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## Cohort profile: EndoVascular treatment and Thrombolysis for Ischemic Stroke Patients (EVA-TRISP) Registry: Basis and methodology of a pan-European prospective ischemic stroke revascularization treatment registry

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-042211
Article Type:	Cohort profile
Date Submitted by the Author:	29-Jun-2020
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Keywords:	Stroke < NEUROLOGY, Stroke medicine < INTERNAL MEDICINE, Neurology < INTERNAL MEDICINE

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5 **(EVA-TRISP) Registry: Basis and methodology of a pan-European prospective ischemic**  
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**Running title:** EVA-TRISP Registry Methodology

**Number of words in manuscript body:** 6399

**Number of words in abstract:** 298

**Number of tables:** 2

**Number of figures:** 1 (EVA-TRISP centers)

**Number of references:** 57

**Number of appendices:** 2

**Appendix 1:** EVA-TRISP Investigators (in alphabetical order by country)

**Appendix 2:** EVA-TRISP database items

For peer review only

## ABSTRACT

### Purpose

The Thrombolysis in Ischemic Stroke Patients (TRISP) collaboration was a concerted effort initiated 2010 with the purpose to address relevant research questions about the effectiveness and safety of intravenous thrombolysis (IVT). The collaboration also aims to prospectively collect data on patients undergoing endovascular treatment (EVT) and hence the name of the collaboration change from TRISP to EVA-TRISP. The methodology of the former TRISP registry for patients treated with IVT has already been published. This paper focuses on describing the EVT part of the registry.

### Participants

All centers committed to collecting predefined variables on consecutive patients prospectively. We aim for accuracy and completeness of the data, and adapting local databases to investigate novel research questions.

Herein, we introduce the methodology of a recently constructed academic investigator-initiated open collaboration EVT registry built as an extension of existing IVT registry in patients with acute ischemic stroke (AIS).

### Findings to date

Currently, the EVA-TRISP network includes 20 stroke centers with considerable expertise in EVT and maintenance of high-quality hospital-based registries.

Following several successful randomized controlled trials (RCTs), many important clinical questions remain unanswered in the (EVT) field and some of them will unlikely be investigated in

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3 future RCTs. Prospective registries with high-quality data on EVT-treated patients may help  
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5 answering some of these unanswered issues, especially on safety and efficacy of EVT in specific  
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7 patient subgroups.  
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### 12 **Future plans**

14 This collaborative effort aims at addressing clinically important questions on safety and efficacy  
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16 of EVT in conditions not covered by RCTs. The TRISP registry generated substantial novel data  
17  
18 supporting stroke physicians in their daily decision-making considering IVT candidate patients.  
19  
20 While providing observational data on EVT in daily clinical practice, our future findings may  
21  
22 likewise be hypothesis-generating for future research as well as for quality improvement (on  
23  
24 EVT). The collaboration welcomes participation of further centers fulfilling the commitment and  
25  
26 the outlined requirements.  
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### 33 **Key words**

34  
35 acute ischemic stroke, benchmarking, collaboration, endovascular treatment, large-artery  
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37 occlusion, outcome, quality, recanalization, registry, stroke, thrombectomy, thrombolysis  
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## Strengths and limitations of this study

- The EVA-TRISP collaboration offers a platform to pool individual patient data from prospective registries of patients with ischemic stroke undergoing revascularization therapies.
- The large sample size (currently >13 000 EVT from 20 centres), high completeness of data and standardized data ascertainment are strengths of EVA-TRISP.
- EVA-TRISP will provide data from everyday clinical practice and address clinically important questions about safety and outcomes of patients with ischemic stroke treated with EVT who are neither covered by randomized controlled trials.
- Data is derived from registries that are neither monitored nor randomized. There will be no control group without EVT which disallows the assessment of effectiveness of EVT in study populations.

## INTRODUCTION

Timely recanalization improves outcomes in patients with AIS<sup>1,2</sup>. Safety and efficacy of recanalization strategies, namely IVT and more recently EVT (including mechanical thrombectomy with various techniques and devices in AIS patients with anterior circulation large-artery occlusions), have been well-documented in several randomized controlled trials (RCTs)<sup>3-9</sup>. A meta-analysis of five RCTs revealed an average 2.5-fold reduction in disability through EVT in large-vessel occlusions compared with standard care, including IVT<sup>10</sup>. Early

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3 recanalization is currently the cornerstone of acute stroke treatment with increasing use globally.  
4  
5 This benefit is substantially higher with earlier achievement of recanalization and diminishes  
6  
7 with longer onset-to-treatment intervals<sup>2, 11, 12</sup>. Previous research has explicitly shown that IVT  
8  
9 with alteplase within 4.5 hours of symptom onset improved AIS patient outcomes<sup>13</sup>.  
10  
11 Following the results of these RCTs, EVT is recommended as standard of care in patients with  
12  
13 intracranial large vessel occlusion in several guidelines<sup>14-16</sup>. Consequently, health systems all  
14  
15 over the world adapted themselves to identify and quickly transfer eligible patients to centers  
16  
17 offering EVT. Simultaneously, capacity, logistics, know-how and 24/7 coverage were developed  
18  
19 to cope with the quickly increasing demand for this intervention. Moreover, two recent RCTs  
20  
21 showed benefit with EVT in patients treated up to 16 or 24 hours after stroke onset given that  
22  
23 presence of a considerable amount of salvageable brain tissue had to be demonstrated with  
24  
25 appropriate imaging methods<sup>17, 18</sup>.  
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30  
31 Relevant questions in the daily clinical work of treating stroke patients suffering from large  
32  
33 vessel occlusions remain. First, EVT-RCTs included a highly selective patient population  
34  
35 increasing chances to demonstrate efficacy and to exclude patients who presumably have low  
36  
37 chances for a favorable outcome and patients who have high risk for serious complications.  
38  
39 Secondly, the seven published EVT trials<sup>3, 5-9, 19</sup> analyzed altogether only included 1754  
40  
41 randomized patients (of whom 869 underwent EVT) with the single smallest trial including only  
42  
43 65 patients (of whom 33 underwent EVT)<sup>8</sup>. Usually, after a novel treatment is proved effective, a  
44  
45 new wave of assumptions and extrapolations for treating a broader domain of patients begins. As  
46  
47 all these excluded patient subgroups cannot be studied in future RCTs, in most cases judgments  
48  
49 for treating or not treating with EVT will be based on limited knowledge. Some remaining  
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51 questions will eventually be answered with a long delay, but some will never be answered in  
52  
53 forthcoming RCTs. However, stroke physicians keep facing patients where evidence-based data  
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3 do not explicitly contribute to decision-making for these individuals, in which available  
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5 treatments may very well have a potential benefit as well. Here, prospective high-quality  
6  
7 multicenter registries including large numbers of patients representing many subgroups not  
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9 included or not separately analyzed within RCT settings may offer helpful information for basing  
10  
11 clinical judgments while being aware that the level of certainty will not reach that gained from  
12  
13 RCTs. These registries may also give strong clues on how trial results are implemented to clinical  
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15 practice and how daily practice safety and efficacy levels match with those gained in RCTs.  
16  
17 Further, registry-based data deliver hints in generating new and adequate hypotheses for future  
18  
19 RCTs. Another important aspect is the recently developing new field of clot property-research:  
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21 interested centers can collect detached clots and ship to laboratories where macroscopic and  
22  
23 microscopic properties of the clot coupled with clinical data can be further investigated and may  
24  
25 open new avenues in understanding stroke mechanisms. Lastly, quality is a central indicator in  
26  
27 health care and registry-based data can be utilized in comparisons and for improving individual  
28  
29 center acute stroke care pathways. As a prerequisite, such data have to be based on well-  
30  
31 maintained registries containing a large number of detailed, clearly-defined, and well-  
32  
33 characterized variables. EVA-TRISP registry aims at meeting these prerequisites. Utilizing our  
34  
35 decade-long experience from the multinational TRISP registry<sup>20</sup>, we are now aiming to build a  
36  
37 prospective multinational registry of AIS patients treated with EVT including detailed clinical,  
38  
39 laboratory, and imaging data for future analyses. We are presenting herein the current versions of  
40  
41 the clinical and imaging database items of the EVA-TRISP registry. Additionally, we will discuss  
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43 a selection of specific related topics.  
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## 56 **COHORT DESCRIPTION**

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5 The Thrombolysis in Ischemic Stroke Patients (TRISP) collaboration was a concerted effort  
6 initiated 2010 by 11 European stroke centers with the purpose to address clinically relevant  
7 research questions about the effectiveness and safety of IVT, and currently 20 stroke centers from  
8 nine different countries participate in the collaboration (see Figure 1 and Appendix 1 for a list of  
9 member sites and investigators). As the collaboration also aims to prospectively collect granular  
10 and high-quality data on all consecutive stroke patients undergoing EVT, the name changes from  
11 TRISP to EVA-TRISP.  
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21 EVA-TRISP (former TRISP) operates as an independent, non-profit, investigator-driven open  
22 platform that focuses on generating high quality data for clinical research purposes. The EVA-  
23 TRISP research initiatives are characterized by informal, project-driven and relaxed work  
24 processes based on a high level of mutual trust and understanding between participating  
25 collaborators, and no formal scientific leadership committees have so far been implemented or  
26 deemed necessary. Internal communication principally takes place via e-mail and  
27 teleconferences. The EVA-TRISP collaboration also hosts an annual face-to-face meeting during  
28 the European Stroke Organisation (ESO) conference, and this forum is utilized for overall  
29 strategic planning and major decisions. Brief meeting minutes from the teleconferences and the  
30 annual face-to-face meeting are disseminated to all participating centers. The collaboration  
31 welcomes new collaborators and project proposals from all stroke centers that fulfill the  
32 requirements as stated below. The collaboration particularly aims at supporting young  
33 researchers. Thus, with the exception of the very first paper<sup>21</sup>, first authors of the publications  
34 generated by the TRISP invariably have been young stroke physicians or PhD-students. The  
35 methodology of the TRISP registry has previously been published<sup>20</sup>, and currently, data on more  
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3 than 18,000 IVT-treated patients are available in the registry. This paper focuses on describing  
4  
5 the EVT part of the registry.  
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7  
8 The EVA-TRISP registry aims to prospectively collect granular and high-quality data on all  
9  
10 consecutive AIS patients undergoing both IVT and/or EVT. The overall purpose is to provide a  
11  
12 means to address clinically important research questions on the safety and effectiveness of IVT  
13  
14 and/or EVT in AIS patients that are typically not covered by RCTs or single center research  
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16 initiatives. Furthermore, the EVA-TRISP aims at providing a large data source for various stroke  
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18 care quality improvement initiatives. All EVA-TRISP centers have a proven track-record for  
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20 delivering high-quality and high-volume stroke patient care. Every EVA-TRISP center offers  
21  
22 stroke management that fulfill the criteria of Stroke Centers or Stroke Units as proposed by the  
23  
24 ESO<sup>22</sup>. The simple idea of the EVT part of the EVA-TRISP registry is that experienced stroke  
25  
26 centers with expertise in both EVT implementation and in the maintenance of hospital-based  
27  
28 EVT databases pool their data together. An advantage of the EVA-TRISP registry is the  
29  
30 availability of substantially more variables than in other large-scale registries. We strive for a  
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32 commitment by the collaborators to provide data of high accuracy and completeness as well as  
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34 towards a willingness among collaborators to swiftly adapt the local databases by adding new  
35  
36 variables of interest. This enables a potential for explorative insights in the putative prognostic  
37  
38 importance of variables with unknown influence on outcome or risk of complications, such as  
39  
40 symptomatic intracranial hemorrhage (sICH). Strengths and limitations of the EVA-TRISP  
41  
42 registry in general and compared to other existing EVT registries are discussed below (please see  
43  
44 Discussion).

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47 The currently participating centers all have agreed to fulfill the prerequisites that are summarized  
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49 in Table 1. Participation in other registries does not preclude participation in the EVA-TRISP  
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51 registry. A standard database template has been developed by an international expert group  
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3 consisting of stroke physicians and scientists in collaboration with all members leading to the  
4 current standard version of the registry (see Appendix 2-Registry data elements) that have been  
5 agreed upon by all EVA-TRISP member sites. This comprehensive dataset includes over 110  
6 items and covers a wide range of data elements, including demographics, pre-stroke health  
7 information, acute phase management, and long-term outcomes including three months and one-  
8 year modified Rankin Scale (mRS) as well as detailed laboratory data and imaging findings. An  
9 add-on imaging repository is currently under preparation and will be implemented within the near  
10 future. Electronic medical records used at all member sites allow for quickly and reliably  
11 collecting additional variables when deemed necessary for new projects.  
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### 26 **Lead of a single project and authorship principles**

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28 The researcher or researchers - usually one or two (rarely three) - who originally presented the  
29 idea and rendered the analysis proposal make(s) the initiation by drafting a standard 1-2 pages  
30 draft stating a clear hypothesis and statistical plan summarizing the project (project proposal).  
31  
32

33 The proposal is circulated to all member centers and discussed for scientific content and  
34 feasibility enriched with input from a large expert community. After that, the enriched plan along  
35 with the list of data items required is recirculated. If a center agrees to participate, the center  
36 contributes data within the in-advance agreed time frame on all consecutive patients with the key  
37 variables of interest. For some projects retrospective collection of data is required. The original  
38 proposal makers are entitled to the first and senior authorships. Co-authorships are distributed  
39 according to contributions. This includes not only mere quantitative means (i.e. number of  
40 patients contributed) but also quality of data (e.g. completeness; considered high across EVA-  
41 TRISP centers), handling and pooling of the multicenter data; maintenance of the pooled data set  
42 (including data cleaning), statistics, contribution to EVA-TRISP in general, and intellectual input  
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3 in details of the design or the analyses of the research project, and lastly intellectual input to the  
4 writing and improving of the manuscript. These criteria are suggestions and the researches taking  
5 the lead in each project take the final responsibility for the fair distribution of authorships.  
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10 Each member site possesses its own data and each member site whose data are utilized, is entitled  
11 to co-authorship(s). Whenever feasible, an abstract approved by all co-authors is submitted to the  
12 forthcoming ESO Conference. All EVA-TRISP member centers and investigators are listed at the  
13 end of the manuscript as a supplement given that the publishing journal's own format allows this  
14 approach.  
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### 23 **Data collection and definitions**

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26 Data on the characteristics of patients treated with EVT are collected prospectively by all  
27 participating centers using standardized definitions and a standardized form. Not all centers have  
28 to provide data on all variables but have given a commitment to add missing variables  
29 retrospectively, if considered relevant to answer a specific research question.  
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35 The dataset includes patient demographics, history, prehospital information, admission data,  
36 details on acute interventions, stroke unit and/or intensive care information, discharge,  
37 rehabilitation, outcome data (three months and one-year outcomes measured by mRS), as well as  
38 detailed laboratory test results, vital signs, and imaging findings (see Appendix 2). Risk factors  
39 and stroke etiology will be determined according to standard approaches across centers<sup>20</sup>.  
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47 Moreover, neuroimaging findings before and after treatment are systematically ascertained and  
48 comprise imaging modality (computed tomography versus magnetic resonance imaging) as well  
49 as specific imaging findings such as hyperdense artery sign, presence and extent of early  
50 ischemic signs, site of vessel occlusion, collateral status, presence of tandem occlusion of  
51 ipsilateral carotid artery, recanalization status immediately after EVT and on follow-up imaging  
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3 (quantified according modified treatment in cerebral ischemia (mTICI) score)<sup>23</sup>, white matter  
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5 disease severity, presence and burden of cerebral microbleeds.  
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8 All patients are monitored for occurrence of hemorrhagic transformation. Follow-up imaging  
9  
10 usually take place close to 24 hours after treatment or earlier in case of clinical worsening. Some  
11  
12 centers perform follow-up imaging only in case of clinical worsening. The definition of  
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14 symptomatic intracerebral hemorrhage (sICH) is in accordance with the definition used in the  
15  
16 European Cooperative Acute Stroke Study II (“an intracranial hemorrhage was defined as  
17  
18 symptomatic if the patient had clinical deterioration causing an increase in the National Institute  
19  
20 of Health Stroke Scale (NIHSS) score of more than or equal to four points and if the hemorrhage  
21  
22 was likely to be the cause of the clinical deterioration”)<sup>24</sup>. The majority of centers additionally  
23  
24 evaluate type of hemorrhagic transformation (hemorrhagic infarction, parenchymal hemorrhage),  
25  
26 indicate whether the bleeding occurred remotely from the infarcted area, and document sICH  
27  
28 according to definitions used in the National Institute of Neurological Disorders and Stroke Trial  
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30 I-II, SITS-MOST and ECASS III definitions<sup>25, 26, 27</sup>. Functional outcomes at three months and  
31  
32 one-year are assessed using the mRS. The mRS is obtained by telephone calls, postal/electronic  
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34 questionnaire, or outpatient visits. If patients cannot be interviewed, close relatives, nurses or  
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36 family doctors are asked for disability status.  
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42 We are currently exploring technical, legal, and ethical as well as financial backgrounds for  
43  
44 establishing an electronic registry to one of the member centers that would allow direct data  
45  
46 insertion from each center and holding the registry compactly in one single file. Otherwise, each  
47  
48 center will maintain own registry within their own electronic system and data will be transferred  
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50 always without personal identifiers for each single analysis looking at one single aspect and  
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52 leading to one mutual international publication. Establishing and maintaining such a large  
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3 database with complete compliance to rules and safety measures is a costly procedure and  
4  
5 requires long-term funding. This option is now under exploration.  
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8 Future plans in the registry include the addition of a neuroradiology imaging bank that will  
9  
10 enable detailed image analysis of patients treated with IVT and/or EVT. The imaging bank will  
11  
12 provide “real-world” diagnostic neuroradiology and, used in combination with detailed clinical  
13  
14 information from the EVA-TRISP registry, analysis of this imaging data will help to (i) create  
15  
16 standardized imaging protocols in acute stroke (i.e. defining optimal threshold for perfusion  
17  
18 parameters), (ii) identify new (i.e. a collateral score for the posterior circulation) and validate  
19  
20 published (i.e. different collateral scores for the anterior circulation) imaging outcome predictors  
21  
22 and imaging-based selection tools for reperfusion therapies, (iii) assess the generalizability of  
23  
24 RCT results to subgroups of patients who would have been excluded based on imaging criteria  
25  
26 (i.e. baseline Alberta Stroke Program Early CT score [ASPECTS] under five, extracranial vessel  
27  
28 pathologies), (iv) improve automated analyzing techniques (i.e. machine and deep learning  
29  
30 algorithms), (v) enhance the accuracy of outcome prediction of different clinical and imaging  
31  
32 parameters by implementing new imaging outcomes (f.i. infarct volume, recanalization status).  
33  
34 Neuroimages from TRISP/EVA-TRISP patients since 2015 will be pooled centrally. All imaging  
35  
36 modalities (non-contrast CT, CT-angiography, CT-perfusion, MRI, MRA, MR-perfusion, and  
37  
38 digital subtraction angiography) at baseline and follow-up (up to three months after stroke onset)  
39  
40 will be eligible for analysis. Image analyses will be performed blinded to clinical information and  
41  
42 treatment decisions, and undergo a central systematic re-evaluation using a specified case report  
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44 form including all predefined imaging variables.  
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51 Stroke-specific image analyzing software (i.e. OSIRIX medical imaging viewer, Quantomo for  
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53 semi-automated volumetric analysis, and Rapid Processing of Perfusion and Diffusion [RAPID]  
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3 for perfusion analysis) could be utilized. A detailed case report form for image analysis will be  
4  
5 designed in review with all collaborators.  
6

7  
8 Lastly, EVA-TRISP investigators prepared a detailed standard operating procedure (SOP) to  
9  
10 ascertain that all members collecting data are well-aware of standard interpretations and follow  
11  
12 identical steps to avoid unnecessary heterogeneities or individual-borne differences. The numbers  
13  
14 of recruited patients in each participating center during the study period until the end of year  
15  
16 2019 are reported in Table 2 along with the population each center is covering for EVT.  
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### 21 **Data ownership, access, use, and publications**

22  
23 Each center is self-financing in data collection and is indisputable owner of own data. If and  
24  
25 when a mutual single databank is constructed, each individual researcher with necessary formal  
26  
27 training and permissions will be able to insert data directly to the central database on the internet  
28  
29 and access to own center's data without limitations. Individual scientists working on a properly  
30  
31 agreed single project and doing data analyses will be granted proper access to all data. In case  
32  
33 that an individual center refrains from participating to a particular analysis, their data will not be  
34  
35 included in that analysis. Any publication that is produced from the registry data will include  
36  
37 authors from each contributing center in accordance to number of patients delivered as well as  
38  
39 active involvement in analyses and writing work. Number of authors and their placement in the  
40  
41 author list may vary regarding the amount of contributions. This will be handled openly and in a  
42  
43 delicate way aiming at mutual consent.  
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### 51 **Data elements and completeness:**

52  
53 A detailed database is aimed to allow investigating various current and future topics. Data  
54  
55 elements are listed in detail in Appendix 2. Over time, new data elements may become necessary  
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3 for new individual projects. Should this occur, investigators will quickly supplement the missing  
4  
5 variables. Patient age, sex, admission NIHSS score, recanalization status before and after  
6  
7 thrombectomy, and three months outcome measured by mRS are obligatory data items and must  
8  
9 be present for all patients (otherwise a patient is not eligible to be included to the registry). In  
10  
11 general, missing data for any variable or patient must not exceed 10%.  
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### 16 17 **Data sources**

18  
19 All paper-based or electronic patient files including laboratory values and imaging data will be  
20  
21 utilized. When feasible, missing data will be completed by reconstructing e.g. NIHSS scores. In  
22  
23 most cases, the local investigators form the local stroke team will be actively seeing the patients  
24  
25 already at the emergency room and at their stroke units and can therefore guarantee completeness  
26  
27 of data in most cases by collecting missing items directly from the patients and their relatives.  
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### 33 **Target population**

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35 All AIS patients designated for EVT and in whom interventionalists gained arterial access are  
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37 within the target population. Therefore, this registry also may include patients with misdiagnosis,  
38  
39 already recanalized leading to premature interruption of the procedure, unsuccessful attempts to  
40  
41 recanalize, and other unforeseeable conditions. Inclusion of patients is not limited to certain EVT  
42  
43 techniques. The registry will include also patients who receive intra-arterial thrombolysis even  
44  
45 without mechanical thrombectomy.  
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### 51 **Registry size and duration**

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53 The registry will include all EVT patients from all member sites. We anticipate that the absolute  
54  
55 numbers and proportions of EVT-treated AIS patients will be increasing over time and annual  
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3 inserts will exceed thousands shortly. The registry size is not limited. One anticipated strength of  
4 this registry is the high patient number together with detailed information on each patient  
5  
6 allowing looking at many issues that are not feasible to investigate within RCTs or even merged  
7  
8 data from all RCTs because of the fact that they included fairly small patient numbers. The use of  
9  
10 the registry will be launched after 5000 patients' data have been inserted and adequately quality-  
11  
12 checked. Similarly, this registry will be utilized as long as EVT is a viable option in stroke  
13  
14 treatment. The unlimited time span requires careful evaluation by ethics committees. If the  
15  
16 consortium decides to end the registry, each center's data will be adequately returned to owners  
17  
18 and the registry data will be deleted achieving absolutely non-retrievable condition according to  
19  
20 technical standard operating procedures (SOPs) of the registry-holding center. Thereafter, each  
21  
22 individual center will be free to decide how to proceed with their own datasets. Similarly, if a  
23  
24 center decides to resign from the registry, their data will be adequately returned and will be  
25  
26 deleted from the main database file after confirmation that the data are safely received by the  
27  
28 local principal investigator. While all patient-related data including clinical, laboratory, and  
29  
30 imaging data are completely anonymized, each center will keep a key file within their local  
31  
32 electronic hospital system with patient identifiers matching to the patient code on the registry  
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34 (e.g. if necessary to go back to patient files). This approach is compliant with current principles  
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36 and is the SOP worldwide.  
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### 47 **Quality control**

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49 Quality control is another crucial step in multicenter large-sized registries since missing data are  
50  
51 a frequent problem impairing the reliability and generalizability of registry-borne data. The EVA-  
52  
53 TRISP registry is different in this sense because data are not yet directly collected to a central  
54  
55 registry, but each center collects own data to their own institutional registry according to a  
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3 standard harmonized database item list and SOP. Later, the data are merged to a single file for  
4  
5 maintenance and analyses. Therefore, missing data are expected to be close to nil. All centers will  
6  
7 be including all consecutive patients attempted with an EVT and doing frequent checks not to  
8  
9 leave any patient out of the registry. Our registry data will likely include all EVTs performed  
10  
11 within a region and population practically equaling to a population-based study, although being  
12  
13 hospital-based, because EVT is available only at stroke centers serving a predefined region and  
14  
15 the inhabitant population in most cases. Most of the required data come from routine procedures  
16  
17 which are standardly collected and recorded in stroke patient care pathways as part of the clinical  
18  
19 routine and therefore almost always retrievable. The whole database will be checked for missing  
20  
21 data as well as illogical entries. It is also feasible to set range limits to database cells to avoid or  
22  
23 reject illogical entries (i.e. range and consistency checks; e.g. NIHSS score cannot be minus or  
24  
25 over 42 points and can only be full points and not decimals; patient age at stroke onset can be  
26  
27 only in digits, and is expected to be from 16 and very rarely over 100). There are other  
28  
29 procedures regarding quality check, for example comparing retrospectively and prospectively  
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31 entered data as well as comparing centers. These approaches will be run at certain milestone  
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33 points.  
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### 42 **Ethics, informed consent, and privacy**

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44 Each center has received necessary official approval from their respective local authorities and/or  
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46 ethical committees according to their national and local rules. These permits include transfer of  
47  
48 data between EVA-TRISP centers. Necessity of individual informed consent is dependent on  
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50 national rules and will be collected if necessary. Data are shared with respect to the EU law  
51  
52 2016/679 about General Data Protection Regulation (GDPR). In the long run, a permanent  
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3 database residing at a member site is aimed. Establishment and maintenance of the permanent  
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5 database at one center will be initiated only after a separate ethics approval.  
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### 11 **Aims of the EVA-TRISP Registry**

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14 The major aim of EVA-TRISP is to address in AIS patients treated with IVT and/or EVT  
15  
16 clinically important questions about safety and outcomes that are not covered by RCTs. The idea  
17  
18 of EVA-TRISP is that experienced stroke centers with a record and expertise in both (I) usage of  
19  
20 IVT and/or EVT and (II) maintenance of hospital-based stroke databases pool their data. In  
21  
22 addition to the characteristics of the EVA-TRISP centers stated above, an advantage of EVA-  
23  
24 TRISP is the availability of more additional variables than in other large-scale registries and the  
25  
26 commitment by the collaborators to I) accuracy and completeness of the data and to II) the  
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28 willingness to adapt the local databases and add quickly new variables retro- and prospectively.  
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### 38 **DISCUSSION**

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41 Endovascular treatment, now fulfilling criteria for the highest level of evidence, has changed  
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43 acute stroke care substantially. Probably approximately 10% of all ischemic stroke patients are  
44  
45 eligible for EVT, but the percentages may grow as more and more patients are brought to the  
46  
47 attention of emergency systems and the treatment indications will likely expand over time<sup>28</sup>. The  
48  
49 rapid developments in acute stroke care put considerable demands on health care systems and  
50  
51 necessitate quick rearrangements for coupling these needs. The published seven RCTs and  
52  
53 following meta-analyses answered most central questions. Nevertheless, there are numerous  
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3 unanswered questions remaining in terms of EVT in acute ischemic stroke. Some of these  
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5 questions will be solved and satisfied via ongoing and forthcoming RCTs. Yet, many other issues  
6  
7 will never or unlikely be tested in RCTs and yet stroke physicians need firm data on these topics  
8  
9 to base their clinical decisions on. Moreover, there are certain patient groups where RCTs are  
10  
11 ethically difficult to organize; such a group is patients with basilar artery occlusion (BAO).  
12  
13 Although a clearly important clinical condition that, untreated, have poor outcomes, BAO  
14  
15 patients were not included in the large EVT trials. An extrapolation from the anterior circulation  
16  
17 EVT trial results to BAO currently have strong support in clinical practice, and thus EVT are  
18  
19 currently offered to BAO patients despite limited direct evidence of treatment effectiveness. A  
20  
21 small multi-center RCT that included 131 patients– the Chinese BEST trial (Basilar artery  
22  
23 occlusion Endovascular intervention versus Standard medical Treatment)<sup>29</sup>– was prematurely  
24  
25 terminated due to slow recruitment and a high crossover rate that severely hampered the  
26  
27 interpretability of the intent-to-treat analysis. Another RCT with 300 patients included is closed,  
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29 but data has not yet been presented<sup>30</sup>. Still, both the per-protocol and the as-treated analyses  
30  
31 favored EVT compared to best medical treatment. Some small-sized registry data showed high  
32  
33 recanalization rates and similar hemorrhagic complication rates as in anterior circulation patients  
34  
35 treated with EVT, but more often futile recanalization. Large-scale registry studies may further  
36  
37 improve our knowledge in this patient group and may help identifying those who will likely  
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39 benefit or not benefit from EVT in a real-life setting<sup>6, 31-33</sup>. In the absence of RCT-based data,  
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41 comprehensive observational data may be useful for individual treatment decisions in clinical  
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43 practice and in evaluating processes of stroke triage and care for IVT or EVT. As a prerequisite,  
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45 such data have to be based on well-maintained registries containing large numbers of detailed,  
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47 clearly-defined, and well-characterized variables. EVA-TRISP registry meets these prerequisites.  
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3 Ideally, the results from such observational studies are verified or falsified by RCTs. However,  
4 with few exceptions (e.g. age limit) this is unlikely to happen. Thus, registry-based data will  
5 reflect the highest level of evidence in several aspects, available currently and in the foreseeable  
6 future.  
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12 Further, we need to continuously follow-up whether the safety and benefit aspects of EVT shown  
13 in RCTs could be correctly translated to routine clinical practice. Indeed, the safety and benefit  
14 may be better, similar, or even worse in daily practice. Registry data can easily be compared to  
15 RCT data especially when basic settings are similar. Additionally, it becomes more and more  
16 feasible to compare centers, patient subgroups and devices. Benchmarking, previously performed  
17 by site visits, is a popular approach for understanding differences and making improvements, can  
18 now be done easily using electronic data<sup>34</sup>.  
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28 Systematically ascertained, comprehensive and high-quality observational data are useful to both  
29 (I) challenge or (II) confirm the clinical usefulness of commonly used but often arbitrary  
30 eligibility criteria. An early example has been the challenge of the usefulness of the upper age  
31 limit of 80 years for IVT based on comprehensive, observational studies. Eventually, the third  
32 International Stroke Trial (IST-3) proved that indeed patients aged 80 years and older benefit  
33 from IVT, too<sup>35</sup>.  
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42 Utilizing the TRISP registry, we examined previously safety of IVT in a number of patient  
43 subgroups where RCT-based data did not exist. Previous publications of TRISP registry (I)  
44 provided insight into safety and efficacy of IVT in subgroups of patients who were excluded in  
45 RCTs (e.g. patients dependent on the help of others prior to stroke), underrepresented or not  
46 specifically addressed (e.g. dissection as cause, impaired renal function, low platelet count, body-  
47 mass-index, prior use of statins, serotonin uptake inhibitors, prior use of novel oral  
48 anticoagulants, patients with seizure at onset)<sup>21, 36-45</sup>, (II) were helpful to evaluate processes of  
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3 acute stroke care such as the meaning of the “off-hour-thrombolysis”, IVT during “working  
4 hours”, or the variable “time” in clinical practice<sup>46-48</sup>, and (III) served to derive, validate, and  
5 compare risk scores for sICH or functional three months outcome<sup>49-51</sup>. These registry-based novel  
6 data contributed to the numbers of patients treated safely and successfully with IVT globally.  
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8 Disease- or intervention-based patient registries with consecutive patients recruited in a  
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10 population- or hospital-based approach are useful in many ways: they help describing the natural  
11 history, determine clinical effectiveness and cost-effectiveness of health care products or  
12 services, measure or monitor safety and harm, measure quality of care, improve quality of care,  
13 and help with benchmarking purposes such as how clinical practices vary, what the best  
14 predictors of treatment practices are, and comparing different practices providing a basis for  
15 further improvements. In such settings, stakeholders are several: the primary stakeholder with the  
16 EVA-TRISP registry is the academic consortium establishing and running the registry. Potential  
17 stakeholders with such a large-scale registry may include public health and regulatory authorities,  
18 product manufacturers, health care service providers, payer and commissioning authorities,  
19 patients and their advocacy groups, treating physician groups, academic institutions, and  
20 professional societies. The EVA-TRISP registry aims at including all patients who underwent  
21 EVT as a treatment for AIS, including patients with misdiagnosis, unsuccessful attempts (EVT is  
22 defined as a puncture to the artery with the aim of recanalization), or other unforeseeable  
23 scenarios. In most countries, registry-based studies are approved by ethics committees with  
24 waving informed consent from individual patients as demanding informed consent would leave  
25 most severe patients out of the registry and cause a severe bias on representability of any finding.  
26  
27 Imaging has become more and more critical in stroke field. In addition to stroke diagnostics and  
28 excluding competing etiologies (e.g. stroke mimics), there are a number of imaging findings  
29 related to increased risk following acute treatments (e.g. leukoaraiosis<sup>52</sup> and microbleeds), or  
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3 findings guiding treatment choices (e.g. major artery occlusion reachable with a catheter), as well  
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5 as findings helpful in prognostics such as ASPECTS<sup>53</sup> or SEDAN<sup>49</sup> scores. Acute stroke patients  
6  
7 are increasingly imaged with a package of standard CT, CT angiography and CT perfusion or in a  
8  
9 similar fashion with an MRI-based package. These imaging modalities are then analyzed quickly  
10  
11 for determining diagnosis, prognosis, and treatment approach. Functional imaging modalities are  
12  
13 increasingly taken into account for patient selection to IVT and EVT instead of strictly deciding  
14  
15 according to time. The former TRISP registry included few items on imaging studies. Imaging  
16  
17 requirements were according to routine thrombolysis: only a non-contrast CT imaging prior to  
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19 thrombolysis was mandatory. Imaging was not in the main focus as image-analysis is usually  
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21 labor-intensive and not always available. Technological improvements may substitute some of the  
22  
23 expert workforce in image analysis already today and in near future. However, with the  
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25 developments in imaging technologies and increased requirements in patient care, now, most  
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27 patients are imaged with CT angiography and CT-perfusion in addition to basic non-contrast CT  
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29 imaging. Less frequently, patients are imaged with a similar versatile package of various MRI  
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31 sequences. Developments in the imaging technology and logistics, decrease in radiation dose  
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33 used with CT imaging, as well as automatic image-analysis software development contributed to  
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35 the progress. Installing imaging scanners into or adjacent to emergency departments or taking  
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37 acute stroke suspect patient directly to the imaging facility by-passing emergency room have also  
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39 improved availability of more detailed imaging. Patient selection for the best individual treatment  
40  
41 is becoming increasingly dependent on neuroimaging with the goal of providing rapid patient-  
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43 specific metrics such as tissue viability, vessel patency status, thrombus characteristics and  
44  
45 cerebral perfusion etc. Imaging findings have also been used for patient selection in some highly  
46  
47 successful IVT and EVT RCTs<sup>4, 5, 54-56</sup>. Detailed imaging information is even more crucial when  
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49 EVT is considered. Therefore, establishing an imaging repository parallel with the EVA-TRISP  
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3 registry received a widespread support from members. To date, the choice of imaging modalities,  
4 parameters and thresholds varies widely across medical centers. No standardized imaging  
5 protocols currently exist, other than joint statements from professional societies<sup>57</sup>. A large,  
6 multicenter neuroimaging registry with state-of-the-art re-evaluation of images combined with  
7 detailed clinical data of IVT/EVT-treated stroke patients would be helpful for validating between  
8 modalities, defining thresholds, enhancing automated assessments and creating standards in  
9 neuroimaging for acute ischemic stroke. For the imaging part of the database we will collect  
10 baseline, interventional and follow-up images (up to three months after stroke onset) from all  
11 stroke patients included in TRISP since 2012. All images will be centrally analyzed using a  
12 predefined, standardized form.  
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### 28 **Strengths and limitations of the EVA-TRISP registry**

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30 Strengths of EVA-TRISP registry include (I) the high completeness level of data with few  
31 missing data, (II) large sample sizes which reduce the risk of bias and allows adjustments for  
32 confounders, (III) the systematic and standardized data ascertainment which increases the  
33 homogeneity of the study population, (IV) the intrinsic motivation of the study personnel, leads  
34 to a high rate of completeness of ascertained data sets, contributing to a high-quality registry, and  
35 (V) the dynamic nature of the EVA-TRISP database due to the commitment of the centers to  
36 adapt the local database and add variables retro- and prospectively. In addition, (VI) a large  
37 number of variables is gathered including those with unknown prognostic importance. This  
38 allows addressing novel yet unidentified research questions. Moreover, (VII) pooling of  
39 individual patient data increases generalizability compared to single center studies, and (VIII) the  
40 fact, that variables and outcomes have been collected irrespective of the present research  
41 question, reduces the risk of a bias. (IX) As most EVA-TRISP centers are regional reference  
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3 centers for acute patient care, particularly for EVT, the EVA-TRISP registry will resemble a  
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5 population-based registry. Limitations are inherent to the design of EVA-TRISP: (I) Data is  
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7 derived from registries that are neither monitored nor randomized. Usually, there will be no  
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9 control group without EVT which disallows the assessment of effectiveness of EVT in study  
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11 populations. (II) As true for all observational studies, analyses based on registers have a higher  
12  
13 risk of bias than RCTs. Thus, we urge to a cautious interpretation of findings and observations.  
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15 (III) All EVA-TRISP centers are experienced in stroke treatment. This expertise implies – as a  
16  
17 downside – a limited generalizability of findings to all stroke providers with less expertise and  
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19 less advanced setting. (IV) The majority of our included patients are Caucasians and from high-  
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21 income countries. Thus, we cannot compare ethnical differences, nor can compare health systems  
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23 with various funding levels. (V) Currently, there is no ‘core lab’ to validate hemorrhagic  
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25 complications and three-month mRS ratings. As valid for other major registries like SITS and  
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27 GWTG, local interpretation of outcome data may differ between sites. Since EVA-TRISP centers  
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29 are mostly high-volume centers with long-standing experience in maintaining IVT databases, this  
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31 bias is likely to be smaller than in most of the other registries.  
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## 42 **SUMMARY**

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47 The EVA-TRISP collaboration is an open platform dedicated to conduct joint research projects in  
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49 AIS patients treated with IVT and/or EVT. EVA-TRISP aims to increase knowledge on safety  
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51 and efficacy of IVT and EVT, study outcomes after IVT and EVT, to evaluate processes of acute  
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53 stroke care as well as document and improve acute stroke care quality. Our previous  
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55 achievements prove that this collaboration has the potential to provide versatile observational  
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3 information on treatment of AIS patients faced during daily clinical practice. Prospective and  
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5 standardized documentation of individual patient data according to consensus definitions is a  
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7 major requirement to maintain the quality of the EVA-TRISP registry. Publishing this  
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9 methodology paper improves the transparency of the registry and collected data. EVA-TRISP  
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11 welcomes participation and project proposals of further centers fulfilling the requirements stated  
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13 above.  
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### 16 17 18 19 **Consent for publication**

20  
21 Not applicable.  
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### 24 25 26 **Availability of data and materials**

27  
28 Not applicable.  
29  
30

### 31 32 33 **Competing interests**

34  
35 The authors declare that they have no competing interests.  
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### 40 41 42 **Patient and public involvement**

43 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of  
44  
45 our research.  
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47

### 48 49 **Funding**

50  
51 None.  
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### 55 56 **Authors' contributions**



1  
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3 Study concept and design: All authors. Data collection: All authors. Manuscript drafting: AN,  
4 SC, HG, SMZ, HE, CK, CHN, PJN, KJ, STE, DS, TT. Study supervision: TT, DS, STE, KJ, PJN,  
5 CHN. Statistical analysis and interpretation: do not apply. Review of the manuscript for  
6 intellectual contribution: All authors. All authors agreed on submitting this last version of the  
7 manuscript to the journal.  
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### 17 **Acknowledgments**

18 We thank Ms. Anu Eräkanto and Ms. Judith Klecki for technical support.  
19  
20  
21  
22  
23

### 24 **Disclosures**

25  
26 TT: Academic grants from the European Union, National Stroke Research Institute of Australia,  
27 Sahlgrenska University Hospital, Sigrid Juselius Foundation, University of Gothenburg, and  
28 Wennerström Foundation. Study contracts with Bayer, Boehringer Ingelheim, Bristol Myers  
29 Squibb, and Portola Pharm. Personal fees from Bayer, Boehringer Ingelheim, Bristol Myers  
30 Squibb, Lumosa Pharmaceuticals, and Portola Pharmaceuticals. TT received speaker's fees from  
31 the University of Donau, Krems, Austria. He holds patents on a treatment aiming to avoid post-  
32 thrombolytic brain edema and intracerebral hemorrhage in stroke (method to prevent brain edema  
33 and reperfusion injury; method to prevent post-thrombolytic hemorrhage formation).  
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44 STE has received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim and  
45 Daiichi-Sankyo. He has served on scientific advisory boards for Bayer, Boehringer Ingelheim,  
46 BMS/Pfizer, and MindMaze and on the editorial board of Stroke. His institutions have received  
47 an educational grant from Pfizer, compensation from Stago for educational efforts and research  
48 support from Daiichi-Sankyo, the Science Funds [Wissenschaftsfonds] of the University Hospital  
49  
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3 Basel, the University Basel, the “Freiwillige Akademische Gesellschaft Basel”, the Swiss Heart  
4  
5 Foundation, and the Swiss National Science Foundation.

6  
7 PL has received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim, and  
8  
9 has served on scientific advisory boards for Bayer, Boehringer Ingelheim, Pfizer/BMS, Amgen,  
10  
11 and Medtronic. His institutions have received research support from Bayer, and Sanofi, the  
12  
13 Science Funds [Wissenschaftsfonds] of the University Hospital Basel, the Swiss Heart  
14  
15 Foundation, and the Swiss National Science Foundation, and the University Hospital Basel  
16  
17 foundation “propatient”.

18  
19 CHN has received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim,  
20  
21 Pfizer Pharma, Bristol-Myers Squibb, Gore and Ass. and Sanofi. His institutions have received  
22  
23 research support or grants from the German Federal Ministry of Research and Education (BMBF)  
24  
25 namely the “Center for Stroke Research Berlin, CSB”, the “Deutsches Zentrum für Herz-  
26  
27 Kreislauf Forschung (DZHK)”, “Deutsches Zentrum für neurodegenerative Erkrankungen  
28  
29 (DZNE)”.

30  
31 SW has received speaker honoraria from Amgen, travel honoraria from Bayer and a research  
32  
33 grant from Boehringer Ingelheim and academic grants from the Swiss National Science  
34  
35 Foundation, the UZH (Clinical Research Priority Program Stroke), the Swiss Heart foundation  
36  
37 and the Olga Mayenfisch foundation.

38  
39 AZ has received speaker fees and consulting fees from Boehringer-Ingelheim, Medtronic,  
40  
41 Cerenovus and advisory board from Daiichi Sankyo and Boehringer-Ingelheim and Stryker.

42  
43 MB is on the editorial board for Springer as Co-editor of "Clinical Neuroradiology". He serves  
44  
45 on advisory boards for Boehringer, Vascular Dynamics and BBraun. He received speaker  
46  
47 honoraria from Guerbet, Bayer, Novartis, Codman, Roche, Teva, Grifols and Merck. He  
48  
49  
50  
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1  
2  
3 received research support from Novartis, Guerbet, Siemens, Hopp foundation, the European  
4 Union, and from Deutsche Forschungs Gesellschaft.”

5  
6  
7 MM is consultant for Acandis, Cerenovus, Medtronic, MicroVention, Route92, Stryker. He  
8 received research support from Balt, MicroVention, Siemens, Stryker.

9  
10  
11 PR is on scientific advisory boards for Bayer and Boehringer-Ingelheim not in relation to the  
12 submitted manuscript. He received funding for travel or speaker honoraria from SITS, and lecture  
13 fees and travel compensation from Boehringer Ingelheim, Bayer, BMS, Pfizer. He is on the  
14 editorial board of the journal *Stroke* as Associate editor (since 2010), of the journal  
15 *Gefäßchirurgie* (editor since 2014), and of the *ESO-Journal* (Editor since 2015). The University  
16 of Heidelberg received research support from Boehringer Ingelheim for the ECASS 4 study, and  
17 funding from the German research foundation for the SPACE-2 study.  
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3 **Table 1. Universal standards and requirements for the databases and centers contributing**  
4 **to EVA-TRISP registry\*.**  
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- 6  
7 - Prospective registry of consecutive patients with systematic check-up of missing cases.  
8 - Comprehensive collection of baseline characteristics according to consensus definitions stated  
9 in this and the previous methodology papers.  
10 - Prospective assessment of hemorrhagic complications (symptomatic intracerebral hemorrhage  
11 according to ECASS II criteria) and functional outcome at 3 and 12 months (according to the  
12 modified Rankin Scale; either telephone interview, postal questionnaire, or follow-up visit).  
13 - Approval of institutional review board to maintain the respective EVT database and to obtain 3-  
14 and 12-month follow-up data.  
15 - EVA-TRISP centers are comprehensive stroke centers with high-volume EVT applications -  
16 typically university hospitals or closely affiliated to university hospitals.  
17 - Treatment of acute ischemic stroke patients with EVT according to guidelines valid at the  
18 relevant time or documentation of deviation therefrom.  
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21 \* EVA-TRISP welcomes participation and project proposals of further centers fulfilling the  
22 commitment and the outlined requirements.  
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**Table 2. EVA-TRISP centers, time period, number of endovascular treatments done, and population-base for EVT (in alphabetical order).**

City	No of stroke EVT (Jan 2015 to Dec 2019)
Amsterdam	864
Basel	413
Belgrade	136 <sup>1</sup>
Berlin	480 <sup>2</sup>
Bern	1422
Bremen	Estimation: 200/year
Brescia	412
Bologna	395
Goettingen	396
Gothenburg	1097
Heidelberg	1500
Helsinki	796 <sup>2</sup>
Jerusalem	249
Larissa	-
Lausanne	732
Lille	1806
Modena	489
Munich	600
St. Gallen	490
Zurich	Estimation: 500

<sup>1</sup>Jan 2018-Dec 2019

<sup>2</sup>Nov 2015-Dec 2019

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**Figure 1.** EVA-TRISP centers.

For peer review only

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**D50;70@(:)C\*** Sami Curtze, Kimmo Lappalainen, Nicolas Martinez-Majander, Jukka Putaala, Gerli Sibolt, Daniel Strbian, Silja Rätty, Turgut Tatlisumak, Marjaana Tiainen (Helsinki University Hospital)

**D970?2(:)C\*** Nicolas Bricout, Marie Bodenant, Regis Bordet, Charlotte Cordonnier, Nelly Dequatre, Hilde Hénon, Didier Leys, Anne-Marie Mendyk (University Lille North de France)

**E29F70A(:)GC\*** Andreas Kastrup, Panagiotis Papanagiotou (University Hospitals Bremen-Mitte and Bremen-Ost); Tim-Bastian Braemswig, Hebung Erdur, Christian H Nolte, Regina von Rennenberg, Jan F Scheitz, Georg Bohner (Charité-Universitätsmedizin, Berlin); Alex Brehm, Jan Liman, Marios Psychogios (University Medical Center Goettingen); Martin Bendszus, Christian Hametner, Markus Möhlenbruch, Peter A Ringleb (University Hospital Heidelberg); Katharina Feil, Lars Kellert, Clemens Küpper (University Hospital Munich LMU)

**E92??2(:)C\*** George Ntaios, Dimitrios Sigris, Ioannis Ioannidis George Karagiorgas, Eftychia Kapsalaki, Marianna Vlychou (University of Thessaly)

**&3972(:)C\*** Jose Cohen, John Gomori, Ronen R Leker (Hadassah-Hebrew University Medical Center, Jerusalem)

**&47;A(:)HC\*** Mauro Magoni, Alessandro Pezzini (University Hospital Brescia); Guido Bigliardi, Luca Verganti, Stefano Vallone, Stefania Maffei (University Hospital Modena), Andrea Zini,

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3 Luigi Simonetti, Mauro Gentile, Luigi Cirillo, Ludovica Migliaccio (IRCCS Istituto di Scienze  
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5 Neurologiche di Bologna)

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10 - =2(\$ 24=29;70@3(:)C\* M Irem Baharoglu, Sophie van den Berg, Paul J Nederkoorn, Yvo B Roos,  
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12 Fianne HM Spaander, Sanne M Zinkstok, Thomas P Zonneveld, Charles Majoie (Academic  
13  
14 Medical Center Amsterdam)

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19 /29>57(:)C\* Mirjana Arsenijevic, Ivana Berisavac, Marko Ercegovac, Dejana R Jovanovic, Visnja  
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21 Padjen, Predrag Stanarcevic, Maja Stefanovic Budimkic, Tamara Svabic Medjedovic, Ivan  
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23 Vukasinovic, Vladimir Cvetic (Clinical Centre of Serbia, Belgrade)

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28 /I2@20(:)C\* Margareta Abrahamson, Arne Allard, Monica Argus, Anke Brederleu, Erik Ceder,  
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30 Maria Davidson, Niclas Dehlfors, Dennis Dunker, Torsteinn Gunnarsson, Lukas Holmegaard,  
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32 Mikael Jerndal, Susanna Johansson, Katarina Jood, Camilla Karlsson, Jan-Erik Karlsson, Birgitta  
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34 Leiram, Miroslav Malac, Inger Nilsson, Annika Nordanstig, Petra Redfors, Alexandros Rentzos,  
35  
36 Turgut Tatlisumak (Sahlgrenska University Hospital, Gothenburg)

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42 /I54J29;70@(:)C\* Leo H Bonati, Stefan T Engelter, Joachim Fladt, Henrik Gensicke, Philippe A  
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44 Lyrer, Gian Marco De Marchis, Nils Peters, Alexandros Polymeris, Sebastian Thilemann,  
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46 Christopher Traenka (University Hospital Basel); Marcel Arnold, Urs Fischer, Jan Gralla, Mirjam  
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48 R Heldner, Hakan Sarikaya, David J Seiffge, Roland Wiest (University Hospital Bern); Olivier  
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50 Bill, Ashraf Eskandari, Patrik Michel, Gaia Sirimarco (Hospitalier Universitaire Vaudois,  
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52 Lausanne); Georg Kägi, Johannes Weber (Kantonsspital St. Gallen); Zsolt Kulcsar, Andreas R  
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54 Luft, Susanne Wegener (University Hospital Zurich)

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The exact list of available variables may slightly differ between centers according to the judgment of local ethics committees.

Patient history

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0<, . >41; +4, 1\$3, \*\*4>=#P\$
  - ! 1+#(4, (\$<4(<F=; +4, 1\$! %' ERD%\$, 1\$>; \*#-41#\$4. ; "#\$U)TUS
  - ' , \*+#(4, (\$<4(<F=; +4, 1\$! %' ERD%\$, 1\$>; \*#-41#\$4. ; "#\$U)TUS
  - E; (=A\$\* <@#. 4-<\$<@; 1"#\$\*41\$\*F\*3#<+#2\$; (#; \$5:, <; -\$3; (#1<@A. ; -\$@A3, ; ++#1F; +4, 1B\$, \*\*\$, :\$  
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  - DA3#\$, :\$>; \*#-41#\$; 1"4, "(: 3@A\$51, 1#B\$RD! B\$ ^ /! 9\$
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^ TB\$24+; ; \$ ^ TB\$ ^ HB\$! R! B\$' R! B\$]! B\$C! 9\$
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  - ! 224+4, 1; -\$I #\*\*#-\$, <<=F\*4, 1\$5A719\$\$
  - 0:\$A#\*B\$=, <; +4, 1\$, :\$; 224+4, 1; -\$I #\*\*#-\$, <<=F\*4, 1\$
  - 01\$<; \*#\$, :\$41+(: <(: 14; -\$; ("#\$I #\*\*#-\$, <<=F\*4, 1\$41\$+@#; 1+#(4, (\$<4(<F=; +4, 1'\$<, =; +#(: =\*\$, 1\$  
>; \*#-41#\$; 1"4, "(: 3@A\$4:\$; \*\*#\*\*>; >=#\$5D! 8\$%<, (#\$U)a9\$
  - /#=#1; 1+\$\*+#1, \*4\*\$5\_ZU[ \$8! %RED97, <<=F\*4, 1\$, :\$#&+(: <(: 14; -\$OR! \$, 1\$>; \*#-41#\$; 1"4, "(: 3@A\$  
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- D, +; \$3#(:F\*4, 1\$=#\*4, 1741:; (<+\$<, (#\$. 4\*. ; +<@\$(: +4, \$14\*F; =A\$, 1\$>; \*#-41#3#(:F\*4, 1\$. ; "#\$  
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- 01\$<; \*#\$, :\$41+(: <(: 14; \$=; ("#\$! #\*\*#-\$, <<=F\*4, 1\$41\$+@#;\$; 1+#(4, (\$<4(<F=; +4, 1'\$<, =; +#(: =\*\$, 1\$J%! \$  
5! %0D87%0/\$"(: 241 "9\$\$\$
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- J; +#\$, :\$(#<; 1; -4M; +4, 1\$, 1\$J%! \$
- D4. #\$, :\$(#<; 1; -4M; +4, 1\$, 1\$J%! \$

Follow up

- DA3#\$, :\$:4(\*+\$, =, ?)F3\$1; +4I #\$. ; "#\$51, 1#B\$8RRDB\$ ^ / 09\$
- J; +#\$, :\$: , =, ?)F3\$. ; "#\$
- D4. #\$, :\$: , =, ?)F3\$. ; "#\$
- DA3#\$, :\$:4(\*+\$, =, ?)F3\$I #\*\*#-\$\$. ; "41"\$51, 1#B\$RD! B\$ ^ / !)DScB\$ ^ / !)REB\$F=(; \*, F129\$
- J; +#\$, :\$: , =, ?)F3\$I #\*\*#-\$\$. ; "41"\$
- D4. #\$, :\$: , =, ?)F3\$I #\*\*#-\$\$. ; "41"\$
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- C; +; \$0RN\$
- %A. 3+, . ; +4<\$0RN\$5ER! %)H\$<(4+#(4; 9\$56789\$

- S+@#(\$0RN\$5%! NBS%JNBS#+<X9\$0:(##\$+##&+P\$
- 80N%%\$; :+#(\$He@\$
- . /%\$; :+#(\$a\$. , 1+@\$
- /#<F((#1+\$\*<@#. 4<\$\*(, -#\$, (\$D0! \$?4@41\$a\$. , 1+@\$51, B\$D0! 5\*9B\$\*(, -#5\*9\$54:\$D0! \$; 12\$\*(, -#B\$<, F1+\$\*(, -#9\$
- . /%\$; :+#(\$T\$A#; (\$

Other

- ^, 24:4#2\$DS! %D\$5W! ! B\$RE\$541<=F241"\$' cS9B\$%! SB\$, +@#(B\$. , (#\$+@; 1\$, 1#B\$F12#+#( . 41#2B\$\*+(, -#\$. 4. 4<\$
- /; (#\$\*3#<4:4<\$\*(, -#<; F\*#\*\$+, \$>#\*\$+F24#2\$41\$. , (#\$2#+; 4\$5<#(14<; =; (+#(A\$24\*\*#<+4, 1B\$41+(; <(; 14; =; (+#(A\$24\*\*#<+4, 1B\$#12, <; (24+4\*B\$I; \*<F-4+4\*B\$<, ; "F=, 3; +@4#\*9\$

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# BMJ Open

## Cohort profile: EndoVascular treatment and Thrombolysis for Ischemic Stroke Patients (EVA-TRISP) Registry: Basis and methodology of a pan-European prospective ischemic stroke revascularization treatment registry

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-042211.R1
Article Type:	Cohort profile
Date Submitted by the Author:	24-Apr-2021
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Secondary Subject Heading:	Neurology
Keywords:	Stroke < NEUROLOGY, Neurology < INTERNAL MEDICINE, Stroke medicine < INTERNAL MEDICINE

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1 **Cohort profile: EndoVascular treatment and Thrombolysis for Ischemic Stroke Patients**  
2 **(EVA-TRISP) Registry: Basis and methodology of a pan-European prospective ischemic**  
3 **stroke revascularization treatment registry**

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- 136 **Running title:** EVA-TRISP Registry Methodology
- 137 **Number of words in manuscript body:** 5929
- 138 **Number of words in abstract:** 310
- 139 **Number of tables:** 2
- 140 **Number of figures:** 1 (EVA-TRISP centers)
- 141 **Number of references:** 57
- 142 **Number of appendices:** 3
- 143 **Appendix 1:** EVA-TRISP Investigators (in alphabetical order by country)
- 144 **Appendix 2:** EVA-TRISP database items
- 145 **Appendix 3:** Names of the ethics committees

For peer review only

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3 146 **ABSTRACT**  
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8 148 **Purpose**  
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10 149 The Thrombolysis in Ischemic Stroke Patients (TRISP) collaboration was a concerted effort  
11  
12 150 initiated 2010 with the purpose to address relevant research questions about the effectiveness and  
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14 151 safety of intravenous thrombolysis (IVT). The collaboration also aims to prospectively collect  
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16 152 data on patients undergoing endovascular treatment (EVT) and hence the name of the  
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18 153 collaboration was changed from TRISP to EVA-TRISP. The methodology of the former TRISP  
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20 154 registry for patients treated with IVT has already been published. This paper focuses on  
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22 155 describing the EVT part of the registry.  
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28 157 **Participants**  
29

30 158 All centers committed to collecting predefined variables on consecutive patients prospectively.  
31  
32 159 We aim for accuracy and completeness of the data, and to adapt local databases to investigate  
33  
34 160 novel research questions.  
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36  
37 161 Herein, we introduce the methodology of a recently constructed academic investigator-initiated  
38  
39 162 open collaboration EVT registry built as an extension of an existing IVT registry in patients with  
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41 163 acute ischemic stroke (AIS).  
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47 165 **Findings to date**  
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49 166 Currently, the EVA-TRISP network includes 20 stroke centers with considerable expertise in  
50  
51 167 EVT and maintenance of high-quality hospital-based registries.  
52

53 168 Following several successful randomized controlled trials (RCTs), many important clinical  
54  
55 169 questions remain unanswered in the (EVT) field and some of them will unlikely be investigated  
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3 170 in future RCTs. Prospective registries with high-quality data on EVT-treated patients may help  
4  
5 171 answering some of these unanswered issues, especially on safety and efficacy of EVT in specific  
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7  
8 172 patient subgroups.  
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10 173

### 12 174 **Future plans**

14 175 This collaborative effort aims at addressing clinically important questions on safety and efficacy  
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16  
17 176 of EVT in conditions not covered by RCTs. The TRISP registry generated substantial novel data  
18  
19 177 supporting stroke physicians in their daily decision-making considering IVT candidate patients.  
20  
21 178 While providing observational data on EVT in daily clinical practice, our future findings may  
22  
23  
24 179 likewise be hypothesis-generating for future research as well as for quality improvement (on  
25  
26 180 EVT). The collaboration welcomes participation of further centers willing to fulfill the  
27  
28 181 commitment and the outlined requirements.  
29

30 182

### 33 183 **Key words**

35 184 acute ischemic stroke, benchmarking, collaboration, endovascular treatment, large-artery  
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37 185 occlusion, outcome, quality, recanalization, registry, stroke, thrombectomy, thrombolysis  
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## 191 **Strengths and limitations of this study**

- 192
- 193 • The EVA-TRISP collaboration offers a platform to pool individual patient data from  
194 prospective registries of patients with ischemic stroke undergoing revascularization  
195 therapies.
  - 196 • The large sample size (currently >13 000 EVT<sup>s</sup> from 20 centers), high level of  
197 completeness of data and standardized data ascertainment are strengths of EVA-TRISP.
  - 198 • EVA-TRISP will provide data from everyday clinical practice and address clinically  
199 important questions about safety and outcomes of patients with ischemic stroke treated  
200 with EVT who are not covered by randomized controlled trials.
  - 201 • Data is derived from registries that are neither monitored nor randomized. There will be  
202 no control group without EVT which disallows the assessment of effectiveness of EVT in  
203 study populations.

## 206 **INTRODUCTION**

207

208 Timely recanalization improves outcomes in patients with AIS<sup>1,2</sup>. Safety and efficacy of  
209 recanalization strategies, namely IVT and more recently EVT (including mechanical  
210 thrombectomy with various techniques and devices in AIS patients with anterior circulation  
211 large-artery occlusions), have been well-documented in several randomized controlled trials  
212 (RCTs)<sup>3-9</sup>. A meta-analysis of five RCTs revealed an average 2.5-fold reduction in disability  
213 through EVT in large-vessel occlusions compared with standard care, including IVT<sup>10</sup>. Early

1  
2  
3 214 recanalization is currently the cornerstone of acute stroke treatment with increasing use globally.  
4  
5 215 This benefit is substantially higher with earlier achievement of recanalization and diminishes  
6  
7 216 with longer onset-to-treatment intervals<sup>2, 11, 12</sup>. Previous research has explicitly shown that IVT  
8  
9 217 with alteplase within 4.5 hours of symptom onset improved AIS patient outcomes<sup>13</sup>.  
10  
11  
12 218 Following the results of these RCTs, EVT is recommended as standard of care in patients with  
13  
14 219 intracranial large vessel occlusion in several guidelines<sup>14-16</sup>. Consequently, health systems all  
15  
16 220 over the world have adapted and identify and quickly transfer eligible patients to centers offering  
17  
18 221 EVT. Simultaneously, capacity, logistics, know-how and 24/7 coverage were developed to cope  
19  
20 222 with the quickly increasing demand for this intervention. Moreover, two recent RCTs showed  
21  
22 223 benefit with EVT in patients treated up to 16 or 24 hours after stroke onset, given that presence of  
23  
24 224 a considerable amount of salvageable brain tissue had been demonstrated with appropriate  
25  
26 225 imaging methods<sup>17, 18</sup>.  
27  
28  
29 226 Relevant questions in the daily clinical work of treating stroke patients suffering from large  
30  
31 227 vessel occlusions remain. Firstly, EVT-RCTs included a highly selective patient population. This  
32  
33 228 increased the chances to demonstrate efficacy and to exclude patients who presumably had a low  
34  
35 229 chance for a favorable outcome and patients who had a high risk for serious complications.  
36  
37  
38 230 Secondly, the seven published EVT trials<sup>3, 5-9, 19</sup> analyzed altogether only included 1754  
39  
40 231 randomized patients (of whom 869 underwent EVT) with the single smallest trial including only  
41  
42 232 65 patients (of whom 33 underwent EVT)<sup>8</sup>. Usually, after a novel treatment is proved effective, a  
43  
44 233 new wave of assumptions and extrapolations for treating a broader domain of patients begins. As  
45  
46 234 all these excluded patient subgroups cannot be studied in future RCTs, in most cases judgments  
47  
48 235 for treating or not treating with EVT will be based on limited knowledge. Some remaining  
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50 236 questions will eventually be answered with a long delay, but some will never be answered in  
51  
52 237 forthcoming RCTs. However, stroke physicians keep facing patients where evidence-based data  
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3 238 do not explicitly contribute to decision-making for these individuals, in which available  
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5 239 treatments may very well have a potential benefit as well. Here, prospective high-quality  
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7 240 multicenter registries including large numbers of patients representing many subgroups, not  
8  
9 241 included or not separately analyzed within RCT settings, may offer helpful information for  
10  
11 242 basing clinical judgments while being aware that the level of certainty will not reach that gained  
12  
13 243 from RCTs. These registries may also give strong clues on how trial results are implemented to  
14  
15 244 clinical practice and how daily practice safety and efficacy levels match with those gained in  
16  
17 245 RCTs. Further, registry-based data deliver hints in generating new and adequate hypotheses for  
18  
19 246 future RCTs. Another important aspect is the recently developing new field of clot property-  
20  
21 247 research: interested centers can collect detached clots and ship them to laboratories where  
22  
23 248 macroscopic and microscopic properties of the clot coupled with clinical data can be further  
24  
25 249 investigated and may open new avenues in understanding stroke mechanisms. Lastly, quality is a  
26  
27 250 central indicator in health care and registry-based data can be utilized in comparisons and for  
28  
29 251 improving individual center acute stroke care pathways. As a prerequisite, such data have to be  
30  
31 252 based on well-maintained registries containing a large number of detailed, clearly-defined, and  
32  
33 253 well-characterized variables. The EVA-TRISP registry aims at meeting these prerequisites.  
34  
35 254 Utilizing our decade-long experience from the multinational TRISP registry<sup>20</sup>, we are now aiming  
36  
37 255 to build a prospective multinational registry of AIS patients treated with EVT including detailed  
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39 256 clinical, laboratory, and imaging data for future analyses. We are presenting herein the current  
40  
41 257 versions of the clinical and imaging database items of the EVA-TRISP registry. Additionally, we  
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43 258 will discuss a selection of specific related topics.  
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## 262 **AIMS OF THE EVA-TRISP REGISTRY**

263 The major aim of EVA-TRISP is to address clinically important questions about safety and  
264 outcomes in AIS patients treated with IVT and/or EVT that are not covered by RCTs. The idea of  
265 EVA-TRISP is that experienced stroke centers with a record and expertise in both (I) usage of  
266 IVT and/or EVT and (II) maintenance of hospital-based stroke databases pool their data. In  
267 addition to the characteristics of the EVA-TRISP centers stated above, an advantage of EVA-  
268 TRISP is the availability of more additional variables than in other large-scale registries and the  
269 commitment by the collaborators to I) submit accurate and complete data and to II) be willing to  
270 adapt the local databases and quickly add new variables retro- and prospectively.

## 272 **COHORT DESCRIPTION**

273  
274 The Thrombolysis in Ischemic Stroke Patients (TRISP) collaboration was a concerted effort  
275 initiated in 2010 by 11 European stroke centers with the purpose to address clinically relevant  
276 research questions about the effectiveness and safety of IVT, and currently 20 stroke centers from  
277 nine different countries participate in the collaboration (see Figure 1 and Appendix 1 for a list of  
278 member sites and investigators). As the collaboration also aims to prospectively collect granular  
279 and high-quality data on all consecutive stroke patients undergoing EVT, the name is changed  
280 from TRISP to EVA-TRISP.

281 EVA-TRISP (former TRISP) operates as an independent, non-profit, investigator-driven open  
282 platform that focuses on generating high quality data for clinical research purposes. The EVA-  
283 TRISP research initiatives are characterized by informal, project-driven and relaxed work  
284 processes based on a high level of mutual trust and understanding between participating  
285 collaborators, and no formal scientific leadership committees have so far been implemented or

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3 286 deemed necessary. Internal communication principally takes place via e-mail and  
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5 287 teleconferences. The EVA-TRISP collaboration also hosts an annual face-to-face meeting during  
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7 288 the European Stroke Organisation (ESO) conference, and this forum is utilized for overall  
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10 289 strategic planning and major decisions. The collaboration welcomes new collaborators and  
11  
12 290 project proposals from all stroke centers that fulfill the requirements as stated below. The  
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14 291 collaboration particularly aims at supporting young researchers. Thus, with the exception of the  
15  
16 292 very first paper<sup>21</sup>, first authors of the publications generated by the TRISP invariably have been  
17  
18 293 young stroke physicians or PhD-students. The methodology of the TRISP registry has previously  
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20 294 been published<sup>20</sup>, and currently data on more than 18,000 IVT-treated patients are available in the  
21  
22 295 registry. This paper focuses on describing the EVT part of the registry.  
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25  
26 296 The EVA-TRISP registry aims to prospectively collect granular and high-quality data on all  
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28 297 consecutive AIS patients undergoing both IVT and/or EVT. The overall purpose is to provide a  
29  
30 298 means to address clinically important research questions on the safety and effectiveness of IVT  
31  
32 299 and/or EVT in AIS patients that are typically not covered by RCTs or single center research  
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34 300 initiatives. Furthermore, the EVA-TRISP aims at providing a large data source for various stroke  
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36 301 care quality improvement initiatives. All EVA-TRISP centers have a proven track-record for  
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38 302 delivering high-quality and high-volume stroke patient care. Every EVA-TRISP center offers  
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40 303 stroke management that fulfills the criteria of Stroke Centers or Stroke Units as proposed by the  
41  
42 304 ESO<sup>22</sup>. The simple idea of the EVT part of the EVA-TRISP registry is that experienced stroke  
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44 305 centers with expertise in both EVT implementation and in the maintenance of hospital-based  
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46 306 EVT databases pool their data together. An advantage of the EVA-TRISP registry is the  
47  
48 307 availability of substantially more variables than in other large-scale registries. We strive for a  
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50 308 commitment by the collaborators to provide data of high accuracy and completeness as well as  
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52 309 towards a willingness among collaborators to swiftly adapt the local databases by adding new  
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3 310 variables of interest. This enables a potential for explorative insights in the putative prognostic  
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5 311 importance of variables with unknown influence on outcome or risk of complications, such as  
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7 312 symptomatic intracranial hemorrhage (sICH). Strengths and limitations of the EVA-TRISP  
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9  
10 313 registry in general and compared to other existing EVT registries are discussed below (please see  
11  
12 314 Discussion).

13  
14 315 The participating centers have all agreed to fulfill the prerequisites that are summarized in Table  
15  
16 316 1. Participation in other registries does not preclude participation in the EVA-TRISP registry. A  
17  
18 317 standard database template has been developed by an international expert group consisting of  
19  
20 318 stroke physicians and scientists in collaboration with all members, leading to the current standard  
21  
22 319 version of the registry (see Appendix 2-Registry data elements) which has been agreed upon by  
23  
24 320 all EVA-TRISP member sites. This comprehensive dataset includes over 110 items and covers a  
25  
26 321 wide range of data elements, including demographics, pre-stroke health information, acute phase  
27  
28 322 management, and long-term outcomes including three months and one-year modified Rankin  
29  
30 323 Scale (mRS) as well as detailed laboratory data and imaging findings. An add-on imaging  
31  
32 324 repository is currently under preparation and will be implemented within the near future.  
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34 325 Electronic medical records used at all member sites allow for additional variables to be collected  
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36 326 quickly and reliably when deemed necessary for new projects.  
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### 47 329 **Target population**

48  
49 330 All AIS patients designated for EVT and in whom interventionalists gained arterial access are  
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51 331 within the target population. Therefore, this registry also may include patients with misdiagnosis,  
52  
53 332 already recanalized leading to premature interruption of the procedure, unsuccessful attempts to  
54  
55 333 recanalize, and other unforeseeable conditions. Inclusion of patients is not limited to certain EVT  
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3 334 techniques. The registry will include also patients who receive intra-arterial thrombolysis even  
4  
5 335 without mechanical thrombectomy.  
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10 337 **Data collection and definitions**

11  
12 338 Data on the characteristics of patients are collected prospectively by all participating centers  
13  
14 339 using standardized definitions and a standardized form. Not all centers have to provide data on all  
15  
16 340 variables but have given a commitment to add missing variables retrospectively, if considered  
17  
18 341 relevant to answer a specific research question.  
19  
20

21 342 The dataset includes patient demographics, history, prehospital information, admission data,  
22  
23 343 details on acute interventions, stroke unit and/or intensive care information, discharge,  
24  
25 344 rehabilitation, outcome data (three months and one-year outcomes measured by mRS), as well as  
26  
27 345 detailed laboratory test results, vital signs, and imaging findings (see Appendix 2). Risk factors  
28  
29 346 and stroke etiology will be determined according to standard approaches across centers<sup>20</sup>.  
30  
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32  
33 347 Moreover, neuroimaging findings before and after treatment are systematically ascertained and  
34  
35 348 comprise imaging modality (computed tomography versus magnetic resonance imaging) as well  
36  
37 349 as specific imaging findings such as hyperdense artery sign, presence and extent of early  
38  
39 350 ischemic signs, site of vessel occlusion, collateral status, presence of tandem occlusion of  
40  
41 351 ipsilateral carotid artery, recanalization status immediately after EVT and on follow-up imaging  
42  
43 352 (quantified according to modified treatment in cerebral ischemia (mTICI) score)<sup>23</sup>, white matter  
44  
45 353 disease severity, presence and burden of cerebral microbleeds.  
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48  
49 354 All patients are monitored for occurrence of hemorrhagic transformation. Follow-up imaging  
50  
51 355 usually takes place close to 24 hours after treatment or earlier in case of clinical worsening. Some  
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53 356 centers perform follow-up imaging only in cases with clinical worsening. The definition of  
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3 357 symptomatic intracerebral hemorrhage (sICH) is in accordance with the definition used in the  
4  
5 358 European Cooperative Acute Stroke Study II (“an intracranial hemorrhage was defined as  
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7 359 symptomatic if the patient had clinical deterioration causing an increase in the National Institute  
8  
9 360 of Health Stroke Scale (NIHSS) score of more than or equal to four points and if the hemorrhage  
10  
11 361 was likely to be the cause of the clinical deterioration”)<sup>24</sup>. The majority of centers additionally  
12  
13 362 evaluate type of hemorrhagic transformation (hemorrhagic infarction, parenchymal hemorrhage),  
14  
15 363 indicate whether the bleeding occurred remotely from the infarcted area, and document sICH  
16  
17 364 according to definitions used in the National Institute of Neurological Disorders and Stroke Trial  
18  
19 365 I-II, SITS-MOST and ECASS III definitions<sup>25, 26, 27</sup>. Functional outcomes at three months and  
20  
21 366 one-year are assessed using the mRS. The mRS is obtained by telephone calls, postal/electronic  
22  
23 367 questionnaires, or outpatient visits. If patients cannot be interviewed, close relatives, nurses or  
24  
25 368 family doctors are asked for disability status.

26  
27 369 We are currently exploring technical, legal, and ethical as well as financial backgrounds for  
28  
29 370 establishing an electronic registry to one of the member centers that would allow direct data  
30  
31 371 insertion from each center and holding the registry compactly in one single file. Otherwise, each  
32  
33 372 center will maintain their own registry within their own electronic system and data will always be  
34  
35 373 transferred without personal identifiers for each single analysis looking at one single aspect and  
36  
37 374 leading to one mutual international publication. Establishing and maintaining such a large  
38  
39 375 database with complete compliance to rules and safety measures is a costly procedure and  
40  
41 376 requires long-term funding. This option is now under exploration.

42  
43 377 Future plans in the registry include the addition of a neuroradiology imaging bank that will  
44  
45 378 enable detailed image analysis of patients treated with IVT and/or EVT. The imaging bank will  
46  
47 379 provide “real-world” diagnostic neuroradiology and, used in combination with detailed clinical  
48  
49 380 information from the EVA-TRISP registry, analysis of this imaging data will help to (i) create



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3 381 standardized imaging protocols in acute stroke (i.e. defining optimal threshold for perfusion  
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5 382 parameters), (ii) identify new (i.e. a collateral score for the posterior circulation) and validate  
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7 383 published (i.e. different collateral scores for the anterior circulation) imaging outcome predictors  
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10 384 and imaging-based selection tools for reperfusion therapies, (iii) assess the generalizability of  
11  
12 385 RCT results to subgroups of patients who would have been excluded based on imaging criteria  
13  
14 386 (i.e. baseline Alberta Stroke Program Early CT score [ASPECTS] under five, extracranial vessel  
15  
16 387 pathologies), (iv) improve automated analyzing techniques (i.e. machine and deep learning  
17  
18 388 algorithms), (v) and enhance the accuracy of outcome prediction of different clinical and imaging  
19  
20 389 parameters by implementing new imaging outcomes (f.i. infarct volume, recanalization status).  
21  
22 390 Neuroimages from TRISP/EVA-TRISP patients since 2015 will be pooled centrally. All imaging  
23  
24 391 modalities (non-contrast CT, CT-angiography, CT-perfusion, MRI, MRA, MR-perfusion, and  
25  
26 392 digital subtraction angiography) at baseline and follow-up (up to three months after stroke onset)  
27  
28 393 will be eligible for analysis. Image analyses will be performed blinded to clinical information and  
29  
30 394 treatment decisions, and undergo a central systematic re-evaluation using a specified case report  
31  
32 395 form including all predefined imaging variables.  
33  
34 396 Stroke-specific image analyzing software (i.e. OSIRIX medical imaging viewer, Quantomo for  
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36 397 semi-automated volumetric analysis, and Rapid Processing of Perfusion and Diffusion [RAPID]  
37  
38 398 for perfusion analysis) could be utilized. A detailed case report form for image analysis will be  
39  
40 399 designed in review with all collaborators.  
41  
42 400 Lastly, EVA-TRISP investigators prepared a detailed standard operating procedure (SOP) to  
43  
44 401 ascertain that all members collecting data are well-aware of standard interpretations and follow  
45  
46 402 identical steps to avoid unnecessary heterogeneities or individual-borne differences. The numbers  
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48 403 of recruited patients in each participating center during the study period until the end of year  
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50 404 2019 are reported in Table 2 along with the population each center is covering for EVT.  
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405

**406 Data elements and completeness**

407 A detailed database is aimed to facilitate the investigation of various current and future topics.

408 Data elements are listed in detail in Appendix 2. Over time, new data elements may become

409 necessary for new individual projects. Should this occur, investigators will quickly supplement

410 the missing variables. Patient age, sex, admission NIHSS score, recanalization status before and

411 after thrombectomy, and three months outcome measured by mRS are obligatory data items and

412 must be present for all patients (otherwise a patient is not eligible to be included to the registry).

413 In general, missing data for any variable or patient must not exceed 10%.

414

**415 Data sources**

416 All paper-based or electronic patient files including laboratory values and imaging data will be

417 utilized to capture the EVA-TRISP registry data points. Based on these different sources

418 alongside repeated clinical evaluations undertaken by the dedicated EVA-TRISP collaborator,

419 registry data points that initially remain missing during the early stroke treatment process will in

420 the majority of cases be possible to reconstruct and thereafter reported to the local registry (e.g.

421 NIHSS scores). In most cases, the local EVA-TRISP investigators form the local stroke team and

422 will be actively seeing the patients already in the emergency room and/or at their own stroke

423 units and can therefore guarantee completeness of data in most cases.

424

**425 Quality control**

426 Quality control is another crucial step in multicenter large-sized registries since missing data are

427 a frequent problem impairing the reliability and generalizability of registry-borne data. The EVA-

428 TRISP registry is different in this sense because data are not yet directly collected to a central

1  
2  
3 429 registry, but each center collects their own data to their own institutional registry according to a  
4  
5 430 standard harmonized database item list and SOP. Thus, clear variable definitions are easily  
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7 431 available for the user when data are entered. It is the responsibility of the local EVA-TRISP  
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9 432 collaborator (usually a senior stroke physician) to check and account for the validity and  
10  
11 433 completeness of all data points introduced to the local registry. Therefore, missing data are  
12  
13 434 expected to be very low. Furthermore, all centers have agreed to include all consecutive patients  
14  
15 435 attempted with an EVT and all centers will undertake frequent spot checks against internal  
16  
17 436 hospital administrative systems covering EVT procedures, as to not leave any patient out of the  
18  
19 437 registry. Therefore our registry data will likely include all EVTs performed within a region and  
20  
21 438 population, practically equaling to a population-based study, although being hospital-based,  
22  
23 439 because EVT is usually available only at stroke centers serving a predefined region and the  
24  
25 440 inhabitant population. Most of the required data come from routine procedures which are  
26  
27 441 standardly collected and recorded in stroke patient care pathways as part of the clinical routine  
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29 442 and therefore these data points are almost always retrievable. In the subsequent quality control  
30  
31 443 process, the data files from the individual participating centers are merged into a single file for  
32  
33 444 further maintenance analyses. Pseudonymized individual center data are sent to the center leading  
34  
35 445 the specific project using encrypted transfer protocols. The subsequent data management of the  
36  
37 446 merged database will implement checks for missing data along with checks for range,  
38  
39 447 consistency and illogical data (e.g. NIHSS score cannot be minus or over 42 points and can only  
40  
41 448 be full points and not decimals; patient age at stroke onset can be only in digits, and is expected  
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43 449 to be from 16 and very rarely over 100). Also other procedures regarding quality check will be  
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45 450 implemented at milestone points, such as comparing the performance of data reporting among  
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47 451 centers.  
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### 453 **Registry size and duration**

454 The registry will include all EVT patients from all member sites. We anticipate that the absolute  
455 numbers and proportions of EVT-treated AIS patients will be increasing over time and annual  
456 inserts will exceed thousands shortly. The registry size is not limited. One anticipated strength of  
457 this registry is the high patient number together with detailed information on each patient which  
458 will allow us to look at many issues that are not feasible to investigate within RCTs or even  
459 merged data from all RCTs because of the fact that they include fairly small patient numbers. The  
460 use of the registry will be launched after 5000 patients' data have been inserted and adequately  
461 quality-checked. Similarly, this registry will be utilized as long as EVT is a viable option in  
462 stroke treatment. The unlimited time span requires careful evaluation by ethics committees. If the  
463 consortium decides to end the registry, each center's data will be adequately returned to the  
464 owners and the registry data will be deleted achieving an absolutely non-retrievable condition  
465 according to technical standard operating procedures (SOPs) of the registry-holding center.  
466 Thereafter, each individual center will be free to decide how to proceed with their own datasets.  
467 Similarly, if a center decides to resign from the registry, their data will be adequately returned  
468 and will be deleted from the main database file after confirmation that the data are safely received  
469 by the local principal investigator. While all patient-related data including clinical, laboratory,  
470 and imaging data are completely anonymized, each center will keep a key file within their local  
471 electronic hospital system with patient identifiers matching to the patient code in the registry (e.g.  
472 if necessary to go back to patient files). This approach is compliant with current principles and is  
473 the SOP worldwide.

474

### 475 **Lead of a single project and authorship principles**

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2  
3 476 The researcher or researchers - usually one or two (rarely three) - who originally present the idea  
4  
5 477 and render the analysis proposal make(s) the initiation by drafting a standard 1-2 pages draft  
6  
7 478 stating a clear hypothesis and statistical plan summarizing the project (project proposal). The  
8  
9  
10 479 proposal is circulated to all member centers and discussed for scientific content and feasibility  
11  
12 480 enriched with input from a large expert community. After that, the enriched plan along with the  
13  
14 481 list of data items required is recirculated. If a center agrees to participate, the center contributes  
15  
16 482 data within the in-advance agreed time frame on all consecutive patients with the key variables of  
17  
18 483 interest. For some projects retrospective collection of data is required. The original proposal  
19  
20 484 makers are entitled to the first and senior authorships. Co-authorships are distributed according to  
21  
22 485 contributions. This includes not only mere quantitative means (i.e. number of patients  
23  
24 486 contributed) but also quality of data (e.g. completeness; considered high across EVA-TRISP  
25  
26 487 centers), handling and pooling of the multicenter data; maintenance of the pooled data set  
27  
28 488 (including data cleaning), statistics, contribution to EVA-TRISP in general, and intellectual input  
29  
30 489 in details of the design or the analyses of the research project, and lastly intellectual input to the  
31  
32 490 writing and improving of the manuscript. These criteria are suggestions and the researches taking  
33  
34 491 the lead in each project take the final responsibility for the fair distribution of authorships.  
35  
36 492 Each member site possesses its own data and each member site whose data is utilized is entitled  
37  
38 493 to co-authorship(s). Whenever feasible, an abstract approved by all co-authors is submitted to the  
39  
40 494 forthcoming ESO Conference. All EVA-TRISP member centers and investigators are listed at the  
41  
42 495 end of the manuscript as a supplement given that the publishing journal's own format allows this  
43  
44 496 approach.  
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#### 53 498 **Data ownership, access, use, and publications**

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3 499 Each center is self-financing in data collection and is the indisputable owner of their own data. If  
4  
5 500 and when a mutual single databank is constructed, each individual researcher with the necessary  
6  
7 501 formal training and permissions will be able to insert data directly to the central database on the  
8  
9 502 internet and have access to the researcher's own center's data without limitations. Individual  
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11 503 scientists working on a properly agreed upon single project and doing data analyses will be  
12  
13 504 granted proper access to all data. In case that an individual center refrains from participating in a  
14  
15 505 particular analysis, their data will not be included in that analysis. Any publication that is  
16  
17 506 produced from the registry data will include authors from each contributing center in accordance  
18  
19 507 to number of patients delivered as well as active involvement in analyses and writing work.  
20  
21 508 Number of authors and their placement in the author list may vary according to the amount of  
22  
23 509 contributions. This will be handled openly and in a delicate way aiming at mutual consent.  
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### 30 511 **Ethics, informed consent, and privacy**

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32  
33 512 Each center has received necessary official approval from their respective local authorities and/or  
34  
35 513 ethical committees according to their national and local rules (Appendix 3). These permits  
36  
37 514 include transfer of data between EVA-TRISP centers. Necessity of individual informed consent is  
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39 515 dependent on national rules and will be collected if necessary. Data are shared with respect to the  
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41 516 EU law 2016/679 about General Data Protection Regulation (GDPR). In the long run, the aim is  
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43 517 to have a permanent database residing at a member site. Establishment and maintenance of the  
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45 518 permanent database at one center will be initiated only after a separate ethics approval.  
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## 50 51 520 **DISCUSSION**

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3 522 Endovascular treatment, now fulfilling the criteria for the highest level of evidence, has changed  
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5 523 acute stroke care substantially. Probably approximately 10% of all ischemic stroke patients are  
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7 524 eligible for EVT, but the percentages may grow as more and more patients are brought to the  
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9 525 attention of emergency systems and the treatment indications will likely expand over time<sup>28</sup>. The  
10  
11 526 rapid developments in acute stroke care put considerable demands on health care systems and  
12  
13 527 necessitate quick rearrangements for coupling these needs. The seven published RCTs and  
14  
15 528 following meta-analyses answered most central questions. Nevertheless, there are numerous  
16  
17 529 unanswered questions remaining in terms of EVT in acute ischemic stroke. Some of these  
18  
19 530 questions will be solved and satisfied via ongoing and forthcoming RCTs. Yet, many other issues  
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21 531 will never or unlikely be tested in RCTs and stroke physicians need firm data on these topics to  
22  
23 532 base their clinical decisions on. Moreover, there are certain patient groups where RCTs are  
24  
25 533 ethically difficult to organize; such a group is patients with basilar artery occlusion (BAO).  
26  
27 534 Although a clearly important clinical condition which untreated has a poor outcome, BAO  
28  
29 535 patients were not included in the large EVT trials. An extrapolation from the anterior circulation  
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31 536 EVT trial results for BAO has currently a strong support in clinical practice, and thus EVT is  
32  
33 537 currently offered to BAO patients despite limited direct evidence of treatment effectiveness. A  
34  
35 538 small multi-center RCT that included 131 patients– the Chinese BEST trial (Basilar artery  
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37 539 occlusion Endovascular intervention versus Standard medical Treatment)<sup>29</sup>– was prematurely  
38  
39 540 terminated due to slow recruitment and a high crossover rate that severely hampered the  
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41 541 interpretability of the intent-to-treat analysis. Another RCT with 300 patients included is closed,  
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43 542 but data has not yet been presented<sup>30</sup>. Still, both the per-protocol and the as-treated analyses  
44  
45 543 favored EVT compared to best medical treatment. Some small-sized registry data showed high  
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47 544 recanalization rates and similar hemorrhagic complication rates as in anterior circulation patients  
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3 545 treated with EVT, but more often futile recanalization. Large-scale registry studies may further  
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5 546 improve our knowledge in this patient group and may help identifying those who will likely  
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7 547 benefit or not benefit from EVT in a real-life setting<sup>6, 31-33</sup>. In the absence of RCT-based data,  
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10 548 comprehensive observational data may be useful for individual treatment decisions in clinical  
11  
12 549 practice and in evaluating processes of stroke triage and care for IVT or EVT. As a prerequisite,  
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14 550 such data have to be based on well-maintained registries containing large numbers of detailed,  
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16 551 clearly-defined, and well-characterized variables. The EVA-TRISP registry meets these  
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18 552 prerequisites. Ideally, the results from such observational studies are verified or falsified by  
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20 553 RCTs. However, with few exceptions (e.g. age limit) this is unlikely to happen. Thus, registry-  
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22 554 based data will reflect the highest level of evidence in several aspects, available currently and in  
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24 555 the foreseeable future.  
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28 556 Further, we need to continuously follow-up whether the safety and benefit aspects of EVT shown  
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30 557 in RCTs could be correctly translated to routine clinical practice. Indeed, the safety and benefit  
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32 558 may be better, similar, or even worse in daily practice. Registry data can easily be compared to  
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34 559 RCT data especially when basic settings are similar. Additionally, it becomes more and more  
35  
36 560 feasible to compare centers, patient subgroups and devices. Benchmarking, previously performed  
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38 561 by site visits, is a popular approach for understanding differences and making improvements, and  
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40 562 can now be done easily using electronic data<sup>34</sup>.  
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44 563 Systematically ascertained, comprehensive and high-quality observational data are useful to both  
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46 564 (I) challenge or (II) confirm the clinical usefulness of commonly used but often arbitrary  
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48 565 eligibility criteria. An early example has been the challenge of the usefulness of the upper age  
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50 566 limit of 80 years for IVT based on comprehensive, observational studies. Eventually, the third  
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52 567 International Stroke Trial (IST-3) proved that indeed patients aged 80 years and older benefit  
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54 568 from IVT, too<sup>35</sup>.  
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3 569 Utilizing the TRISP registry, we previously examined the safety of IVT in a number of patient  
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5 570 subgroups where RCT-based data did not exist. Previous publications of the TRISP registry (I)  
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7 571 provided insight into safety and efficacy of IVT in subgroups of patients who were excluded in  
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9 572 RCTs (e.g. patients dependent on the help of others prior to stroke), underrepresented or not  
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11 573 specifically addressed (e.g. dissection as cause, impaired renal function, low platelet count, body-  
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13 574 mass-index, prior use of statins, serotonin uptake inhibitors, prior use of novel oral  
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15 575 anticoagulants, patients with seizure at onset)<sup>21, 36-45</sup>, (II) facilitated the evaluation process of  
16  
17 576 acute stroke care such as the meaning of the “off-hour-thrombolysis”, IVT during “working  
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19 577 hours”, or the variable “time” in clinical practice<sup>46-48</sup>, and (III) served to derive, validate, and  
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21 578 compare risk scores for sICH or functional three months outcome<sup>49-51</sup>. These registry-based novel  
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23 579 data contributed to the numbers of patients treated safely and successfully with IVT globally.  
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25 580 Ongoing and planned research projects within the EVA-TRISP registry collaboration that may  
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27 581 fill important knowledge gaps are investigations on (I) stroke due to cervical artery dissection,  
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29 582 (II) stroke with low baseline NIHSS, (III) stroke specifically in the ACA-territory, (IV) stroke  
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31 583 patients with preexisting dependency, (V) significance of cerebral collaterals, (VI) significance of  
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33 584 tandem occlusions and (VII) stroke patients with active cancer.  
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35 585 Disease- or intervention-based patient registries with consecutive patients recruited in a  
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37 586 population- or hospital-based approach are useful in many ways: they help describe the natural  
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39 587 history, determine clinical effectiveness and cost-effectiveness of health care products or  
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41 588 services, measure or monitor safety and harm, measure quality of care, improve quality of care,  
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43 589 and help with benchmarking purposes such as how clinical practices vary, what the best  
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45 590 predictors of treatment practices are, and comparing different practices providing a basis for  
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47 591 further improvements. In such settings, stakeholders are several: the primary stakeholder with the  
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3 592 EVA-TRISP registry is the academic consortium establishing and running the registry. Potential  
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5 593 stakeholders with such a large-scale registry may include public health and regulatory authorities,  
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7 594 product manufacturers, health care service providers, payer and commissioning authorities,  
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10 595 patients and their advocacy groups, treating physician groups, academic institutions, and  
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12 596 professional societies. The EVA-TRISP registry aims at including all patients who underwent  
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14 597 EVT as a treatment for AIS, including patients with misdiagnosis, unsuccessful attempts (EVT is  
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16 598 defined as a puncture to the artery with the aim of recanalization), or other unforeseeable  
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18 599 scenarios. In most countries, registry-based studies are approved by ethics committees with  
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20 600 waving informed consent from individual patients as demanding informed consent would leave  
21  
22 601 most severe patients out of the registry and cause a severe bias on representability of any finding.  
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24 602 Imaging has become more and more critical in the stroke field. In addition to stroke diagnostics  
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26 603 and excluding competing etiologies (e.g. stroke mimics), there are a number of imaging findings  
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28 604 related to increased risk following acute treatments (e.g. leukoaraiosis<sup>52</sup> and microbleeds), or  
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30 605 findings guiding treatment choices (e.g. major artery occlusion reachable with a catheter), as well  
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32 606 as findings helpful in prognostics such as ASPECTS<sup>53</sup> or SEDAN<sup>49</sup> scores. Acute stroke patients  
33  
34 607 are increasingly imaged with a package of standard CT, CT angiography and CT perfusion or in a  
35  
36 608 similar fashion with an MRI-based package. These imaging modalities are then analyzed quickly  
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38 609 for determining diagnosis, prognosis, and treatment approach. Functional imaging modalities are  
39  
40 610 increasingly taken into account for patient selection to IVT and EVT instead of strictly deciding  
41  
42 611 according to time. The former TRISP registry included few items on imaging studies. Imaging  
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44 612 requirements were according to routine thrombolysis: only a non-contrast CT imaging prior to  
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46 613 thrombolysis was mandatory. Imaging was not the main focus as image-analysis is usually labor-  
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48 614 intense and not always available. Technological improvements may substitute some of the expert  
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56 615 workforce in image analysis already today and in the near future. However, with the

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3 616 developments in imaging technologies and increased requirements in patient care, currently most  
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5 617 patients are imaged with CT angiography and CT-perfusion in addition to basic non-contrast CT  
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7 618 imaging. Less frequently, patients are imaged with a similar versatile package of various MRI  
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10 619 sequences. Developments in the imaging technology and logistics, decrease in radiation dose  
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12 620 used with CT imaging, as well as automatic image-analysis software development contributed to  
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14 621 the progress. Installing imaging scanners into or adjacent to emergency departments or taking  
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16 622 acute stroke suspect patients directly to the imaging facility by-passing the emergency room have  
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18 623 also improved the availability of more detailed imaging. Patient selection for the best individual  
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20 624 treatment is becoming increasingly dependent on neuroimaging with the goal of providing rapid  
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22 625 patient-specific metrics such as tissue viability, vessel patency status, thrombus characteristics  
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24 626 and cerebral perfusion etc. Imaging findings have also been used for patient selection in some  
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26 627 highly successful IVT and EVT RCTs<sup>4, 5, 54-56</sup>. Detailed imaging information is even more crucial  
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28 628 when EVT is considered. Therefore, the establishing of an imaging repository parallel with the  
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31 629 EVA-TRISP registry received a widespread support from members. To date, the choice of  
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33 630 imaging modalities, parameters and thresholds varies widely across medical centers. No  
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35 631 standardized imaging protocols currently exist, other than joint statements from professional  
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37 632 societies<sup>57</sup>. A large, multicenter neuroimaging registry with state-of-the-art re-evaluation of  
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39 633 images combined with detailed clinical data of IVT/EVT-treated stroke patients would be helpful  
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41 634 for validating between modalities, defining thresholds, enhancing automated assessments and  
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43 635 creating standards in neuroimaging for acute ischemic stroke. For the imaging part of the  
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45 636 database we will collect baseline, interventional and follow-up images (up to three months after  
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47 637 stroke onset) from all stroke patients included in TRISP since 2012. All images will be centrally  
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49 638 analyzed using a predefined, standardized form.  
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### 640 **Strengths and limitations of the EVA-TRISP registry**

641 Strengths of EVA-TRISP registry include (I) the high completeness level of data with few  
642 missing data, (II) large sample sizes which reduce the risk of bias and allows adjustments for  
643 confounders, (III) the systematic and standardized data ascertainment which increases the  
644 homogeneity of the study population, (IV) the intrinsic motivation of the study personnel which  
645 leads to a high rate of completeness of ascertained data sets, contributing to a high-quality  
646 registry, and (V) the dynamic nature of the EVA-TRISP database due to the commitment of the  
647 centers to adapt the local database and add variables retro- and prospectively. In addition, (VI) a  
648 large number of variables is gathered including those with unknown prognostic importance. This  
649 allows addressing novel yet unidentified research questions. Moreover, (VII) pooling of  
650 individual patient data increases generalizability compared to single center studies, and (VIII) the  
651 fact that variables and outcomes have been collected irrespective of the present research question,  
652 reduces the risk of a bias. (IX) As most EVA-TRISP centers are regional reference centers for  
653 acute patient care, particularly for EVT, the EVA-TRISP registry will resemble a population-  
654 based registry. Limitations are inherent to the design of EVA-TRISP: (I) Data is derived from  
655 registries that are neither monitored nor randomized. Usually, there will be no control group  
656 without EVT which disallows the assessment of effectiveness of EVT in study populations. (II)  
657 As true for all observational studies, analyses based on registers have a higher risk of bias than  
658 RCTs. Thus, we urge to a cautious interpretation of findings and observations. (III) All EVA-  
659 TRISP centers are experienced in stroke treatment. This expertise implies – as a downside – a  
660 limited generalizability of findings to all stroke providers with less expertise and less advanced  
661 settings. (IV) The majority of our included patients are Caucasians and from high-income  
662 countries. Thus, we cannot compare ethnical differences, nor can we compare health systems  
663 with various funding levels. (V) Currently, there is no ‘core lab’ to validate hemorrhagic

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3 664 complications and three-month mRS ratings. As valid for other major registries like SITS and  
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5 665 GWTG, local interpretation of outcome data may differ between sites. Since EVA-TRISP centers  
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7 666 are mostly high-volume centers with long-standing experience in maintaining IVT databases, this  
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10 667 bias is likely to be smaller than in most of the other registries.  
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## 15 16 17 670 **SUMMARY**

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21 672 The EVA-TRISP collaboration is an open platform dedicated to conduct joint research projects in  
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23 673 AIS patients treated with IVT and/or EVT. EVA-TRISP aims to increase knowledge on the safety  
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25 674 and efficacy of IVT and EVT, study outcomes after IVT and EVT, to evaluate processes of acute  
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27 675 stroke care as well as to document and improve acute stroke care quality. Our previous  
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29 676 achievements prove that this collaboration has the potential to provide versatile observational  
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31 677 information on treatment of AIS patients during daily clinical practice. Prospective and  
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33 678 standardized documentation of individual patient data according to consensus definitions is a  
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35 679 major requirement to maintain the quality of the EVA-TRISP registry. Publishing this  
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37 680 methodology paper improves the transparency of the registry and collected data. EVA-TRISP  
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39 681 welcomes participation and project proposals of further centers fulfilling the requirements stated  
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41 682 above.  
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## 48 49 684 **Consent for publication**

50  
51 685 Not applicable.  
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## 57 687 **Availability of data and materials**

1  
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3 688 Not applicable.  
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8 690 **Competing interests**  
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10 691 The authors declare that they have no competing interests.  
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14 693 **Patient and public involvement**  
15

16 694 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination  
17  
18 695 plans of our research.  
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21 696  
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23 697 **Funding**  
24

25 698 None.  
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30 700 **Authors' contributions**  
31

32 701 Data collection: AN, SC, HG, SMZ, HE, CK, JEK, NMM, GS, PAL, CT, MIB, JFS, NB, HH,  
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35 702 DL, AE, PM, CH, PAR, MA, UF, HS, DJS, AP, AZ, VP, DRJ, ARL, SW, LK, KF, GK, AR, KL,  
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38 703 RRL, JC, JG, AB, JL, MP, AK, PP, JG, Mauro M, CM, GB, IV, VC, JW, ZK, MB, Markus M,  
39

40 704 GN, EK, KJ, CHN, PJN, STE, DS, TT. Manuscript drafting: AN, SC, HG, SMZ, HE, CK, CHN,  
41

42 705 PJN, KJ, STE, DS, TT. Study supervision: TT, DS, STE, KJ, PJN, CHN. Statistical analysis and  
43

44 706 interpretation: does not apply. Review of the manuscript for intellectual contribution: AN, SC,  
45

46 707 HG, SMZ, HE, CK, JEK, NMM, GS, PAL, CT, MIB, JFS, NB, HH, DL, AE, PM, CH, PAR,  
47

48 708 MA, UF, HS, DJS, AP, AZ, VP, DRJ, ARL, SW, LK, KF, GK, AR, KL, RRL, JC, JG, AB, JL,  
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50

51 709 MP, AK, PP, JG, Mauro M, CM, GB, IV, VC, JW, ZK, MB, Markus M, GN, EK, KJ, CHN, PJN,  
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53 710 STE, DS, TT . All authors agreed on submitting this last version of the manuscript to the journal.  
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3 712 **Acknowledgments**  
4

5 713 We thank Ms. Anu Eräkanto and Ms. Judith Klecki for technical support.  
6  
7  
8 714

9  
10 715 **Disclosures**  
11

12 716 TT: Academic grants from the European Union, National Stroke Research Institute of Australia,  
13

14 717 Sahlgrenska University Hospital, Sigrid Juselius Foundation, University of Gothenburg, and  
15

16 718 Wennerström Foundation. Study contracts with Bayer, Boehringer Ingelheim, Bristol Myers  
17

18 719 Squibb, and Portola Pharm. Personal fees from Bayer, Boehringer Ingelheim, Bristol Myers  
19

20 720 Squibb, Lumosa Pharmaceuticals, and Portola Pharmaceuticals. TT received speaker's fees from  
21

22 721 the University of Donau, Krems, Austria. He holds patents on a treatment aiming to avoid post-  
23

24 722 thrombolytic brain edema and intracerebral hemorrhage in stroke (method to prevent brain edema  
25

26 723 and reperfusion injury; method to prevent post-thrombolytic hemorrhage formation).  
27

28 724 STE has received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim and  
29

30 725 Daiichi-Sankyo. He has served on scientific advisory boards for Bayer, Boehringer Ingelheim,  
31

32 726 BMS/Pfizer, and MindMaze and on the editorial board of Stroke. His institutions have received  
33

34 727 an educational grant from Pfizer, compensation from Stago for educational efforts and research  
35

36 728 support from Daiichi-Sankyo, the Science Funds [Wissenschaftsfonds] of the University Hospital  
37

38 729 Basel, the University Basel, the "Freiwillige Akademische Gesellschaft Basel", the Swiss Heart  
39

40 730 Foundation, and the Swiss National Science Foundation.  
41

42 731 PL has received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim, and  
43

44 732 has served on scientific advisory boards for Bayer, Boehringer Ingelheim, Pfizer/BMS, Amgen,  
45

46 733 and Medtronic. His institutions have received research support from Bayer, and Sanofi, the  
47

48 734 Science Funds [Wissenschaftsfonds] of the University Hospital Basel, the Swiss Heart  
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3 735 Foundation, and the Swiss National Science Foundation, and the University Hospital Basel  
4  
5 736 foundation “propatient”.  
6  
7 737 CHN has received funding for travel or speaker honoraria from Bayer, Boehringer Ingelheim,  
8  
9 738 Pfizer Pharma, Bristol-Myers Squibb, Gore and Ass. and Sanofi. His institutions have received  
10  
11 739 research support or grants from the German Federal Ministry of Research and Education (BMBF)  
12  
13 740 namely the “Center for Stroke Research Berlin, CSB”, the “Deutsches Zentrum für Herz-  
14  
15 741 Kreislauf Forschung (DZHK)”, “Deutsches Zentrum für neurodegenerative Erkrankungen  
16  
17 742 (DZNE)”.  
18  
19 743 SW has received speaker honoraria from Amgen, travel honoraria from Bayer and a research  
20  
21 744 grant from Boehringer Ingelheim and academic grants from the Swiss National Science  
22  
23 745 Foundation, the UZH (Clinical Research Priority Program Stroke), the Swiss Heart foundation  
24  
25 746 and the Olga Mayenfish foundation.  
26  
27 747 AZ has received speaker fees and consulting fees from Boehringer-Ingelheim, Medtronic,  
28  
29 748 Cerenovus and advisory board from Daiichi Sankyo and Boehringer-Ingelheim and Stryker.  
30  
31 749 MB is on the editorial board for Springer as Co-editor of "Clinical Neuroradiology". He serves  
32  
33 750 on advisory boards for Boehringer, Vascular Dynamics and BBraun. He received speaker  
34  
35 751 honoraria from Guerbet, Bayer, Novartis, Codman, Roche, Teva, Grifols and Merck. He received  
36  
37 752 research support from Novartis, Guerbet, Siemens, Hopp foundation, the European Union, and  
38  
39 753 from Deutsche Forschungs Gesellschaft.  
40  
41 754 MM is consultant for Acandis, Cerenovus, Medtronic, MicroVention, Route92, Stryker. He  
42  
43 755 received research support from Balt, MicroVention, Siemens, Stryker.  
44  
45 756 PR is on scientific advisory boards for Bayer and Boehringer-Ingelheim not in relation to the  
46  
47 757 submitted manuscript. He received funding for travel or speaker honoraria from SITS, and lecture  
48  
49 758 fees and travel compensation from Boehringer Ingelheim, Bayer, BMS, Pfizer. He is on the  
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3 759 editorial board of the journal *Stroke* as Associate editor (since 2010), of the journal  
4  
5 760 *Gefäßchirurgie* (editor since 2014), and of the *ESO-Journal* (Editor since 2015). The University  
6  
7 761 of Heidelberg received research support from Boehringer Ingelheim for the ECASS 4 study, and  
8  
9 762 funding from the German research foundation for the SPACE-2 study.  
10  
11  
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3 **1031 Table 1. Universal standards and requirements for the databases and centers contributing**  
4 **1032 to the EVA-TRISP registry\*.**

- 5 1033  
6 1034 - Prospective registry of consecutive patients with systematic check-up of missing cases.  
7 1035 - Comprehensive collection of baseline characteristics according to consensus definitions stated  
8 1036 in this and the previous methodology papers.  
9 1037 - Prospective assessment of hemorrhagic complications (symptomatic intracerebral hemorrhage  
10 1038 according to ECASS II criteria) and functional outcome at 3 and 12 months (according to the  
11 1039 modified Rankin Scale; either telephone interview, postal questionnaire, or follow-up visit).  
12 1040 - Approval of institutional review board to maintain the respective EVT database and to obtain 3-  
13 1041 and 12-month follow-up data.  
14 1042 - EVA-TRISP centers are comprehensive stroke centers with high-volume EVT applications -  
15 1043 typically university hospitals or closely affiliated to university hospitals.  
16 1044 - Treatment of acute ischemic stroke patients with EVT according to guidelines valid at the  
17 1045 relevant time or documentation of deviation therefrom.  
18 1046

19 1047 \* EVA-TRISP welcomes participation and project proposals of further centers fulfilling the  
20 1048 commitment and the outlined requirements.  
21 1049

**Table 2. EVA-TRISP centers, time period, number of endovascular treatments done, and population-base for EVT (in alphabetical order).**

City	No of stroke EVT (Jan 2015 to Dec 2019)
Amsterdam	864
Basel	413
Belgrade	136 <sup>1</sup>
Berlin	480 <sup>2</sup>
Bern	1422
Bremen	Estimation: 200/year
Brescia	412
Bologna	395
Goettingen	396
Gothenburg	1097
Heidelberg	1500
Helsinki	796 <sup>2</sup>
Jerusalem	249
Larissa	-
Lausanne	732
Lille	1806
Modena	489
Munich	600
St. Gallen	490
Zurich	Estimation: 500

<sup>1</sup>Jan 2018-Dec 2019

<sup>2</sup>Nov 2015-Dec 2019



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3 1058 **Figure 1.** EVA-TRISP centers.  
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For peer review only

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3 **APPENDIX 1: EVA-TRISP Investigators (in alphabetical order by country)**  
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8 **Finland (1):** Sami Curtze, Kimmo Lappalainen, Nicolas Martinez-Majander, Jukka Putaala,  
9  
10 Gerli Sibolt, Daniel Strbian, Silja Rätty, Turgut Tatlisumak, Marjaana Tiainen (Helsinki  
11  
12 University Hospital)  
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15  
16  
17 **France (1):** Nicolas Bricout, Marie Bodenant, Regis Bordet, Charlotte Cordonnier, Nelly  
18  
19 Dequatre, Hilde Hénon, Didier Leys, Anne-Marie Mendyk (University Lille North de France)  
20  
21  
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23  
24 **Germany (5):** Andreas Kastrup, Panagiotis Papanagiotou (University Hospitals Bremen-Mitte  
25  
26 and Bremen-Ost); Tim-Bastian Braemswig, Hebung Erdur, Christian H Nolte, Regina von  
27  
28 Rennenberg, Jan F Scheitz, Georg Bohner (Charité-Universitätsmedizin, Berlin); Alex Brehm,  
29  
30 Jan Liman, Marios Psychogios (University Medical Center Goettingen); Martin Bendszus,  
31  
32 Christian Hametner, Markus Möhlenbruch, Peter A Ringleb (University Hospital Heidelberg);  
33  
34 Katharina Feil, Lars Kellert, Clemens Küpper (University Hospital Munich LMU)  
35  
36  
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39

40 **Greece (1):** George Ntaios, Dimitrios Sigris, Ioannis Ioannidis George Karagiorgas, Eftychia  
41  
42 Kapsalaki, Marianna Vlychou (University of Thessaly)  
43  
44  
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47 **Israel (1):** Jose Cohen, John Gomori, Ronen R Leker (Hadassah-Hebrew University Medical  
48  
49 Center, Jerusalem)  
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54 **Italy (3):** Mauro Magoni, Alessandro Pezzini (University Hospital Brescia); Guido Bigliardi,  
55  
56 Luca Verganti, Stefano Vallone, Stefania Maffei (University Hospital Modena), Andrea Zini,  
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3 Luigi Simonetti, Mauro Gentile, Luigi Cirillo, Ludovica Migliaccio (IRCCS Istituto di Scienze  
4 Neurologiche di Bologna)  
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10 **The Netherlands (1):** M Irem Baharoglu, Sophie van den Berg, Paul J Nederkoorn, Yvo B Roos,  
11 Fianne HM Spaander, Sanne M Zinkstok, Thomas P Zonneveld, Charles Majoie (Academic  
12 Medical Center Amsterdam)  
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19 **Serbia (1):** Mirjana Arsenijevic, Ivana Berisavac, Marko Ercegovac, Dejana R Jovanovic, Visnja  
20 Padjen, Predrag Stanarcevic, Maja Stefanovic Budimkic, Tamara Svabic Medjedovic, Ivan  
21 Vukasinovic, Vladimir Cvetic (Clinical Centre of Serbia, Belgrade)  
22  
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28 **Sweden (1):** Margareta Abrahamson, Arne Allard, Monica Argus, Anke Brederleu, Erik Ceder,  
29 Maria Davidson, Niclas Dehlfors, Dennis Dunker, Torsteinn Gunnarsson, Lukas Holmegaard,  
30 Mikael Jerndal, Susanna Johansson, Katarina Jood, Camilla Karlsson, Jan-Erik Karlsson, Birgitta  
31 Leiram, Miroslav Malac, Inger Nilsson, Annika Nordanstig, Petra Redfors, Alexandros Rentzos,  
32 Turgut Tatlisumak (Sahlgrenska University Hospital, Gothenburg)  
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42 **Switzerland (5):** Leo H Bonati, Stefan T Engelter, Joachim Fladt, Henrik Gensicke, Philippe A  
43 Lyrer, Gian Marco De Marchis, Nils Peters, Alexandros Polymeris, Sebastian Thilemann,  
44 Christopher Traenka (University Hospital Basel); Marcel Arnold, Urs Fischer, Jan Gralla, Mirjam  
45 R Heldner, Hakan Sarikaya, David J Seiffge, Roland Wiest (University Hospital Bern); Olivier  
46 Bill, Ashraf Eskandari, Patrik Michel, Gaia Sirimarco (Hospitalier Universitaire Vaudois,  
47 Lausanne); Georg Kägi, Johannes Weber (Kantonsspital St. Gallen); Zsolt Kulcsar, Andreas R  
48 Luft, Susanne Wegener (University Hospital Zurich)  
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## APPENDIX 2. EVA-TRISP DATABASE DOMAINS AND ITEMS

The exact list of available variables may slightly differ between centers according to the judgment of local ethics committees.

### Patient history

- Age
- Sex
- Pre-stroke mRS
- Independent prior to stroke (Y/N)
- Risk factor atrial fibrillation present and known (Y/N)
- Risk factor diabetes present and known (Y/N) (Y/N)
- Risk factor hypertension present and known(Y/N)
- Risk factor hypercholesterolemia present and known (Y/N)
- Risk factor coronary artery disease present and known(Y/N)
- Risk factor prior ischemic stroke (clinical diagnosis) (Y/N)
- If prior ischemic stroke, prior treatment with IVT/EVT (Y/N)
- Risk factor current smoking (or stopped <2y) (Y/N)
- Pre-IVT use of statins (Y/N as well as name and dosage)
- Pre-IVT use of antihypertensive (Y/N as well as name and dosage)
- Pre-IVT use of antiplatelets (Y/N as well as name and dosage)
- Pre-IVT use of anticoagulants (Y/N as well as name and dosage)
- All medications (name and dosage as free text)

## Pre-hospital

- Date of stroke onset (last seen well)
- Time of stroke onset (last seen well)
- Date of stroke onset (first seen sick)
- Time of stroke onset (first seen sick)
- Stroke onset witnessed? (Y/N)
- Wake-up stroke? (Y/N)
- Epileptic seizure at stroke onset (Y/N)

## Admission

- Date of hospital arrival
- Time of hospital arrival
- Was patient transferred from another hospital? (Y/N)
- IVT administered at other hospital? (Y/N)
- NIHSS at admission
- Systolic blood pressure on admission [mmHg]
- Diastolic blood pressure on admission [mmHg]
- Weight (exact / estimated)
- Height (exact / estimated)
- Glucose on admission [mmol/l]
- Creatinine on admission [umol/l]

- International Normalized Ratio prior to IVT (point of care test / actual lab value)
- If direct oral anticoagulants (DOAC), specific assay/level of DOAC
- Platelets on admission  $\times 10^9$  [/l]
- Hemoglobin on admission [g/dl]
- Leukocytes on admission  $\times 10^9$  [/l]
- C-Reactive Protein on admission [mg/l]

#### Acute interventions

- Type of intervention (IVT, bridging, EVT)
- Date of IVT administration
- Time of IVT administration
- Dosage of rtPA IVT (0.6 mg/kg, 0.9 mg/kg, <50% of dose or complete)
- Angioedema related to IVT (Y/N)
- Exclusion criteria IVT (received IVT, delays, major prestroke handicap, imaging contraindication, bleeding risk, stroke missed/uncertain, other)
- Exclusion criteria IVT [free text]
- Date of EVT groin puncture
- Time of EVT groin puncture
- Intra-arterial thrombolytic drug (Y/N)
- Name and dosage of intra-arterial thrombolytic drug [free text]
- General anesthesia during EVT (Y/N)

- Type of endovascular treatment (none, stent retriever, aspiration, distal retriever, distal aspiration, Balloon angioplasty, permanent intracranial stent, extracranial stent, other [combination possible])
- Number of attempts for each treatment
- Name of device(s)
- Tandem stenosis/occlusion present (Y/N)
- Extracranial thrombectomy (no, ICA, VA)
- Extracranial permanent stent (no, ICA, VA)
- Only attempt to perform EVT
- EVT stopped early because (initiated, but access-to-clot-problems, tried, but artery already recanalized, other)
- EVT stopped early reason [free text]
- EVT complications (no, vessel perforation, vasospasm, dissection, SAH/ICH, device detachment/misplacement, embolization to new territory, access-site complications, early reocclusion, other [free text] [combination possible])
- Time of EVT end of procedure

### Imaging

- Type of baseline image (none, CT, MR)
- Date of baseline image
- Time of baseline image



- 1
- 2
- 3 • Territory of infarction (ICA, MCA, ACA, PCA, Cerebellum, Brainstem [combination
- 4 possible]
- 5
- 6
- 7
- 8 • Side of infarction (left anterior circulation, right anterior circulation, posterior circulation
- 9 [combination possible]
- 10
- 11
- 12
- 13 • Anterior circulation ASPECTS on baseline image 0-10
- 14
- 15 • Posterior circulation ASPECTS on baseline image 0-10
- 16
- 17
- 18 • Early ischemic changes in suspected area (focal parenchymal hypoattenuation, loss of
- 19 gray-white matter differentiation, focal edema manifested by sulcal or ventricular
- 20 effacement) (Y/N)
- 21
- 22
- 23
- 24 • Occluded vessel with hyperdense artery sign (-> column CD) (Y/N)
- 25
- 26
- 27
- 28 • Type of baseline angiography (none, CTA, MRA)
- 29
- 30 • Site of main intracranial occlusion on baseline angiography (none, ICA-I, ICA-L/T, prox
- 31 M1, distal M1, M2, ACA, PCA, BA, VA)
- 32
- 33 • Other occlusion site, please specify [free text]
- 34
- 35
- 36 • Additional vessel occlusion (y/n)
- 37
- 38 • If yes, location of additional vessel occlusion
- 39
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- 42 • In case of intracranial large vessel occlusion in the anterior circulation: collaterals on
- 43 baseline angiography if assessable (TAN Score 0-3)
- 44
- 45
- 46 • Relevant stenosis (>50% NASCET)/occlusion of extracranial ICA on baseline angiography
- 47 (Y/N)
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- 51 • Relevant stenosis (>50% NASCET)/occlusion of extracranial VA on baseline angiography
- 52 (Y/N)
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- 3 • Type of baseline perfusion modality (none, CTP, MRP)
- 4
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- 6 • Mismatch ratio according to local modalities (Y/N)
- 7
- 8 • Total perfusion lesion/infarct core mismatch ratio visually on baseline perfusion image
- 9
- 10 (f.i. 1.2 = perfusion lesion is 20% larger than core) (number)DSA (Y/N)
- 11
- 12
- 13 • In case of intracranial large vessel occlusion in the anterior circulation: collaterals on DSA
- 14
- 15 (ASITN/SIR grading)
- 16
- 17
- 18 • Complete recanalization on DSA (mTICI=2b/3) (Y/N)
- 19
- 20 • Date of recanalization on DSA
- 21
- 22
- 23 • Time of recanalization on DSA
- 24
- 25
- 26
- 27

#### 28 Follow up

- 29
- 30 • Type of first follow-up native image (none, NCCT, MRI)
- 31
- 32 • Date of follow-up image
- 33
- 34
- 35 • Time of follow-up image
- 36
- 37
- 38 • Type of first follow-up vessel imaging (none, CTA, MRA-TOF, MRA-CE, ultrasound)
- 39
- 40 • Date of follow-up vessel imaging
- 41
- 42 • Time of follow-up vessel imaging
- 43
- 44
- 45 • Complete recanalization on follow-up vessel imaging (CTA/MRA/US) (Y/N)
- 46
- 47 • mTICI
- 48
- 49
- 50 • Any intracerebral hemorrhage (ICH)
- 51
- 52 • Fatal ICH
- 53
- 54
- 55 • Symptomatic ICH (ECASS-2 criteria) (Y/N)
- 56
- 57
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- 60

- Other ICH (SAH, SDH, etc.) [free text]
- NIHSS after 24h
- mRS after 3 months
- Recurrent ischemic stroke or TIA within 3 months (no, TIA(s), stroke(s) (if TIA and stroke, count stroke)
- mRS after 1 year

#### Other

- Modified TOAST (LAA, CE (including PFO), SAO, other, more than one, undetermined, stroke mimic
- Rare specific stroke causes to be studied in more detail (cervical artery dissection, intracranial artery dissection, endocarditis, vasculitis, coagulopathies)

### Appendix 3: Names of the ethics committees

City	Ethics committees
Amsterdam	Anonymized registry based research does not need ethical approval in The Netherlands
Basel	The ethics committee Basel (Ethikkommission Nordwest- und Zentralschweiz (EKNZ))
Belgrade	The ethics committee of Clinical Centre of Serbia
Berlin	The ethical review committee of the Charité–University Medicine Berlin
Bern	The cantonal ethics Committee Bern
Bremen	The local ethic committee of the Ärztekammer Bremen
Bologna	Local regulations do not require approval by the ethics board for observational studies using registry data in IRCCS (Institute for Treatment and Research)
Brescia	EC ASST spedali civili university hospital Brescia
Goettingen	The ethics committee in Goettingen approved it (No.: 16/2/16).
Gothenburg	The regional ethical board of Gothenburg
Heidelberg	Ethik kommission der Medizinischen Fakultät Heidelberg
Helsinki	Local regulations do not require approval by the ethics board for retrospective studies using registry data
Larissa	Participation in EVA-TRISP does not require ethics approval in Greece
Jerusalem	Hadassah Medical Organization (HMO) Jerusalem
Lausanne	The ethics commission for research on humans of the Canton of Vaud has approved the scientific use data from the ASTRAL registry
Lille	Comité de Protection des Personnes Nord Ouest IV Lille, France
Modena	The study was approved by local EC called "Comitato Etico Area Vasta Emilia Nord"
Munich	The ethics committee of the chamber of physicians at Ludwig-Maximilians University LMU Munich
St. Gallen	Each study project has been approved by the ethical committee
Zurich	The ethics commission Zurich, Switzerland.