fatal recurrent stroke, fatal/non-fatal myocardial infarction, bleeding complications and hospitalizations at 12 months
- New use of anticoagulants at 12 months
- Quality of life

Inclusion criteria

- Any stroke/TIA without previously detected AF
- If TIA: corresponding lesion on brain MRI/CT OR if no corresponding lesion on brain imaging: Speech disturbance or paresis at the index event AND duration of symptoms >10 minutes required

- For Patients age 50-59 years at least one of the following risk factors: prior stroke/TIA to index stroke (includes covert/silent strokes on neuroimaging), diabetes, hypertension, current smoking, or heart failure
- Index event within 72h
- CHA_2DS_2-Vasc score >3
- Written informed consent from patient or approved proxy

Exclusion criteria

- Any history of AF/atypical flutter or any documented AF/atypical flutter
- Indication for oral anticoagulation at inclusion
- Absolute contraindication for oral anticoagulation at inclusion
- Implanted pacemaker device or cardioverter/defibrillator
- Life expectancy <1y for reasons other than stroke
- Age <50 years or pregnancy

Study Size

442 patients (randomized in Group 1: 221 patients and Group 2: 221 patients) from 5 study centres with a follow-up time of 12 months to detect 20% silent strokes and 7% symptomatic strokes. Thus, we first assume a total proportion of combined events of 25%, 27% or 29% in the control group (see for detail statistical plan).

Study duration

Minimum 12 months per patient. Inclusion of all patients 2 years from all study centre initiations. In total approximately 3 years until final analysis.

Study device

Commercially released implantable loop recorder. Home Monitoring.

Procedures

- Screening of eligible patients either by automated AF-detection or by daily manual monitor-checks during Stroke Unit admission.
- Randomization according study protocol.
- Implantation of the loop recorder during in-hospital stay.
- 24h-72h Holter-ECG-monitoring during in-hospital stay in accordance with the center-specific SOP/protocol for patients with acute stroke or TIA**.**
- Ambulatory Holter-ECG-monitoring in accordance with the center-specific SOP/protocol for patients with acute stroke or TIA**.**

Advantages and strengths

- First randomized study to analyze ECGs gapless with implantable loop recorders, which will be implanted within 5 days after the index event. Loop recorder implantation will be performed during in-hospital stay while patients are still ECG-monitored, thus avoiding any gaps in ECG monitoring, especially early after the index event. Following this, detection rates of AF might be higher early after stroke or TIA.
- First randomized study to include patients with cryptogenic stroke and patients with known etiology which is in contrast to previous (CRYSTAL AF) and currently ongoing (STROKE AF) trials.
- First study to use the CHA_2DS_2-Vasc score as an inclusion criterion in stroke patients without prior AF.
- An existing network of excellent stroke-units will be used. Gapless monitoring will be provided by direct ECG monitoring after admission to the stroke-unit. Participating centers will either use automated AF-detection methods or will manually perform daily monitor-checks of recorded heart rhythm.

ABSTRACT

Background: Up to 20% of patients with ischemic stroke (IS) or transient ischemic attack (TIA) have a prior history of atrial fibrillation (AF). AF can be detected by different monitoring strategies in up to 23% of patients with cryptogenic or non-cardioembolic IS/TIA. However, most studies had substantial gaps in monitoring time especially early after the index event. Following this, AF rates would be higher if patients underwent continuous monitoring early after IS/TIA avoiding any gaps in monitoring. In addition, the few existing randomized studies focused on patients with cryptogenic stroke, but did not focus otherwise specifically on patients at high risk for AF (patients at higher age or high CHA_2DS_2-VASC scores).

Study design: This is a randomized, multicenter, controlled trial. In total, 442 patients aged ≥ 50 years with acute IS or TIA admitted at one of the participating stroke centers in Austria will be included. Patients with previously diagnosed AF, indications or contraindications for oral anticoagulation, and/or implanted pacemaker or cardioverter defibrillator will be excluded. All patients will be randomized in either (Group 1) gapless ECG-monitoring (with implantation of an implantable loop recorder directly after ECG-monitoring during stroke unit admission) or convention care (Group 2) by the use of standard ECG-monitoring with 24-72h-Holter ECG during hospital admission and/or after discharge in the ambulatory setting according to the post-stroke follow-up protocols of the treating stroke center. In all patients the CHA2DS2-VASc score will be assessed. All patients will be followed for a minimum of 12 months after inclusion. The estimated duration of the study will be three years.

Outcomes: The primary outcome is detection of AF within 12 months or occurrence of re-stroke / detection of silent re-stroke by MRI. Secondary rhythmologic endpoints will be time to AF, the total number of AF episodes and AF burden. In addition, patients will be stratified by the within 12 months number of secondary clinical endpoints (any fatal/non-fatal cardioembolic events, fatal/non-fatal myocardial infarction, bleeding complications, hospitalizations, rate of anticoagulation treatment and quality of life).

3. BACKGROUND AND RATIONALE

In Austria 22.000 individuals (0.25%) suffer an ischemic stroke (IS) every year and about 60.000 are affected by disability thereafter *(Austrian Stroke Society, 2014)*. Risk of stroke is 5-fold increased in atrial fibrillation (AF)[1] independently of whether AF is paroxysmal or persistent[2]. Up to 20% of patients with ischemic stroke have a previous history of AF but incidence rates increase steeply with age.[3] In stroke-patients >80 years of age the incidence of AF-related stroke has increased 3-fold during the last 35 years and another 3-fold increase is expected by 2050.[3] Detection of AF is of central importance after stroke or transient ischemic attack (TIA) as risk of recurrent stroke can be effectively reduced by oral anticoagulation with warfarin[4] and novel oral anticoagulants[5].

Over the last years a number of external and implantable methods for detection of occult AF have been developed (summarized in Table 1).[6] They vary with respect to invasiveness (external vs. implantable), possibility of detection of asymptomatic events (i.e. patient triggered event recorders and implantable loop recorders (ILR)), monitoring duration (short in repeated ECGs, Holter ECG and in-patient telemetry, long in patient triggered event recorders and implantable loop recorders), costs (high in outpatient telemetry and implantable devices) and patient compliance.[6] Monitoring methods have been tested in several observational studies[7-9] with average detection rates of AF of about 10% with a higher yield in studies screening selected patients (mostly cryptogenic strokes).

Four randomized, controlled studies of cardiac monitoring after IS/TIA have been published: two smaller pilot studies (one analyzing cardiac outpatient telemetry[10] and the other 7-days external loop recording[11]) and two RCTs analyzing 30 days of external loop recording[12] and implantable loop recording[13]. Taken together, the results of the two large randomized controlled trials (EMBRACE and CRYSTAL AF) suggest that approximately 10 patients need to be screened with prolonged monitoring to establish one new diagnosis of atrial fibrillation. Based on these published data and expert opinion, guidelines[14] suggest that prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event. However, even though according to published guidelines additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered in stroke patients to document silent atrial fibrillation, in clinical practice the majority of patients still does not receive any extended ambulatory external or implantable ECG-monitoring. A reason for that might be the restricted availability of external event recorders, not well established or possible inter-disciplinary cooperation or ILR associated costs.[15]

A shortcoming of previous studies was the relatively long delay between hospital discharge and start of ambulatory ECG monitoring. In the randomized controlled trials EMBRACE and CRYSTAL-AF patients were randomized to ECG monitoring techniques 75.1 ± 38.6 days and 38.1 ± 27.6 days, after the qualifying event, respectively.

Table 1 Different methods of cardiac monitoring *(adapted from: Seet, Circulation 2011)*

Method	Advantages	Disadvantages
Noninvasive		
Continuous in-hospital telemetry	- Accurate diagnosis - Detects asymptomatic events	- Requires inpatient monitoring - Restricts patient movement - Expensive
Holter-ECG	- Easy to use - Continuous recording - Detects asymptomatic events	- Short monitoring period - Symptom-diary required
Patient-triggered event recorder	- Longer monitoring periods - Correlation with symptoms	- No detection of asymptomatic events - Patient-participation required
Mobile cardiovascular telemetry	- Continuous recording - Detects asymptomatic events	- Patient compliance, skin irritation - Expensive
Invasive		
Implantable loop recorder	- Longer periods of follow-up - Internet-based data transmission - Detects asymptomatic events	- False positive and false negative detections - Expensive and invasive

In a meta-analysis[8] of studies reporting the detection of post- stroke AF the monitoring techniques were stratified into four sequential phases of screening: phase 1 consisted of admission ECG; phase 2 comprised serial ECG, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry, and in-hospital Holter-ECG monitoring; phase 3 consisted of ambulatory Holter-ECG monitoring; and phase 4 consisted of mobile cardiac outpatient telemetry, external loop recording, and ILR. Overall according to this meta-analysis in 23.7% of patients with ischemic stroke AF can detected by screening. The probability to detect AF was 7.7% in phase 1, 4.2% in phase 2, 7.5% in phase 3 and 4.3% in phase 4.

Therefore, in about a third of patients AF can be detected by the first ECG at admission, and in about half of the patients by in-hospital ECG-screening. However, in most of the studies included into phase 2 duration of in-hospital ECG-screening was short (i.e. < 72h). Only few previous studies[11, 16-19] analyzed prolonged ECG monitoring (≥7days) within 14 days of the

cerebrovascular event by various methods (Holter ECG monitoring, external loop recorders) and yielded detection rates between 10-20% as compared to standard monitoring (12-lead ECG and/or 24h Holter ECG). In the randomized controlled pilot study of Higgins et al. 100 patients with ischemic stroke were randomized either to 7 days of noninvasive cardiac-event monitoring or to standard monitoring (12-lead ECG and 24h Holter ECG monitoring).[11] The external devices were applied within 7 days after the index event. After 90 days sustained episodes of AF were significantly more often detected in patients undergoing prolonged cardiac-event monitoring (22% vs 8%). Recently, two large randomized studies comparing 7 day Holter Monitoring[20] and 10 day Holter Monitoring[21] early after IS. The first (MonDAFIS) did not find an effect of systematic ECG monitoring on the rate of oral anticoagulation use after 12 months. The second (FIND-AF Randomized), showed that enhanced and prolonged monitoring early in patients with acute stroke aged 60 years or older was better than standard care for the detection of AF (14% versus 5% after 6 months).

So far, there is only one small observational study[22] analyzing incidence rates of AF using ILRs early after IS. In the randomized controlled CRYSTAL AF study[13] the median time to randomization was 38.1 ± 27.6 days. In the STROKE-AF study[23] which analyzes incidence rates of AF in stroke patients with known etiology by comparing continuous cardiac monitoring using a ILR with standard monitoring, patients are randomized within 10 days but not using a gapless approach. The randomized STROKE-AF[23] and the recent PER-DIEM[24] and MonDAFIS studies[20] showed that prolonged ECG monitoring with an insertable cardiac monitor (ICM) yields high AF detection rates not just in patients with a cryptogenic stroke, but also in patients with small-vessel or large artery disease. The STROKE-AF[23] trial had a relatively short time to ICM-monitoring of 5 [3-8] days. However, this study only included patients with small-vessel or large-artery disease. In the MONDAFIS study[20], the time to prolonged monitoring was 17 [11-21] hours, but this study only applied additional monitoring of 7-days.

We demonstrated very recently with our published GEMS-AF-study[25] (Gapless Electrocardiogram-Monitoring in Stroke at high risk of Atrial Fibrillation Study) that gapless ECG-monitoring without any interruption in monitoring time is a feasible and effective approach to increase detection rates of AF after an ischemic stroke substantially. In GEMS-AF[25] detection rate after 6 month was 15.5% and 2/3 of all AF diagnoses were made within the first 30 days of monitoring. Relevantly, in GEMS AF[25] ILR implantation occurred after thorough telemetric ECG monitoring on stroke units with a median duration of 70 hours. During telemetry AF was detected in another 7 cases which were not included into the final analysis.

It is still an open question what duration of AF is associated with an increased stroke risk. Most studies used a 30-second duration as a threshold.[26] Accordingly, in clinical practice, most physicians use this threshold for initiation of anticoagulant treatment in patients with AF after stroke/TIA. However, most recently, data from the population-based OXVASC study questioned this approach.[27] In this study, patients after stoke/TIA underwent ambulatory

ECG-monitoring (Novacor-R Test). Patients in whom AF was detected were stratified according to AF duration (<2min/≥2min). Of note, patients with AF duration <2min were not anticoagulated. At the end of the study (mean follow up: 2.3years) those with AF duration of <2min had a similar risk of recurrent stroke as compared to patients without AF.

Studies analyzing prolonged monitoring methods (including the CRYSTAL-AF[13] and EMBRACE[12] trials) mostly focused on patients with cryptogenic stroke. However, in a population based study of patients with ischemic stroke or TIA, risk of newly detected AF as well as of AF-related cardioembolic events was similar in patients with cryptogenic stroke and those with non-cardioembolic stroke (i.e. large artery disease and small vessel disease events combined).[28] A randomized pilot study of noninvasive cardiac event monitoring included unselected patients with non-cardioembolic stroke and reported high detection-rates of AF (see above).[11] Therefore, studies focusing exclusively on patients with cryptogenic stroke (or embolic stroke of undetermined source[29]) might underestimate proportions of AF and demand of oral anticoagulation. Yet, selection of patients at particular high risk for AF and recurrent cardioembolic events after stroke or TIA is crucial. Clinical scores have been developed to assess risk stratification for cardioembolic events in patients with AF (i.e. CHADS2 score and the CHA_2DS_2VASc-Score) and have been associated with total duration of AF (lower CHADS2-scores in patients with low AF burden). In addition, previous studies also indicated usefulness of the CHADS2- and CHA_2DS_2VASc-Scores for prediction of AF in patients after stroke[30,31]. In the recent study of Baturova et al, CHADS2-scores ≥4 and CHA_2DS_2VASc scores ≥5 predicted new onset AF in patients after ischemic stroke during 10 years of follow-up.[31] Importantly, this study did not focus on cryptogenic stroke specifically but reported data on an unselected population of ischemic stroke.

Relevantly, detection of AF cannot be equated with prevention of cerebrovascular and peripheral embolic events. None of the previous studies analyzing different strategies of ECG monitoring after stroke was powered to show an effect on prevention of clinical events. A meta-analysis of ILR after stroke including the CRYSTAL AF, STROKE AF and PER DIEM studies did not detect a significant reduction in cerebrovascular events. However, despite including data of 1233 randomized patients numbers of recurring events were low (n=94) and below the approximately 500 stroke events needed to adequately power a definitive evaluation of stroke reduction with ILR.[32,33] However, in a meta-analysis of prolonged ECG monitoring after stroke/TIA not exclusively focusing on ILR and including also observational studies prolonged monitoring was associated with a lower risk (RR 0.58, 95% CI 0.41, 0.82) of recurrent stroke.[34]

Previous studies suggested that covert brain infarction (CBI) could be used as surrogate for assessing stroke therapies.[32, 35] In the recently published PACIFIC Stroke trial occurrence of CBI was 3 times higher than of clinical stroke events.[36] Patients with CBI are at increased risk of subsequent clinically manifest ischemic stroke.[37] In summary these data show that diagnosis of CBI in patients after acute ischemic stroke is of value, in particular in patients with atrial fibrillation and that CBI might be used as a surrogate for clinical manifest ischemic stroke in clinical studies.

4. HYPOTHESIS AND AIMS OF THE STUDY

4.1 Primary Hypothesis

We hypothesize that in patients with acute ischemic stroke or TIA gapless implantation of a loop recorder with the subsequent detection of unknown atrial fibrillation results in a decrease of acute ischemic strokes and systemic embolism infarction after 12 months compared to routine ECG monitoring by increasing detection rates of atrial fibrillation and the number of patients treated with oral anticoagulation.

4.2 Aims

Aims: The study aims to establish the disease managing capability of gapless ECG-monitoring in stroke/TIA patients by directly comparing this approach to standard ECG-monitoring in a randomized study design. This will allow to directly infer the clinical usefulness and potentially superiority of gapless ECG-monitoring and thereby might have immediate implications for clinical practice. The following specific objectives will be investigated:

Primary Objective: to assess, whether early implantation of an ILR during stroke-unit-admission, without disruption of monitoring time, (i.e. “gapless”) results in a reduction of the composite endpoint of recurrent ischemic stroke or TIA or systemic embolism and covert brain infarcts detected by MRI after one year as compared to routine ECG monitoring

Secondary objectives:

1) to assess, whether early implantation of an ILR results in higher detection rates of atrial fibrillation
2) to assess, whether early implantation of an ILR results in a different use of anticoagulation for prophylaxis of thromboembolism
3) to assess, whether early implantation of an ILR results in a reduction of clinical endpoints, ie. Ischemic stroke/TIA/systemic embolism
4) to assess, whether early implantation of a ILR results in a reduction of covert brain infarcts
5) to assess, whether left atrial measures on echocardiography (diameter, volume, strain) have an impact on outcome
6) to assess, whether the new AI algorithm within the provided device can reduce inadequate detection rates of atrial fibrillation within the given population

5. DESIGN OF THE CLINICAL INVESTIGATION: MULTICENTER, RANDOMIZED CONTROLLED OPEN LABEL STUDY WITH BLINDED OUTCOME ASSESSMENT.

5.1 Definitions

AF is defined as an episode of irregular heart rhythm without detectable p-waves. Historically, a sustained rhythm disturbance is defined as an episode lasting more than 30sec. In case of AF in stroke there is common agreement, that any AF episode lasting more than 2 minutes serves as a clear threshold for medical decision making such as oral anticoagulation. For ischemic stroke and TIA the standard World Health Organization definitions are used.[38]

5.2 Population

5.2.1 Study population

Consecutive patients with acute ischemic stroke admitted to the stroke-unit of one of the participating study-centers.

5.2.2 Inclusion criteria

- Any stroke/TIA without previously detected AF
- if TIA: corresponding lesion on brain MRI/CT OR if no corresponding lesion on brain imaging: Speech disturbance or paresis at the index event AND duration of symptoms >10 minutes required
- Age ≥ 50 and; for patients age 50-59 years at least one of the following risk factors: prior stroke/TIA to index stroke (includes covert/silent strokes on neuroimaging), diabetes, hypertension, current smoking, or heart failure
- Index event within 72h
- Written informed consent by the patient

5.2.3 Exclusion criteria

- Any history of AF/atypical flutter or any documented AF/atypical flutter prior to inclusion
- Indication for oral anticoagulation at inclusion
- Absolute contraindication for oral anticoagulation at inclusion
- Implanted pacemaker device or cardioverter/defibrillator
- Age below 50 years
- Life expectancy <1y for reasons other than stroke

5.2.4 Point of enrollment

After inclusion and exclusion criteria are verified during the monitoring on the stroke unit and eligible patients (or a approved proxy) have signed the informed consent form.

5.2.5 Primary endpoint

Recurrent ischemic stroke or TIA, systemic embolism and/or any covert cerebral infarction detected in the follow-up MRI performed after 12 months

5.2.6 Secondary endpoints

- Time to first detection of AF / atrial flutter
- newly established oral anticoagulation with VKA or NOAC
- recurrent ischemic stroke or TIA
- covert ischemic stroke
- death
- AF burden, total number of AF episodes
- Any fatal/non-fatal cardioembolic events, fatal/non-fatal recurrent stroke, fatal/non-fatal myocardial infarction, bleeding complications and hospitalizations at 12 months
- Quality of life

5.2.7 Females of childbearing potential

Not included.

5.2.8 Duration of the clinical investigation

3 years

5.2.9 Withdrawal and replacement of subjects

Subjects may prematurely discontinue from the clinical investigation at any time. Premature discontinuation from the study is to be understood when the subject did not undergo EOS examination and / or all pivotal assessments during the clinical investigation, i.e. three complete dosage-time profiles.

Subjects must be withdrawn under the following circumstances:

- at their own request
- if the investigator feels it would not be in the best interest of the subject to continue
- if the subject violates conditions laid out in the consent form / information sheet or disregards instructions by the clinical investigation personal
- if an ILR removal or extraction for any reason is performed

In all cases, the reason why subjects are withdrawn must be recorded in detail in the CRF and in the subject's medical records. Should the clinical investigation be discontinued prematurely, all clinical investigation materials (complete, partially completed and empty CRFs) will be retained. *Follow-up of patients withdrawn from the clinical investigation:*
In case of premature discontinuation after treatment with the medical device, the investigations scheduled for the EOS visit will be performed within 14 days after discontinuation. The subjects will be advised that participation in these investigations is voluntary. Furthermore, they may request that from the time point of withdrawal no more data will be recorded and that all biological samples collected in the course of the clinical investigation will be destroyed.

5.2.10 Premature termination of the clinical investigation

The sponsor has the right to close this clinical investigation at any time. The IEC and the competent regulatory authority must be informed.

The clinical investigation or single dose steps will be terminated prematurely in the following cases:

- If adverse event/adverse devise effect occur which are so serious that the risk-benefit ratio is not acceptable
- If the number of dropouts is so high that proper completion of the clinical investigation cannot realistically be expected.
- If the inclusion phase exceeds more than 3 years

6. METHODS

6.1 Planned participating study centers (in total 6-8 centers)

Since 2003, a network of Austrian stroke units is collecting data on standard characteristics and acute management of all patients with stroke admitted to one of the participating centers (Austrian Stroke Unit Registry, ASUR). In biannual meetings of participating stroke neurologists, details about scoring procedures and variable assessment and patient management are thoroughly discussed. The ASUR is part of a governmental quality assessment program for stroke care in Austria financed by the Federal Ministry of Health. All centers planned to participate in this study are part of this network:

- Univ. Klinik für Neurologie, Wien
- Abteilung für Neurologie, Krankenhaus der Barmherzigen Brüder, Wien
- Abteilung für Neurologie, Klinik Landstraße, Wien
- Univ. Klinik für Neurologie, Salzburg
- Univ. Klinik für Neurologie, Linz
- Univ. Klinik für Neurologie, Innsbruck

in cooperation with:

- Univ. Klinik für Innere Medizin II, Abteilung für Kardiologie, MedUniWien
- Abteilung für Innere Medizin II, Krankenhaus der Barmherzigen Brüder, Wien
- 2. Med. Abteilung mit Kardiologie und internistischer Intensivmedizin, Klinik Landstraße, Wien
- Universitätsklinik für Innere Medizin II - Kardiologie, Internistische Intensivmedizin und Notaufnahme, SALK Salzburg
- Klinik für Kardiologie und Intensivmedizin, Kepler Universitäts Klinikum Linz
- Univ. Klinik für Innere Medizin III, Kardiologie und Angiologie, Innsbruck
- Kardinal Schwarzenberg Klinikum GmbH, Schwarzach im Pongau

6.2 Treatment duration and modification

The ILR will stay implanted until battery depletion or if the diagnosis and therapy will not demand any further prolonged monitoring.

6.3 Medical Device

6.3.1 Medical device and it´s characteristics

- Abbott Assert IQ of Abbott´s insertable cardiac monitor system (ICM) with remote monitoring will be used.
- Assert IQ ICM is an insertable automatically activated and patient- activated monitoring system that records subcutaneous ECG and is indicated in the following cases:
  • Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias
  • Patients who experience transient symptoms such as dizziness, palpitation, syncope, and chest pain that may suggest a cardiac arrhythmia
- Patients can use their smartphone to automatically transfer device data via a mobile App, even outside the home.
- Or use provided Remote Monitoring Devices and the App to the patients.
- Smart memory management eliminates the need for manual transmissions.

All patients will be implanted with an ILR for continuous monitoring. This device continuously classifies the heart rhythm of the patient through the analysis of the beat-to-beat variability of cardiac cycles. The device stores the amount of AF per day (daily AF-burden) and during the overall follow-up period (cumulative AF-burden). In addition, ECG segments are stored for a defined number of episodes for visual confirmation of AF episodes. Patients were provided with the Patient Assistant, an external device that allows patients to manually trigger the storage of an ECG in the implanted device for example while having symptoms.

Patient gets a patient activator to store symptomatic ECG data in the device. Device programming: Reason for monitoring: “Cryptogenic Stroke” (use standard detection settings for cryptogenic stroke: Balanced AF detection sensitivity, Aggressive Ectopy Rejection, AF Threshold: All Epsiodes, AF Only, Wireless Data Priority: Tachy, Pause, Brady), 4 symptom related episodes with a maximum duration of 7.5 min each. Remote Monitoring: Patients receive hardware for remote monitoring. The remote monitoring system transmits data wireless once a day without any action from the patient needed. No additional costs apply for the patient or the clinic. Storage Instructions: data will be stored on an USB stick. Patients will be identified by ID Numbers, which will be stored together with the patients’ names securely in a safe locker. Installation and handling instructions according to standard

operation procedure (SOP). Delivery & storage conditions of the medical device according to SOP. Packaging and labeling of the medical devise according to SOP. Accountability of medical devices according to SOP. Intended Use according to SOP. Initial treatment: according to SOP. Maintenance treatment: according to SOP. *Reactions and side effect of the medical device:* possible infection with the need to remove the device. In/Decrease of the treatment frequency: n.a.

6.3.2 Summary of the ILR implantation procedure

Device: Insertable Cardiac Monitoring (ICM) System (ILR).
The procedure is performed either in a cardiologic or neurologic ward or in a treatment room located in the outpatient department which is close to the Cath Lab on the same floor
The room has a washbasin for scrubbing

- Implanter: Gloves,
- Patient: Small drape with a chest hole
- Programmer is in another room
- Anesthesia: 1 Syringe, 1 Needles
- Skin sterilization: Cleaning solution
- Wound closure: Steri- Strips
- Surgical materials: if necessary a scalpel
- Surgical marker is not used for this procedure
- In order to ensure device orientation the implanter locates the ribs and sternum by palpitation supine and upright
- Patient arrives immediate before the procedure
- The patient is placed in a bed
- The nurse prepares the patient (0-2 minutes preparation time)
    - Monitoring in not need for this procedure
    - If necessary trichotomy is performed in the patient
- The entire procedure takes approximately 8-10 minutes
    - For all patients, the physician ensures the right orientation of the device asking the patient to sit and lay down
    - Sterilization (2 minutes), draping the patient, anesthesia in 2-3 sites (left, right and middle), ILR insertion, compression (1-4 minutes) and wound closure
    - The wound is closed with Steri -Strip and a surgical band-aid is placed to protect the wound
    - Sensing verification and programing are performed after the procedure by the cardiologist in the PM and ICD Outpatient ambulance or at ward where the patient is treated.
    - Antibiotics prophylactic regimen is deemed not needed for this procedure but it would be for immunocompromised patients
- After programming the patient could leave the hospital.
- Data privacy laws limit the use of remote monitoring technologies in Vienna
- Before discharge the patient receives considerations about the follow-up regimen

6.3.3 Interruption of treatment

- Premature permanent discontinuation of the treatment due to patient demand
- Premature permanent discontinuation due to an adverse event
- Premature permanent discontinuation due to other reason than adverse event

6.3.4 Concomitant medication

Not allowed: any kind oral anticoagulation (coumarines, NOACs)

6.4 Randomization and stratification

Eligible patients will be randomly assigned via block randomization (with block length of 8) stratified by center. Randomization will be performed using the "Randomizer" software.

6.5 Benefit and risk assessment

- *Potential risks and discomforts*

All equipment and implantable devices in this observational study are market-released in the participating countries (depending on geography e.g. CE mark or FDA approved) and used according to medical, technical and ethical standards without any change to the intended use of the device. Since the products will be used in accordance with their labeling, it is not anticipated that patients enrolled in this study will be exposed to any risks beyond those normally associated with their device or their subcutaneous implant procedure. Patients are treated according general clinical practice. Therefore, no additional risks are associated with participation in this study. There are potential risks and discomforts associated with receiving a subcutaneous cardiac monitor. Standard risks, as described in the ILR Clinician Manual, are: device rejection phenomena including local tissue reaction; device migration; pocket infection and erosion through the skin.

- *Potential benefits*: The benefit of newly detected AF leading to an improved therapy in secondary prevention of IS/TIA.

6.6 Clinical investigation procedures

6.6.1 Screening investigation

- 12-lead ECG
- Gapless monitoring will be provided by direct ECG monitoring after admission to the stroke-unit. Participating centers will either use automated AF-detection methods[41] or will perform manually daily monitor-checks of recorded heart rhythm.
- Routine stroke work-up including intracranial imaging including CCT OR MRI, Ultrasound of extra cranial / intracranial brain-arteries, TTE/TEE, routine blood tests.

6.6.2 Procedures

- **Implantation of the ILR** during Stroke-Unit-admission.
- **cMRI:** The required study MRIs are to be performed:
  1) either before randomization (as a clinically initiated MRI) or within 72 hours after randomization (as a study initiated MRI) for all participants and
  2) a final study MRI will be performed for all participants after 12 Months
  Covert brain ischemia (CBI): CBI will be diagnosed according to predefined definitions (Gutierrez, Stroke 2020). In patients with previously detected AF any CBI will be classified as cardioembolic (caused by AF) regardless of the territory.
- **24h-72h Holter-ECG-monitoring** during in-hospital stay in accordance with the center-specific SOP/protocol for patients with acute stroke or TIA

- **Ambulatory Holter-ECG-monitoring** in accordance with the center-specific SOP/protocol for patients with acute stroke or TIA
- **Laboratory test** (1 EDTA-tube) for analysis of blood-biomarkers during admission on the Stroke-Unit (within 96 hours after the qualifying event): nt-proBNP, hsTNT, mr-ANP, Copeptin

6.6.3 Follow-up – schedule of activities

visit	1	2	3	4
time	screening/inclusion	3Mo	6Mo	12Mo
type	site	site	Tel	site
Administrative procedures				
signed informed consent	x			
inclusion & exclusion criteria	x			
Demographics	x			
Medical history	x			
Medication	x	x	x	x
clinical procedures/assessments				
mRS	x	x	x	x
NIHSS	x	x		x
ECG	x	x		x
Adverse events		x	x	x
outcome events		x	x	x
MRI	x			x
Lab. Biomarkers	x			

6.7 Statistical plan

6.7.1 Statistical analysis plan

The primary endpoint is a combined binary endpoint silent stroke on MRI and/or symptomatic stroke after 52 weeks. The main study hypothesis is that less ischemic strokes either silent or clinically, are detected in the group of patients with implanted ILR than with the standard of care regimen. The according null hypothesis is that on average ILR implantation is not associated with a lower incidence of ischemic strokes/TIA/systemic embolisms/covert brain infarcts than the standard regimen.

A study participant who dies before week 52 without having experienced a symptomatic ischemic stroke may not have had a post-randomization MRI performed to assess if s/he experienced a covert brain infarct before death. This data would be meaningful for the analysis but can no longer be collected due to death. The same holds true for participants who refuse to undergo a second MRI and/or that have a missing MRI at randomization.

To analyse the primary objective (comparison of combined endpoint of ischemic strokes either silent or clinically after 52 weeks between groups) a Chi-square test will be performed

for events which occur within 52 weeks. The significance level for will be set to 0.05 (two-sided). The proportion of events for each group and 95% confidence intervals will be calculated. The analysis will be based on the ITT population including all subjects who were randomized. If there are subjects, which drop-out/die after randomization and before the 52 weeks follow-up, without an event being observed, several sensitivity analyses will be performed.
- Last observation carried forward: The last available information about the status of the event will be used for the analysis.
- Worst case analysis: Subjects, who drop out of the study early without an event having occurred, are counted as event in the analysis.
Additionally, an analysis based on the PP population will be performed.

Secondary a logistic regression based on the ITT population will be calculated with the dependent variable event and the independent variables group, stroke center, age, sex, stroke aetiology and stroke severity. Odds ratios, corresponding 95% confidence intervals, and p-values will be reported. A Cox regression will be performed for time till symptomatic stroke considering group, center, age and stroke center, age, sex, stroke aetiology and stroke severity. Subjects without event within 52 weeks or with silent stroke at second MRI will be censored after 52 weeks. Hazard ratios, corresponding 95% confidence intervals, and p-values will be reported. For the secondary analyses, again the significance level for will be set to 0.05 (two-sided). All other secondary objectives will be analysed descriptively: Mean values and standard deviation (or median and interquartile range, where appropriate) will be calculated for continuous data and 95% confidence intervals of mean or median will be calculated. For categorical data absolute and relative frequencies (with 95% confidence interval) will be reported. Eligible patients will be randomly assigned via block randomization (with block length of 8) stratified by center.

6.7.2 Sample size planning
Group comparison: *Loop recorder + standard of care (treatment group) versus standard of care (control group).*
Primary endpoint: *Combined binary endpoint silent stroke on MRI and/or symptomatic stroke after 52 weeks*

52 weeks*:* Assumptions for control group after 52 weeks: 20% silent strokes, 7% symptomatic strokes. Thus we first assume a total proportion of combined events of 25%, 27% or 29% in the control group. Given a sample size of 199 in each group, a two-group Chi-Square test will have 80% power to detect the difference between control group proportion of 20% and treatment group proportion of 10% (significance level of 5%). Considering a dropout rate of 10%, a total sample size of 442 for both groups is needed. Several scenarios can be found in the following table (power of 80% and significance level of 5% each). (Nquery + Nterim 4.0)

Proportion control group	Proportion treatment group	Sample size per group	Sample size per group considering drop-out rate 10%	TOTAL Sample size considering drop-out rate 10%
20	10	199	221	442
20	8	131	146	292
20	11	253	281	562
20	12	329	366	732
22	10	146	163	326
22	12	221	246	492
25	10	100	111	222
25	14	203	226	451
25	18	540	600	1200
27	10	81	90	180
27	14	151	168	335
27	18	337	374	748
29	10	68	76	151
29	14	117	130	260
29	18	233	259	518

26 weeks: Comment: “on anticoagulation treatment” after 26 weeks is not considered as primary endpoint anymore. Anticoagulation treatment is expected to lower the rate of strokes and is standard of care in case of atrial fibrillation (thus also part of the control group with possibly the same rates after 26 weeks). However, with the loop recorder, the anticoagulation treatment might start earlier and lower the rate of strokes after 26 weeks.

Assumptions for control group after 26 weeks: 14% silent strokes (according to Placebo group in Shoamanesh et al.), 5% symptomatic strokes (according to Placebo group in Shoamanesh et al.). Thus we first assume a total proportion of combined events of 18%, 19% or 20% in the control group.

Given a sample size of 199 in each group, a two-group Chi-Square test will have 80% power to detect the difference between control group proportion of 20% and treatment group proportion of 10% (significance level of 5%). Considering a dropout rate of 10%, a total sample size of 442 for both groups is needed. Several scenarios can be found in the following table (power of 80% and significance level of 5% each). (Nquery + Nterim 4.0)

Proportion control group	Proportion treatment group	Sample size per group	Sample size per group considering drop-out rate 10%	TOTAL Sample size considering drop-out rate 10%
20	10	199	221	442
20	11	253	281	562
20	12	329	366	732
19	10	240	267	534
19	11	312	347	694
19	12	419	466	932
18	10	295	328	656
18	11	396	440	880
18	12	555	617	1234

6.7.3 Software

The statistical analyses will be performed using the software package R or SAS.

Eligible patients will be randomly assigned via block randomization (with block length of 8) stratified by center. Randomization will be performed using the “Randomizer” software.

7. DOCUMENTATION AND DATA MANAGEMENT

7.1 Documentation of study results

A subject screening and enrollment Log will be completed for all eligible or non-eligible subjects with the reasons for exclusion.

7.1.1 Case report form (CRF)

For this study a paper-based CRF will be used. For each subject enrolled, regardless of study drug initiation, a CRF must be completed and signed by the Investigator or a designated sub-Investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason will be noted on the CRF. Case report forms are to be completed on an ongoing basis.

Screening failures will not be documented in the CRF. CRF entries and corrections will only be performed by study site staff, authorized by the Investigator. The entries will be checked by trained personnel (Monitor) and any errors or inconsistencies will be checked immediately. The monitor will collect original completed and signed CRFs at the end of the study. A copy of the completed and signed CRFs will remain on site.

Please indicate a responsible person, to whom original CRF´s would be passed.

f.e.: Data Manager: Coordinating center for clinical studies, Medical University of Vienna (KKS). Special provisions may apply for electronic CRFs

7.1.2 Data Collection

Data collected at all visits are entered into an interactive form. The CRFs will be source documents verified following guidelines established before study onset as detailed in the Monitoring Plan. Maintenance of the study database will be performed by the KKS or others.

7.2 Safekeeping

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file with all essential study documents, and subject clinical source documents.

The investigator's file will contain the CIP/amendments, Manual for Medical Device, data clarification and query forms, EC/IRB and Regulatory Authority approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per European Standard of EN ISO 14155 and regulatory requirements. Subject clinical source documents include, but are not limited to subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc. These two categories of documents must be kept on file by the investigator for as long as needed to comply with national regulations. If source documents are not durable as long as needed (e.g. ECG printouts) they must be preserved as a copy. No study document should be destroyed without prior written approval from the Department of Neurology and Cardiology. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

7.3 Quality Control and Quality Assurance

7.3.1 Periodic Monitoring

The monitor will contact and visit the investigator regularly and will be allowed, on request, to have access to all source documents needed to verify the entries in the CRFs and other CIP-related documents provided that subject confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the CIP and the completeness, consistency and accuracy of the data being entered on them. The monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs/SADEs and the recording of the main efficacy, safety, and tolerability endpoints. In compliance with the regulatory requirements at least 3 monitoring visits are needed. An initiation visit, one routine visit and a final visit after the last patient had finished the study. The monitor will be working according to SOPs and will provide an ISO 14155-compliant monitoring report after each visit for the sponsor

and the investigator. Depending on the quality of the data, additional monitoring visits will be necessary according to the sponsor's discretion. Monitoring will be conducted by the KKS. 6 monitoring visits are planned; 100% of source data will be checked by the monitor (which means 100% SDV).

7.3.2 Audits and Inspections

Upon request, the investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor or to regulatory authority inspectors. The main purpose of an audit or inspection is to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

7.4 Reporting and Publication

Final report: Within one year after the final completion of the study, a full Final Report will be written by the principal investigators. The Investigator will be asked to review and sign the Final Report.

Publication of study results: For any planned publications first and senior authorship will be kept by Thomas Pezawas and Stefan Greisenegger.

7.5 Expenses – budget plan

Category:	Tasks:	Amount		hrs	rate	cost
Setup	overhead hospital infrastructrue	10 percent of overall costs			10 percen	€ 31.033
	Protocol review		PM			
	Produce Monitor manual		LCRA			
	Produce Project Plan		CRA			
	Produce datamanagement manual		CTA			
	Produce SAE manual		Legal			
	Filing set-up		DM			
	ICF review		Safety			
	set up vendors					
Management		€ 140.902				
	(Kick-off) meeting client f2f		PM			
	(Kick-off) meeting team f2f		LCRA			
	Client meetings TC		CRA	3440	€ 41	€ 140.902
	Investigator meeting (PM + LCRA)		CTA			
	Communication		Valorization 2027			€ 3.522
	Project Management meetings					
	Team meetings					
	Project Management Reporting					
	Country reporting					
	Site reporting					
Regulatory						
	HA submission		CRA			
	EC submission		PM			
Monitoring		€ 27.500				
	Site initation visits		LCRA			
	site monitoring visits (recr period)		CRA	1000	€ 28	€ 27.500
	site monitoring visits (fu period)					
	Site close-out visits					
	Site management					
Filing						
	File checks		LCRA			
	File completion		CTA			
	File completion supervision					
Finance		€ 138.400	MRI	€ 442	€ 200	€ 88.400
	Site payments		PM			
			CTA			
			Site fee 5sites	10000		€ 50.000
Contracting sites						
	Contracting		PM			
			Legal			
Datamanagement						
	Datamanagement		DM			
Planning and reporting						
	Planning and reporting		PPA			
Total tasks						
Pass Through costs						
	Investigator payments					
	Translations					
	Monitoring Travel(incl. parking, food&beverages, hotel)					
	EC/RA Fees					
	Site file production/copying					
	Courier Costs					
	Phone & Fax, office supplies					
	System licenses (Research online)					
TOTAL:	**€ 310.325**	**€ 341.358**	*			

			h/year	75% of max	hourly rate	expenses per year
CRA=PhD	Salary 4100-4400 before tax	13x/year	1290	30h/week	40,96 €	€ 52.836,00
	2 years 75% for Vienna and surroundings		2580			€ 105.672,00
	2 years 25% for Insbruck and surroundings		860			€ 35.224,00
	Summ		3440			€ 140.896,00
	Valorization 2027 5%					€ 3.522

8 ETHICAL AND LEGAL ASPECTS

8.1 Informed consent of subjects

Following comprehensive instruction regarding the nature, significance, impact and risks of this clinical investigation, the patient must give written consent to participation in the study. During the instruction the patients are to be made aware of the fact that they can withdraw their consent – without giving reasons – at any time without their further medical care being influenced in any way. In addition to the comprehensive instructions given to the patients by the investigator, the patients also receive a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress. The patients must agree to the possibility of study-related data being passed on to relevant authorities. Patients must be informed in detail of their obligations in relation to the proband insurance in order not to jeopardize insurance cover.

8.2 Acknowledgement / approval of the clinical investigation

The investigator will submit this CIP and any related document provided to the subject (such as subject information used to obtain informed consent) to an Ethics Committee (EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the clinical investigation, and should be documented in a dated letter to the investigator. Serious Adverse Events /Serious Adverse Device Effects have to be reported to the ethics committee and to the Austrian Agency for health and Food Safety (AGES). Adverse events / Adverse device effects- whether serious and/or unexpected, and possibly endangering the safety of the study participants are likewise to be reported to the ethics committee. The clinical investigation shall be performed in full compliance with the valid legal regulations according to the Medical Device Law (MPG Medizinproduktegesetz as actual amended) of the Republic of Austria and the ISO 14155 (as actual amended). The study must be notified to the AGES and EC.

8.2.1 Changes in the Conduct of the Clinical Investigation Plan

Amendments of the clinical investigation plan

Proposed amendments must be submitted to the appropriate CA and ECs. Substantial amendments may be implemented only after CA/EC approval has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving CA/EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Termination of the clinical investigation: If the sponsor or the investigator decides to terminate the clinical investigation before it is completed, they will notify each other in writing stating the reasons of early termination. In terminating the study, the sponsor and the investigator will ensure the adequate consideration is given to the protection of the subject interests. The investigator, sponsor or designated CRO will notify the relevant

regulatory authorities and EC. Documentation will be filed in the Trial Master (Clinical Investigation) clinical investigation and Investigator Files.

8.3 Insurance

During their participation in the clinical investigation the patients will be insured as defined by legal requirements. The investigator of the clinical investigation will receive a copy of the insurance conditions of the 'patients insurance'. The sponsor is providing insurance in order to indemnify (legal and financial coverage) the investigator/center against claims arising from the clinical investigation, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of clinical investigation-related injuries will comply with the applicable regulations. Details on the existing patients insurance are given in the patient information sheet.

8.4 Confidentiality

The information contained in this document, especially unpublished data, is the property of the Medical University of Vienna. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the principal investigators, except to the extent necessary to obtain informed consent from those persons to whom the medical device may be treated with.

8.5 Ethics and legal requirements

8.5.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the General Assembly, 2013).

8.5.2 Good Clinical Practice (according EN ISO 14155)

ISO 14155 addresses good clinical practices for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety and performance of medical devices for regulatory purposes.
It specifies general requirements intended to:

- protect the rights, safety and well-being of human subjects,
- ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,
- assist sponsors, monitors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

The investigator of the clinical investigation shall guarantee that only appropriately trained personnel will be involved in this. All clinical investigations must follow the European Standard of EN ISO 14155 and the regulatory requirements.

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