Full Consensus documents from the ESO-Karolinska Stroke Update Conference, Stockholm 11-13 November 2018

Conference chair: Niaz Ahmed and Thorsten Steiner for the ESO-KSU session participants.

Authors: Niaz Ahmed[1], Heinrich Audebert[2], Guillaume Turc[3], Charlotte Cordonnier[4], Hanne Christensen[5], Simona Sacco[6], Else Charlotte Sandset[7], George Ntaios[8], Andreas Charidimou[9], Danilo Toni[10], Christian Pristipino[11], Martin Köhrmann[12], Joji Kuramatsu[13], Götz Thomalla[14], Robert Mikulik[15], Gary A Ford[16], Joan Martí-Fàbregas[17], Urs Fischer[18], Magnus Thoren[1], Erik Lundström[19], Gabriel JE Rinkel[20], H. Bart Van Der Worp[20], Marius Matusevicius[21], Georgios Tsivgoulis[22], Haralampos Milionis[23], Marta Rubiera[24], Robert Hart[25], Tiago Moreira[1], Maria Lantz[1], Christina Sjöstrand[1], Grethe Andersen[26], Peter Schellinger[27], Konstantinos Kostulas[1], Katharina Sunnerhagen[28], Boris Keselman[1], Eleni Korompoki[29], Jan Purrucker[30], Pooja Khatri[31], William Whiteley[32], Eivind Berge[33], Michael Mazya[1] , Diederik WJ Dippel[34], Satu Mustanoja[35], Mads Rasmussen[36], Åsa Kuntze Söderqvist[37], Irene Escudero-Martínez[38]and Thorsten Steiner[39].

1. Department of Neurology, Karolinska University Hospital, and Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (NA Conference Chair).
2. Department of Neurology, Charité - Universitätsmedizin Berlin, Hindenburgdamm 30, 12203 Berlin, Germany. Center for Stroke Research, Charité - Universitätsmedizin Berlin, Berlin, Germany.
3. Department of Neurology, GHU Paris Psychiatrie et Neurosciences & Université de Paris & INSERM U1266, Paris, France.
4. Department of Neurology, Stroke Unit, Roger Salengro Hospital, 59037 Lille, France
5. Department of Neurology Neurology, Stroke Consultant at Bispebjerg & Frederiksberg Hospitals, Copenhagen, Denmark.
6. Department of Applied Clinical sciences and Biotechnology, Section of Neurology, University of L'Alquila, L'Alquila, Italy.
7. Department of Neurology, Oslo University Hospital, Oslo, Norway.
8. Department of Internal Medicine, Larissa University Hospital, School of Medicine, University of Thessaly, Biopolis, Larissa, Greece.
9. Department of Neurology, Massachusetts General Hospital Stroke Research Center, Harvard Medical School, Boston, MA, USA.
10. Emergency Department Stroke Unit Hospital Policlinico Umberto I, Dept. of Human Neurosciences, 'Sapienza' University, Rome, Italy.
11. Interventional Cardiology Unit San Filippo Neri-ASL RM1 Hospital, Rome, Italy.
12. Department of Neurology, Universitaetsklinikum Erlangen, Erlangen, Germany Department of Neurology, University Duisburg- Essen, Essen, Germany
13. Department of Neurology, University Hospital Erlangen, Erlangen, Germany.
14. Department of Neurology, University Medical Center Hamburg-Eppendorf, Germany.

15. International Clinical Research Centre and Department of Neurology, St. Anne's University Hospital in Brno and Medical Faculty, Masaryk University, Brno, Czech Republic
16. Oxford University Hospitals NHS Foundation Trust, University of Oxford, UK.
17. Department of Neurology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau (IIB Sant Pau), Barcelona, Spain.
18. Stroke Centre Bern, Clinical Trial Unit Bern, University of Bern, Bern, Switzerland.
19. Department of Neuroscience, Neurology, Uppsala University; Akademiska sjukhuset, Uppsala, Sweden.
20. Department of Neurology and Neurosurgery, Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands.
21. Karolinska Institute, Department of Clinical Neuroscience, Karolinska University Hospital, Stockholm, Sweden.
22. Second Department of Neurology, National & Kapodistrian University of Athens, Athens, Greece.
23. Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece.
24. Department of Neurology, Vall d'Hebron Hospital, Barcelona, Spain.
25. Population Health Research Institute, Hamilton Health Sciences, Hamilton, Ontario, Canada.
26. Department of Neurology, Aarhus University Hospital, Aarhus, Denmark.
27. Departments of Neurology and Neurogeriatry, John Wesling Medical Center Minden, Ruhr University Bochum, Minden, Germany
28. Clinical Neuroscience, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Sweden.
29. Department of Clinical Therapeutics, Medical School of Athens, Alexandra Hospital, Athens, Greece.
30. Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany.
31. Department of Neurology, University of Cincinnati Medical Center, USA.
32. Centre for Clinical Brain Sciences, University of Edinburgh, UK.
33. Department of Internal Medicine and Cardiology, Oslo University Hospital, Oslo, Norway
34. Erasmus MC University Medical Center, Rotterdam, the Netherlands.
35. Department of Neurology, Helsinki University, Central Hospital, Helsinki, Finland.
36. Department of Anaesthesia and Intensive Care, Section of Neuroanaesthesia, Aarhus University Hospital, Denmark
37. Department of Clinical Neuroscience, Karolinska Institutet and Department of Neuroradiology, Karolinska University Hospital, Stockholm, Sweden.
38. Department of Neurology, Virgen del Rocio University Hospital, Sevilla, Spain; Instituto de Biomedicina de Sevilla, Spain.
39. Department of Neurology, Klinikum Frankfurt Höchst, Frankfurt.
Department of Neurology, Heidelberg University Hospital, Germany (Conference Chair).

Corresponding author:

Niaz Ahmed, Department of Clinical Neuroscience, Karolinska Institutet,

Stroke Research Unit, Department of Neurology R2:03, Karolinska

University Hospital–Solna, SE-171 76 Stockholm, Sweden.

Email: niaz.ahmed@sll.se

The full document, which is available as online supplement contains background, issues, conclusions and references, used to establish ESO-Karolinska recommendations for each session (except for the short sessions).

Grading criteria: Strength of evidence defined by the Karolinska Stroke Update consensus meeting:

Ahmed, Niaz et al. "Recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 13-15 November 2016" European stroke journal vol. 2,2 (2017): 95-102.

Grade A evidence: Strong support from randomized controlled trials and statistical reviews (at least one randomized controlled trial plus one statistical review)

Grade B evidence: Support from randomized controlled trials and statistical reviews (one randomized controlled trial or one statistical review)

Grade C evidence: No reasonable support from randomized controlled trials, recommendations based on small randomised and/or non-randomised controlled trials evidence.

Session 1: Pre-hospital management, Patient selection

Chairs: Heinrich Audebert (Berlin) and Guillaume Turc (Paris) Secretary: Magnus Thoren (Stockholm).

The following Consensus Statement was (if approved) adopted by the 12th ESO Karolinska Stroke Update meeting on November 12th/13th, 2018.

The consensus statement was proposed by a writing committee (in alphabetical order: Dr Heinrich Audebert, Dr Urs Fischer, Dr Magnus Thoren and Dr Guillaume Turc) and proposed by the chairs of the session, Dr Heinrich Audebert (Germany) and Dr Guillaume Turc (France) and the session secretary Dr Magnus Thoren (Sweden), together with the speakers of the session, Dr Urs Fischer (Switzerland). The statement was then finally approved by the participants of the meeting, after listening to the different presentations.

Session 1 - Talk 1) What is proven (glyceryl trinitrate, oxygen, preconditioning, mobile stroke units)?

Speaker: *Heinrich Audebert (Berlin).*

1. For acute ischemic stroke patients: Does prehospital glyceryl trinitrate application improve outcome?
2. Does prehospital oxygen supply improve outcome in ischemic stroke patients
3. Does pre-conditioning lead to better outcomes in ischemic or hemorrhagic stroke.
4. For acute ischemic stroke patients: Do mobile stroke units reduce time to treatment?
5. For acute ischemic stroke patients: Do mobile stroke units improve outcome?

Background:

The majority of patients with acute stroke receive first aid and transport to hospital by emergency medical services (EMS). Pre-hospital management on ambulances is therefore usually the first phase of medical care. Over the last two decades, multiple clinical assessment instruments have been developed to improve identification of stroke patients by paramedics in order to deliver patients to stroke-ready hospitals services. In order to speed-up in-hospital work-up, pre-notification of stroke teams by ambulance crews has been recommended. With the lack of prehospital imaging however, the phase of pre-hospital care has traditionally not been regarded as a setting where specific treatment can be applied. This has changed with the implementation of CT scanners on ambulances and the introduction of neuroprotective strategies that have potential benefit in ischemic stroke without harm in hemorrhagic stroke.

For acute ischemic or hemorrhagic stroke patients: Does prehospital glyceryl trinitrate application improve outcome?

The search “stroke” and “nitroglycerin” | “glyceryl nitrate” |“nitric oxide” and “prehospital” | ”ambulance” resulted in one feasibility trial (RIGHT) conducted on ambulances using transdermal (patch) glyceryl trinitrate (GTN) in stroke patients with systolic blood pressure >140 mmHG and onset <4h[8]. The study was designed to investigate the feasibility and acceptability of trial conduction in

non-physician staffed ambulances. The study showed that paramedics could successfully enroll 41 of 80 originally planned patients with acute stroke into an ambulance-based trial and systolic blood pressure was lower with glyceryl nitrate patch application. Functional outcome was better in the GTN group with no significant differences in mortality and serious adverse events.

A systematic review and meta-analysis[9] from randomized trials analyzing the effects of GTN in stroke patients, mostly in the hospital setting but including the above-mentioned RIGHT trial, did not reveal any effect on clinical outcomes at day 90 in the entire cohort of included patients. However, there were beneficial shifts in the mRS and reduced death in the subgroup of patients randomized within 6 hours from stroke onset.

A large-scale randomized trial "Rapid Intervention with Glyceryl trinitrate in hypertensive stroke Trial-2" (RIGHT-2) trial has been just published. The results of this trial have shown that prehospital treatment with transdermal GTN does not seem to improve functional outcome in patients with presumed stroke. [10]

Recommendations:

There is currently no evidence to recommend the application of GTN in the prehospital field (Grade B).

Does prehospital oxygen supply improve outcome in ischemic stroke patients?

Hypoxemia is frequently observed in stroke patients. Sulter et al[11] report in an observational study that 63% of acute hemiparetic stroke patients developed oxygen desaturations below 94% during a 48h in-hospital monitoring period.

The search "stroke" and "oxygen" and "prehospital" | "ambulance" did not provide any prospective controlled studies.

A recent review and meta-analysis on effects of oxygen therapy on mortality and morbidity in acutely ill adults included five studies in acute stroke patients treated in-hospital[12]. Overall (including other conditions such as critical care and cardiac diseases), higher target oxygen supply increased the relative risk of in-hospital death and mortality during follow-up without any significant improvement in other patient-important outcomes. The effects in acute stroke patients were similar to the entire group of patients. It is important to note that the majority of studies excluded patients with hypoxemia at baseline and oxygen supplementation is therefore still recommended to a titrated dose of 94%[13]. The two largest randomized trials in stroke patients[14, 15] did not show any benefit regarding functional outcome. The Norwegian trial of Ronning et al[14] showed an increased 7-month mortality in the pre-specified subgroup of patients with severe stroke.

The Penumbral Rescue by Normobaric O2 Administration in Patients With Ischemic Stroke and Target Mismatch ProFile (PROOF) trial (NCT03500939) is currently underway and investigates high-flow 100% oxygen inhalation via a sealed non-breather face-mask with reservoir. However, this trial will be conducted during in-hospital care.

Recommendations:

There is no evidence available from pre-hospital trials. Results from one meta-analysis of trials performed during in-hospital care suggest that oxygen treatment is harmful do not support the use of oxygen supply in non-hypoxemic patients in pre-hospital stroke management (Grade C).

Does pre-/perconditioning lead to better outcomes in ischemic or hemorrhagic stroke?

Remote ischemic preconditioning is neuroprotective in animal models[16, 17] of acute cerebral ischemia and remote ischemic perconditioning reduced infarct size in acute ST-segment elevation myocardial infarction[18].

The search "stroke" and "preconditioning | perconditioning" and "prehospital" | "ambulance" yielded one randomized clinical study[19]. The overall results were neutral but adjusted tissue survival analysis suggested that prehospital remote perconditioning with 4 cycles of inflation and deflation of a blood pressure cuff reduced tissue risk of infarction (based on PWI/DWI mismatch).

Several randomized controlled trials investigating the effects of remote ischemic preconditioning are currently underway. Some evaluate the effect on change in Diffusion-Weighted Imaging infarction volume (e.g. NCT02189928, RESCUE-BRAIN, in-hospital setting) and others investigate effects on functional outcome (e.g. NCT03375762, REMOTE-CAT and NCT03481777, RESIST, both pre-hospital setting)

Recommendations:

There is currently not sufficient evidence to recommend remote ischemic perconditioning in prehospital stroke care (Grade C).

For acute ischemic stroke patients: Do mobile stroke units reduce time to treatment?

The search resulted in two unblinded randomized controlled[1, 2] trials and two registry based studies[3, 5] that compared time from alarm (dispatch) to treatment (start of intravenous thrombolysis) in patients who were either cared on mobile stroke units (MSU) or in conventional ambulances. All mentioned studies used MSU models specific to local settings. In the two German randomized trials, the MSUs were staffed with a neurologist trained as an emergency physician, a paramedic and a radiology technician/neuroradiologist. The MSU concept intends to start thrombolysis at the scene (before patient transport to hospital).

Median reduction in alarm-to-needle time ranged from 24 to 41min.

The largest trial (PHANTOM-S)[2] reported an increase in thrombolysis rate from 21% to 33% of ischemic stroke patients and an almost 10-fold higher proportion of patients treated within 60 minutes from onset (10.1% versus 1.1%)[4].

For acute ischemic stroke patients: Do mobile stroke units improve outcome?

The search resulted in two randomized controlled trials that were neither designed nor powered to show a difference in functional outcome. The reported outcomes at 7 days were similar between patients treated on MSU or in conventional EMS regarding mortality[1, 2], modified Rankin Scale (mRS)[1] and discharge home[2]. A registry-based comparison between patients treated either on the Stroke Emergency Mobile or on normal ambulances in Berlin (total N = 658) yielded a non-significantly better disability free outcome (mRS 0-1) (OR: 1.40; 95%-CI: 1.00-1.97, primary outcome) and a significantly better functional outcome over the full range of the mRS ($p<0.00001$) in adjusted regression analyses[5]. Two large scale randomized controlled trials investigating functional outcome 3 months after stroke are underway[6, 7]. Cost-effective estimates based on the two randomized

controlled trials on projecting improved outcomes by earlier start of thrombolysis suggested reasonable cost-effectiveness potentials.[20,21]

Recommendations:

Mobile stroke units can be used to effectively reduce time to intravenous thrombolysis that is related to better outcome. However, there is currently not sufficient evidence whether and to what extent mobile stroke units improve outcome of acute ischemic stroke patients. Further evaluation is needed with regard to adaptation of the MSU concept to different health care settings.

Because of costs and resource use of mobile stroke units, their routine use can currently not be recommended (Grade C).

References

1. Walter S, Kostopoulos P, Haass A, Keller I, Lesmeister M, Schlechtriemen T, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: A randomised controlled trial. *Lancet Neurol*. 2012;11:397-404
2. Ebinger M, Winter B, Wendt M, Weber JE, Waldschmidt C, Rozanski M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: A randomized clinical trial. *JAMA*. 2014;311:1622-1631
3. Taqui A, Cerejo R, Itrat A, Briggs FB, Reimer AP, Winners S, et al. Reduction in time to treatment in prehospital telemedicine evaluation and thrombolysis. *Neurology*. 2017;88:1305-1312
4. Ebinger M, Kunz A, Wendt M, Rozanski M, Winter B, Waldschmidt C, et al. Effects of golden hour thrombolysis: A prehospital acute neurological treatment and optimization of medical care in stroke (phantom-s) substudy. *JAMA Neurol*. 2015;72:25-30
5. Kunz A, Ebinger M, Geisler F, Rozanski M, Waldschmidt C, Weber JE, et al. Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: An observational registry study. *Lancet Neurol*. 2016;15:1035-1043
6. Ebinger M, Harmel P, Nolte CH, Grittner U, Siegerink B, Audebert HJ. Berlin prehospital or usual delivery of acute stroke care - study protocol. *Int J Stroke*. 2017;12:653-658
7. Yamal JM, Rajan SS, Parker SA, Jacob AP, Gonzalez MO, Gonzales NR, et al. Benefits of stroke treatment delivered using a mobile stroke unit trial. *Int J Stroke*. 2018;13:321-327
8. Ankolekar S, Fuller M, Cross I, Renton C, Cox P, Sprigg N, et al. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: The rapid intervention with glyceryl trinitrate in hypertensive stroke trial (right, isrctn66434824). *Stroke*. 2013;44:3120-3128
9. Bath PM, Woodhouse L, Krishnan K, Anderson C, Berge E, Ford GA, et al. Effect of treatment delay, stroke type, and thrombolysis on the effect of glyceryl trinitrate, a nitric oxide donor, on outcome after acute stroke: A systematic review and meta-analysis of individual patient from randomised trials. *Stroke Res Treat*. 2016;2016:9706720
10. The RIGHT-2 investigators. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. Lancet 2019; 393: 1009–20.
11. Sulter G, Elting JW, Stewart R, den Arend A, De Keyser J. Continuous pulse oximetry in acute hemiparetic stroke. *J Neurol Sci*. 2000;179:65-69
12. Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (iota): A systematic review and meta-analysis. *Lancet*. 2018;391:1693-1705

13. Glober NK, Sporer KA, Guluma KZ, Serra JP, Barger JA, Brown JF, et al. Acute stroke: Current evidence-based recommendations for prehospital care. *The western journal of emergency medicine*. 2016;17:104-128
14. Ronning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke*. 1999;30:2033-2037
15. Roffe C, Nevatte T, Sim J, Bishop J, Ives N, Ferdinand P, et al. Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke: The stroke oxygen study randomized clinical trial. *JAMA*. 2017;318:1125-1135
16. Hoda MN, Siddiqui S, Herberg S, Periyasamy-Thandavan S, Bhatia K, Hafez SS, et al. Remote ischemic perconditioning is effective alone and in combination with intravenous tissue-type plasminogen activator in murine model of embolic stroke. *Stroke*. 2012;43:2794-2799
17. Hahn CD, Manlhiot C, Schmidt MR, Nielsen TT, Redington AN. Remote ischemic per-conditioning: A novel therapy for acute stroke? *Stroke*. 2011;42:2960-2962
18. McLeod SL, Iansavichene A, Cheskes S. Remote ischemic perconditioning to reduce reperfusion injury during acute st-segment-elevation myocardial infarction: A systematic review and meta-analysis. *Journal of the American Heart Association*. 2017;6
19. Hougaard KD, Hjort N, Zeidler D, Sorensen L, Norgaard A, Hansen TM, et al. Remote ischemic perconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: A randomized trial. *Stroke*. 2014;45:159-167
20. Dietrich M, Walter S, Ragoschke-Schumm A, Helwig S, Levine S, Balucani C, Lesmeister M, Haass A, Liu Y, Lossius HM, Fassbender K. Is prehospital treatment of acute stroke too expensive? An economic evaluation based on the first trial. *Cerebrovasc Dis.* 2014;38(6):457-63
21. Gyrd-Hansen D, Olsen KR, Bollweg K, Kronborg C, Ebinger M, Audebert HJ. Cost-effectiveness estimate of prehospital thrombolysis: results of the PHANTOM-S study. *Neurology*. 2015 Mar 17;84(11):1090-7.

Session 1 - Talk 2) Prehospital identification of candidates for mechanical thrombectomy

Speaker: *Urs Fischer (Bern).*

1. Can clinical scores reliably predict a large artery occlusion (LAO) in unselected patients with a suspected acute ischaemic stroke (AIS) in the prehospital setting?
2. Different clinical scores have been designed to predict LAO in AIS patients: are all scores equally predictive or are several scores superior to others?
3. Should cut-off levels be recommended to triage patients?

Background:

Randomized controlled trials have consistently shown that mechanical thrombectomy with stent retrievers with additional administration of intravenous thrombolysis when indicated is superior to intravenous thrombolysis alone in anterior circulation stroke patients with large artery occlusion (LAO). Because the effect of MT diminishes over time, stroke systems of care need to rapidly identify

patients with LAO[1]. LAOs can be reliably detected during emergency department stroke assessments by computed tomography angiography (CTA) or magnetic resonance angiography (MRA), but these techniques are not routinely available in the prehospital setting. Therefore, a rapid clinical identification of patients with LAO is crucial for patient selection and immediate referral to centers with facilities for mechanical thrombectomy (MT), i.e. CSC.

Within the last few years, several clinical scores have been designed to predict LAO in the prehospital phase. These scales should help paramedics triaging prehospital patients who test positive in the field for a suspected LAO directly to a CSC, potentially bypassing non-MT centers. However, prehospital studies assessing the diagnostic accuracy of LAO prediction scales for identifying LAO in patients with suspected acute ischaemic stroke (AIS) are lacking. Furthermore, no randomized trial evaluating such scales for prehospital triage has been completed so far.

Can clinical scores reliably predict a large artery occlusion (LAO) in unselected patients with a suspected acute ischaemic stroke (AIS) in the prehospital setting?

First generation prehospital stroke prediction scales (i.e. Cincinnati Prehospital Stroke Scale (CPSS)[2], Face-Arm-Speech-Time (FAST)[3], and the Los Angeles Prehospital Stroke Screen (LAPSS)[4]) have facilitated triage of suspected stroke patients - regardless of LAO status - to centers capable of providing intravenous thrombolysis, whereas second generation prehospital stroke prediction scales (Rapid Arterial Occlusion Evaluation Scale (RACE)[5], Cincinnati Stroke Triage Assessment Tool (C-STAT)[6], Los Angeles Motor Scale (LAMS)[7], Field Assessment Stroke Triage for Emergency Destination (FAST-ED)[8], Vision, Aphasia, and Neglect (VAN)[9], 3-Item Stroke Scale (3I-SS)[10], Gaze-Face-Arm-Speech-Time (G-FAST)[11], Prehospital Acute Stroke Severity (PASS), Emergency Medical Stroke Assessment (EMSA)[12]) aim to identify stroke patients with LAOs rather than all ischemic stroke patients.[13]

An ideal LAO prediction score should be short and simple, should include items that are associated with LAO, should be easy to teach to prehospital personnel and finally easy to use in the prehospital setting with an overall high specificity and sensitivity for a LAO. Additionally, the scale should be validated by prehospital providers in a cohort of suspected stroke patients, inclusive of stroke mimics, ICH and TIA.[2] However, most second generation LAO prediction scores have several limitations: almost all scales have not been derived from a prospective cohort of suspected strokes in the prehospital setting, including patients with intracerebral haemorrhages and stroke mimics, with every patient undergoing CTA or MRA imaging on emergency department arrival.[2]

A recent systematic review assessing the accuracy of LAO prediction instruments[14] found that the most frequently externally validated LAO prediction instruments were the NIHSS, CPSSS, LAMS, and RACE.[3] Area under the ROC curve ranged from 0.70 to 0.85, indicating moderate to good discrimination of the presence versus absence of LAO in individual patients. In a meta-analysis, sensitivity was up to 87% and specificity up to 90%, however, no scale provided both high sensitivity and specificity. With a positive LAO prediction test, the probability of LAO (the positive predictive value) could be 50% to 60% (depending on the LAO prevalence in the population), but the probability of LAO with a negative test (the false negative rate) could still be ≥10%.

Recommendations:

Prehospital scales provide only a gross estimate of the presence or absence of a LAO. They are inadequate to exclude LAO with certainty and many triage positive patients may have no LAO (Grade C).

Different clinical scores have been designed to predict LAO in AIS patients: are all scores equally predictive or are several scores superior to others?

The authors of the above-mentioned systematic review failed to find convincing evidence for the superiority of any prediction instrument.[3] However, in most included studies, there was no direct comparison of different scales. The predictive accuracy of five different scales were compared in one population of stroke codes in which the prevalence of LAO was 15%, without any scale being superior.[15] There are important qualitative features of different scales beyond accuracy, such as simplicity.[2] At present, only a few LAO prediction scales have been studied in the prehospital suspected stroke patient population.

Recommendations:

Because none of the currently published scales has both high sensitivity and specificity and there is no evidence for the superiority of any prediction instrument, we cannot recommend the prioritization of one particular scale over the others. Further efforts are needed to prospectively test and validate the different scores in unselected patients with suspected stroke in the prehospital setting by paramedics (Grade C).

Should cut-off levels be recommended to triage patients?

Several published clinical scores to predict LAO appear to have sensitivity in the range of 75-80%, resulting in 20-25% of patients with large artery occlusion being missed at optimal score cut-off levels. At the same cut-off levels, 12-25% of triage positive patients would not have a large artery

occlusion. [16,17] If a high sensitivity cut-off is chosen specificity becomes low and vice versa. [16,17] However, the preferred cut-off level of any triage score is most likely to differ depending on geography, population density and hospital infrastructure. In the proximity of CSC, we suggest aiming for a highly sensitive triage tools in order to identify most patients with LAO. In areas with long distances to the next MT stroke center a high specificity to detect LAO might be reasonable in order to avoid unnecessary transports.

Recommendations:

Recommended cut-off level of any triage score depends on the geographic situation and hospital infrastructure. In the proximity of MT capable stroke centers, we suggest aiming for a highly sensitive triage tool in order to identify most patients with LAO. In areas with long distances to the next MT stroke center a high specificity to detect LAO is reasonable (Grade C).

References

1. Saver JL, Goyal M, Hill MD; HERMES Collaborators. Time to endovascular thrombectomy for acute stroke: reply. *JAMA.* 2017;317:1175–1176. doi: 10.1001/jama.2017.0373.
2. Brandler ES, Sharma M, Sinert RH, Levine SR. Prehospital stroke scales in urban environments: a systematic review. *Neurology.* 2014;82(24):2241–9.
3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018. doi: STR.0000000000000158.
4. Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying Stroke in the Field Prospective Validation of the Los Angeles Prehospital Stroke Screen (LAPSS). *Stroke.* 2000;31:71-76.
5. Zaidi SF, Shawver J, Espinosa Morales A, Salahuddin H, Tietjen G, Lindstrom D, et al. Stroke care: initial data from a county-based bypass protocol for patients with acute stroke. *J Neurointerv Surg.* 2017;9(7):631–5. https://doi.org/10.1136/neurintsurg-2016- 012476.
6. Katz BS, McMullan JT, Sucharew H, Adeoye O, Broderick JP. Design and validation of a prehospital scale to predict stroke se- verity: Cincinnati Prehospital Stroke Severity Scale. *Stroke.* 2015;46(6):1508–12.
7. Llanes JN, Kidwell CS, Starkman S, Leary MC, Eckstein M, Saver JL. The Los Angeles Motor Scale (LAMS): a new measure to characterize stroke severity in the field. *Prehosp Emerg Care.* 2004;8(1):46–50. doi:S1090312703002806.
8. Lima FO, Silva GS, Furie KL, Frankel MR, Lev MH, Camargo ECS et al. The Field Assessment Stroke Triage for Emergency Destination (FAST-ED): a Simple and Accurate Pre-Hospital Scale to Detect Large Vessel Occlusion Strokes. *Stroke.* 2016 Aug; 47(8): 1997–2002.
9. Teleb MS, Ver Hage A, Carter J, Jayaraman MV, McTaggart RA. Stroke vision, aphasia, neglect (VAN) assessment—a novel emer- gent large vessel occlusion screening tool: pilot study and comparison with current clinical severity indices. *J Neurointerv Surg* 2017 Feb; 9(2):122–126.

10. Singer OC, Dvorak F, du Mesnil de Rochemont R, Lanfermann H, Sitzer M, Neumann-Haefelin T. A simple 3-item stroke scale: comparison with the National Institutes of Health Stroke Scale and prediction of middle cerebral artery occlusion. *Stroke*.2005;36(4):773–6.

11. Clinical Selection Strategies to Identify Ischemic Stroke Patients With Large Anterior Vessel Occlusion Results From SITS-ISTR (Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Registry). *Stroke.* 2017;48:290-297.

12. Gropen TI, Boehme A, Martin-Schild S, Albright K, Samai A, Pishanidar S, et al. Derivation and validation of the Emergency Medical Stroke Assessment and comparison of Large Vessel Occlusion Scales. *J Stroke Cerebrovasc Dis.* 2017. doi:S1052– 3057(17)30569–4.

13. Keenan KJ, Kircher C, McMullan JT. Prehospital Prediction of Large Vessel Occlusion in Suspected Stroke Patients. *Curr Atheroscler Rep.* 2018 May 21;20(7):34.

14. Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, Towfighi A, Whiteley WN, Zahuranec DB; American Heart Association Stroke Council. Accuracy of Prediction Instruments for Diagnosing Large Vessel Occlusion in Individuals With Suspected Stroke: A Systematic Review for the 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke. *Stroke.* 2018;49:e111-e122.

15. Zhao H, Coote S, Pesavento L, Churilov L, Dewey HM, Davis SM et al. Large Vessel Occlusion Scales Increase Delivery to Endovascular Centers Without Excessive Harm From Misclassifications. *Stroke.* 2017 Mar;48(3):568-573. doi: 10.1161/STROKEAHA.116.016056.

16. Turc G, Maier B, Naggara O, Seners P, Isabel C, Tisserand M, et al. Clinical scales do not reliably identify acute ischemic stroke patients with large-artery occlusion. *Stroke.* 2016;47:1466-1472.

17. Heldner MR, Hsieh K, Broeg-Morvay A, Mordasini P, Buhlmann M, Jung S, et al. Clinical prediction of large vessel occlusion in anterior circulation stroke: Mission impossible? *Journal of Neurology*. 2016;263:1633-1640.

Session 1 - Talk 3) Drip-and-ship vs mothership for thrombectomy: What referral system works best for endovascular treatment?

Speaker: *Guillaume Turc (Paris).*

Background:

Different prehospital organizational models have been proposed for patients with acute ischaemic stroke who are potential candidates for mechanical thrombectomy (MT), the two most widely used being drip-and-ship and mothership.

What are the theoretical advantages and disadvantages of the drip-and-ship and mothership models?

Drip-and-ship model

Definition:
The drip-and-ship model consists of transferring the patient to the nearest Primary Stroke Center

(PSC) where intravenous thrombolysis (IVT) can be administered, followed by transfer to a Comprehensive Stroke Center (CSC) of patients candidates for mechanical thrombectomy (MT).

Advantages:

- Earlier treatment with intravenous thrombolysis (IVT) in eligible patients (approximately 20% of stroke codes and 40% of acute ischemic stroke patients within 4.5h after symptom onset).[1]
- Higher proportion of IVT because of more patients with acute stroke work-up completed within 4.5 hours.
- Improved selection of patients eligible for MT based on stroke severity and most importantly vascular neuroimaging,[2,3] ruling out patients with stroke mimics, intracerebral haemorrhage, or without large artery occlusion (LAO). In spite of such a clinical and imaging selection at the PSC, the rate of 'futile' transfers (patients transferred to the CSC but not treated with MT) remains as high as 40%.[4,5]
- Pre-interventional recanalization due to IVT, which occurs in up to 20% of LAO-related strokes but is strongly dependent on thrombus length and site of arterial occlusion.[6]

Disadvantages:

- Delay (or even denial) of MT due to in-hospital attention at the PSC and interhospital transfer.[7] Data from MT trials and registries show that time from onset to reperfusion is usually 1.5 to 2 hours longer for LAO patients under the drip-and-ship model, compared with the mothership model.[8,9] Delays in intrahospital care and interhospital transfers are associated with a lower probability of good outcomes among patients treated with MT.[9]
- Suboptimal identification of MT candidates among patients with onset that is unknown or beyond 6 hours because of lack of advanced imaging capability in many PSC's.
- Risk of transport-related complications .
- Emergency medical services (EMS) resource consumption for inter-hospital transfer (ambulance not available for other emergencies in the same area).

<u>Mothership model</u>

Definition: Direct transfer to a CSC, bypassing the nearest PSC.

Advantages:

- Earlier treatment with MT in eligible patients (approximately 10% of stroke codes and 25% of acute ischemic stroke patients within 6h after symptom onset).[1] In the HERMES collaboration, the benefit of MT over best medical therapy declined with longer time from symptom onset to arterial puncture, the absolute risk difference for mRS ≤2 being 39.2% at 3h, 30.2% at 6h and 15.7% at 8h, without reaching statistical significance for this last time point.[9]
- Higher proportion of patients treated with MT.[10,11]
- Availability of advanced diagnostic and therapeutic options at the CSC.

Disadvantages:

- Admission of patients not eligible for MT. Using current pre-hospital selection tools, this model would result in many endovascular ineligible patients transferred to a CSC.[12,13]

- Resource consumption at the CSC, especially since the time window for MT has been extended to 24h in very selected patients.[14] It has been reported that only 2.7% of ischemic stroke patients presenting within 24 h to a CSC met the DEFUSE-3 or DAWN criteria.[15] Furthermore, the sensitivity of clinical scales such as NIHSS to detect LAO dramatically decreases with time.[16]
- Delay or denial of IVT in cases attended by EMS close to the 4.5h time window, missing their treatment opportunity at the closer facility. This may have clinical outcome consequences, especially for patients with distal occlusion who have a high rate of early recanalization with IVT.[6]
- Risk of transport-related complications.
- Emergency medical services (EMS) resource consumption for MT ineligible patients (ambulance not available for other emergencies in the same area).

Can we define situations in which the mothership or the drip and ship model should be favored?

- No results of randomized controlled trials (RCTs) are currently available, but several RCTs comparing the two models and using different prehospital triage scales are ongoing or planned (RACECAT: NCT02795962; TRIAGE: NCT03542188; PRESTO-F).
- In one large-scale observational U.S. registry (STRATIS) only including patients treated with MT within 8 hours, reperfusion under the mothership paradigm occurred on average 2h earlier compared with the drip-and-ship model.[8] Clinical outcomes were better in the mothership model with 60.0% of patients achieving functional independence (mRS ≤2) compared with 52.2% in the drip-and-ship model (OR 1.38, 95% CI 1.06–1.79; P =0.02). This difference was solely attributable to time saving, with successful reperfusion rates equal to 88% in both groups and without evidence of an independent 'CSC effect'. The registry did not include patients with recanalization prior to interventional angiography.
- Such a superiority of the mothership model was not confirmed in six other observational studies and one RCT of mechanical thrombectomy.[17-23]
- Compared with the drip-and-ship model, the mothership model was associated with significantly shorter onset-to-arterial puncture in all examined studies in a recently published systematic review and meta-analysis of organizational models for MT in patients with acute ischemic stroke, ranging from 23 to 124 minutes time reduction (P<0001 in all studies).[24] However, the mothership model was not associated with a higher likelihood of functional independence (mRS ≤2: Pooled OR 0.96, 95%CI 0.73-1.25; P=0.67; I^2=61%, corresponding to substantial heterogeneity). The rates of successful recanalization and mortality were also not significantly different between the two groups, with a pooled OR of 0.81 (95% 0.63-1.03; P=0.09; I^2=0%) and 0.89 (95%CI 0.73-1.08; P=0.24; I^2=0%), respectively. Of note, the mothership model did not delay IVT, the onset-to-needle time being even significantly shorter than the drip-and-ship model in two studies (23 and 25 minutes, respectively).[17,19]
- Two observational studies have compared drip-and-ship and mothership before and after implementation of a clinical scale for patient triage. In the study by Zaidi et al, all patients with a RACE score ≥5 were taken to a facility with interventional capability.[11] Compared with a historical control group, there was an increase in the rate of MT (20.1% vs. 7.7%, P=0.03) and improvement in the treatment times (median arrival-to-recanalisation times: 101 vs. 205 min, P=0.001). No significant difference was found in the rate of functional independence (90-day mRS ≤2: 50% vs 36.4%, P=0.3). A similar study following the implementation of another screening tool showed similar time reduction.[10] There was significantly higher likelihood of functional independence at 3 months among the patients

treated with MT in the post-interventional period (62% vs. 43%, OR 3.08, 95% CI:1.08-8.78).

- Conditional probability modeling studies have suggested than the drip-and-ship model may be beneficial even if the travel time between the nearest PSC and the CSC is as low as 20 or 10 minutes, but only if the PSC is able to achieve a door-to-needle time of 30 minutes or less.[25,26]
- Another simulation study has suggested that compared with a drip-and-ship approach for all patients with suspected stroke, applying the mothership model in patients a RACE score ≥5 would lead to an absolute increase of 12% in the number of patients transported to CSCs but would reduce the number of secondary transfers by 61%.[27]

Conclusions:

- For patients with a suspected LAO based on current clinical tools on field, there is currently equipoise between drip-and-ship (that prioritizes early IVT) and mother ship (that prioritizes early MT) models. Even though mothership has been consistently associated with a 90 to 120 min reduction in onset-to reperfusion time in patient eligible for MT, this did not translate into significant clinical benefits in all but one observational study.
- Furthermore, it remains difficult in the prehospital field to identify those patients eligible for MT, who represent only approximately 10% of stroke code. Prehospital identification of patients eligible for MT in late time windows might be even more challenging.
- Several randomized controlled trials are ongoing or planned and will hopefully help to determine the most appropriate transportation model based on neurological severity.
- Alternative models such as travelling neurointerventionists and pre-hospital imaging are currently under investigation.[28,29]

Recommendations:

- As there is lack of randomized evidence for superiority of one organizational model, the choice of model should depend on local and regional service organization and patient characteristics (Grade C, expert opinion).
- For patients without identified contraindication to IVT, if estimated transportation time to a comprehensive stroke center is considerably longer than transportation to the nearest primary stroke center (approximately more than 30-45 minutes), the drip-and-ship model should be considered (Grade C, expert opinion).
- Conversely, if the difference in travel time between the nearest primary stroke center and the nearest comprehensive stroke center is below 30 to 45 minutes, or if contraindications to IVT are suspected in the field (i.e. recent surgery, oral anticoagulation…), direct transportation to the comprehensive stroke center should be considered if large artery occlusion is deemed clinically plausible (Grade C, expert opinion).
- We recommend that patients in late time windows (beyond 6h) or with unknown time of symptom onset (wake-up stroke, unwitnessed stroke) have rapid access to advanced imaging (Grade A)
- In case of admission to a primary stroke center, evaluation and treatment for patients with suspected ischemic stroke must be expeditious but should include brain and intracranial arterial imaging to ensure rapid identification of candidates for secondary transfer to a comprehensive stroke center. In case of intravenous thrombolysis, the door-to-needle time should be kept as low as possible, ideally below 30 minutes (Grade C).

- The first picture-to-puncture time and the door-in-door-out time in drip-and-ship patients should be as low as possible, ideally less than 90 minutes and 60 minutes respectively (Grade C).

References

1. Requena M, Perez de la Ossa N, Abilleira S, Cardona P, Urra X, Marti-Fabregas J, et al. Predictors of endovascular treatment among stroke codes activated within 6 hours from symptom onset. *Stroke*. 2018;49:2116-2121

2. Boulouis G, Siddiqui KA, Lauer A, Charidimou A, Regenhardt RW, Viswanathan A, et al. Immediate vascular imaging needed for efficient triage of patients with acute ischemic stroke initially admitted to nonthrombectomy centers. *Stroke*. 2017;48:2297-2300

3. Goyal M, Menon BK, Wilson AT, Almekhlafi MA, McTaggart R, Jayaraman M, et al. Primary to comprehensive stroke center transfers: Appropriateness, not futility. *Int J Stroke*. 2018;13:550-553

4. Fuentes B, Alonso de Lecinana M, Ximenez-Carrillo A, Martinez-Sanchez P, Cruz-Culebras A, Zapata-Wainberg G, et al. Futile interhospital transfer for endovascular treatment in acute ischemic stroke: The madrid stroke network experience. *Stroke*. 2015;46:2156-2161

5. Sablot D, Dumitrana A, Leibinger F, Khlifa K, Fadat B, Farouil G, et al. Futile inter-hospital transfer for mechanical thrombectomy in a semi-rural context: Analysis of a 6-year prospective registry. *J Neurointerv Surg*. 2018

6. Seners P, Turc G, Maier B, Mas JL, Oppenheim C, Baron JC. Incidence and predictors of early recanalization after intravenous thrombolysis: A systematic review and meta-analysis. *Stroke*. 2016;47:2409-2412

7. Prabhakaran S, Ward E, John S, Lopes DK, Chen M, Temes RE, et al. Transfer delay is a major factor limiting the use of intra-arterial treatment in acute ischemic stroke. *Stroke*. 2011;42:1626-1630

8. Froehler MT, Saver JL, Zaidat OO, Jahan R, Aziz-Sultan MA, Klucznik RP, et al. Interhospital transfer before thrombectomy is associated with delayed treatment and worse outcome in the stratis registry (systematic evaluation of patients treated with neurothrombectomy devices for acute ischemic stroke). *Circulation*. 2017;136:2311-2321

9. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CBLM, Dippel DW, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *JAMA*. 2016;316:1279-1288

10. Mohamad N, Hastrup S, Rasmussen M, Andersen MS, Johnsen SP, Andersen G, et al. Bypassing primary stroke centre reduces delay and improves outcomes for patients with large vessel occlusion. *Eur Stroke J*. 2016;1:85–92

11. Zaidi SF, Shawver J, Espinosa Morales A, Salahuddin H, Tietjen G, Lindstrom D, et al. Stroke care: Initial data from a county-based bypass protocol for patients with acute stroke. *J Neurointerv Surg*. 2017;9:631-635

12. Turc G, Maier B, Naggara O, Seners P, Isabel C, Tisserand M, et al. Clinical scales do not reliably identify acute ischemic stroke patients with large-artery occlusion. *Stroke*. 2016;47:1466-1472

13. Heldner MR, Hsieh K, Broeg-Morvay A, Mordasini P, Buhlmann M, Jung S, et al. Clinical prediction of large vessel occlusion in anterior circulation stroke: Mission impossible? *Journal of neurology*. 2016;263:1633-1640

14. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11-21

15. Jadhav AP, Desai SM, Kenmuir CL, Rocha M, Starr MT, Molyneaux BJ, et al. Eligibility for endovascular trial enrollment in the 6- to 24-hour time window: Analysis of a single comprehensive stroke center. *Stroke*. 2018;49:1015-1017

16. Heldner MR, Zubler C, Mattle HP, Schroth G, Weck A, Mono M-L, et al. National institutes of health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. *Stroke*. 2013;44:1153-1157

17. Perez de la Ossa N, Abilleira S, Dorado L, Urra X, Ribo M, Cardona P, et al. Access to endovascular treatment in remote areas: Analysis of the reperfusion treatment registry of catalonia. *Stroke*. 2016;47:1381-1384

18. Gerschenfeld G, Muresan IP, Blanc R, Obadia M, Abrivard M, Piotin M, et al. Two paradigms for endovascular thrombectomy after intravenous thrombolysis for acute ischemic stroke. *JAMA Neurol*. 2017;74:549-556

19. Weber R, Reimann G, Weimar C, Winkler A, Berger K, Nordmeyer H, et al. Outcome and periprocedural time management in referred versus directly admitted stroke patients treated with thrombectomy. *Therapeutic Advances in Neurological Disorders*. 2016;9:79-84

20. Hiyama N, Yoshimura S, Shirakawa M, Uchida K, Oki Y, Shindo S, et al. Safety and effectiveness of drip, ship, and retrieve paradigm for acute ischemic stroke: A single center experience. *Neurol Med Chir (Tokyo)*. 2016;56:731-736

21. Park M-S, Yoon W, Kim J-T, Choi K-H, Kang S-H, Kim BC, et al. Drip, ship, and on-demand endovascular therapy for acute ischemic stroke. *PloS one*. 2016;11:e0150668

22. Park MS, Lee JS, Park TH, Cho YJ, Hong KS, Park JM, et al. Characteristics of the drip-and-ship paradigm for patients with acute ischemic stroke in south korea. *Journal of Stroke and Cerebrovascular Diseases*. 2016;25:2678-2687

23. Goyal M, Jadhav AP, Bonafe A, Diener H, Mendes Pereira V, Levy E, et al. Analysis of workflow and time to treatment and the effects on outcome in endovascular treatment of acute ischemic stroke: Results from the swift prime randomized controlled trial. *Radiology*. 2016;279:888-897

24. Ciccone A, Berge E, Fischer U. Systematic review of organizational models for intra-arterial treatment of acute ischemic stroke. *Int J Stroke*. 2018:1747493018806157

25. Holodinsky JK, Williamson TS, Demchuk AM, Zhao H, Zhu L, Francis MJ, et al. Modeling stroke patient transport for all patients with suspected large-vessel occlusion. *JAMA Neurol*. 2018

26. Milne MS, Holodinsky JK, Hill MD, Nygren A, Qiu C, Goyal M, et al. Drip 'n ship versus mothership for endovascular treatment: Modeling the best transportation options for optimal outcomes. *Stroke*. 2017;48:791-794

27. Schlemm L, Ebinger M, Nolte CH, Endres M. Impact of prehospital triage scales to detect large vessel occlusion on resource utilization and time to treatment. *Stroke*. 2018;49:439-446

28. Ebinger M, Harmel P, Nolte CH, Grittner U, Siegerink B, Audebert HJ. Berlin prehospital or usual delivery of acute stroke care - study protocol. *Int J Stroke*. 2017;12:653-658

29. Wei D, Oxley TJ, Nistal DA, Mascitelli JR, Wilson N, Stein L, et al. Mobile interventional stroke teams lead to faster treatment times for thrombectomy in large vessel occlusion. *Stroke*. 2017;48:3295-3300

Session 2: Acute management of SAH/ ICH

Chairs: Charlotte Cordonnier (Lille) and Hanne Christensen (Copenhagen). Secretary: Erik Lundström (Stockholm).

The following Consensus Statement was (if approved) adopted by the 12th ESO Karolinska Stroke Update meeting on November 12th/13th, 2018.

The consensus statement was proposed by a writing committee (in alphabetical order: Dr Charlotte Cordonnier, Dr Hanne Christensen, Dr Erik Lundström and Dr Gabriel J. E. Rinkel) and proposed by the chairs of the session, Dr Charlotte Cordonnier (France) and Dr Hanne Christensen (Denmark) and the session secretary Dr Erik Lundström (Sweden), together with the speakers of the session, Dr Gabriel J. E. Rinkel (Netherlands). The statement was then finally approved by the participants of the meeting, after listening to the different presentations.

Session 1 - Talk 1) SAH - Which diagnostic test, and when?

Speaker: *Prof. Dr. Gabriel Rinkel*

Background:

Although the term ‘subarachnoid haemorrhage’ (SAH) in itself means nothing else than haemorrhage in the subarachnoid space, in clinical practice we generally use this term for patients who have (or we suspect to have) a ruptured intracranial aneurysm, even if the resulting haemorrhage is only an intracerebral haemorrhage. SAH from a ruptured aneurysm (ASAH) is a subset of stroke that carries a high socio-economic burden on a population level, because of the young age it occurs, the high case

fatality rate and the long-term physical and cognitive consequences that hamper resumption of pre-morbid activities.

The most common cause for haemorrhage in the subarachnoid space is trauma, other causes include reversible vasoconstriction syndrome, cerebral amyloid angiopathy, or venous sinus thrombosis. Arteriovenous malformations or fistulas may also cause a haemorrhage in the subarachnoid space, but usually, this is combined with an intracerebral haemorrhage near the malformation. In most patients with causes other than a ruptured aneurysm, the blood is located in the peripheral cisterns and in these patients ancillary investigations to demonstrate or exclude an intracranial aneurysm are not needed.

In this consensus statement we focus on patients suspected to have SAH from a ruptured aneurysm and on diagnostic tests for making the diagnosis. We do not discuss diagnostic tests for other causes of SAH or diagnostic tests for complications during the clinical course of ASAH (such as rebleeding, delayed cerebral ischaemia, cardiac stunning and other cardiopulmonary complications) or for long-term sequelae (such as cognitive dysfunction).

In diagnosing patients suspected to have ASAH, it is pivotal to first diagnose the SAH, and then to confirm or exclude an aneurysm.

Ancillary investigations for diagnosing subarachnoid haemorrhage

Sensitivity and negative predictive value of CT scanning are high early after the onset but decrease over hours to days. In a large Canadian study in patients presenting at an emergency department of university affiliated, tertiary care, teaching hospitals with acute onset of severe headache within the last two weeks, the overall sensitivity of CT was 92.9% (95% confidence interval [CI] 89.0 to 95.5%). For patients with CT scan done < 6 hours after onset of the headache, the negative predictive value of CT was 100% (95%CI 99.5 to 100%), if CT was interpreted by a neuroradiologist or general radiologist who routinely reports head CT images.(1) Some instances of SAH were initially missed when the CT scans were interpreted by residents or non-radiologists. In a study in the Netherlands on 760 patients admitted to 11 general, non-university affiliated hospital with CT performed within 6 hours after onset, the negative predictive value of CT in patients with acute headache was this study was 99.9% (95% CI 99.3%-100.0%).(2) No instances of ASAH were missed, only one patient with a non-aneurysmal perimesencephalic haemorrhage (see below).

The gold standard for detecting SAH is lumbar puncture and examination of the cerebrospinal fluid (CSF) for bilirubin. In patients with a negative CT scan performed within 6 hours after onset of the headache, yield of CSF examination is extremely low. Since in the Dutch study 1 patient with a perimesencephalic haemorrhage was missed on CT reading by radiologists in general hospitals and a perimesencephalic bleeding pattern is caused by a ruptured aneurysm in one out of 20 patients, one may argue that there still is an indication for CSF examination in patients with a negative CT within 6 hours after headache onset. If lumbar puncture should no longer be performed, a ruptured aneurysm will be missed in one of around 15,200 (760x20) patients with acute headache and a negatively read CT scan. It can be questioned, however, if 15,200 patients should undergo a lumbar puncture to prevent missing a ruptured aneurysm in one of them. A lumbar puncture is associated with discomfort for the patient, costs, and may induce a potentially life-threatening complication such as subdural hematoma or cerebral venous sinus thrombosis in rare cases.

In contrast to the negligible yield of CSF examination in patients who present early after the onset of headache, the yield is considerable in patients who present more than 3 days after headache onset. In a series of 30 patients with sudden headache, a negative CT scan but positive CSF examination (defined as detection of bilirubin >0.05 at wavelength 458 nm), half the patients who presented between 4 and 10 days after headache onset had an aneurysm.(3)

Fluid attenuation inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequences is another tool to detect SAH. In a study on 245 patients with acute onset of headache in whom MR with FLAIR images was performed as initial examination followed by lumbar puncture, sensitivity was 78.6% and negative predictive value 95.3% (95%CI 92.7-97.9%). There are however no large-scale studies investigating the additional value of MR in patients with a negative CT scan.

Ancillary investigations for diagnosing aneurysms

CT-angiography can usually be made immediately after the CT has demonstrated subarachnoid blood, and has according to a meta-analysis published in 2011 a pooled sensitivity of 98% (95%CI 97-99%), and a pooled specificity of 100% (95%CI 97 - 100%).(4, 5) Retrospective single centre studies published later showed varying results for small (<5mm) aneurysms, with sensitivity ranging from 58% to more than 95%.(6, 7) Moreover, CT-angiography can visualize the configuration of the aneurysm and surrounding vessels properly,(8, 9) which is helpful in the decision whether the aneurysm can be clipped or coiled.

If CT-angiography is negative, it is pivotal to assess the pattern of haemorrhage on CT. If the pattern is a typical perimesencephalic one, and the CT-angiogram is of good quality, according to several decision analyses based on all available literature, no further vascular imaging is needed.(10-13) In patients with an aneurysmal pattern of haemorrhage but a negative CT-angiogram, repeated vascular imaging has additional value in detecting aneurysms, and should be considered in all such patients who are eligible for aneurysm occlusion.(6, 7, 14, 15) In most of the published series catheter angiography was used for such repeated imaging, but there are no studies comparing CTA and DSA for this second imaging. If even this second vascular imaging is negative, repeated imaging one week later still can find an aneurysm in up to 5% of patients according to two single centre studies.(14, 16) A repeated CT-angiography several weeks after a negative CT-angiogram and negative catheter angiogram detected a vascular lesion (one aneurysm and one small AVM) in two out of 25 patients (8%) in a single centre study using a standardized diagnostic approach.(17)

Consensus Statement:

In patients suspected to have subarachnoid haemorrhage from a ruptured aneurysm, CT scanning is a sensible first line investigation. If this CT scan is performed within 6 hours after onset of the headache and negative according to a staff radiologist experienced in reading brain CT scans, lumbar puncture is not indicated. If the CT scan is performed later than 6 hours after the onset of headache, there is still an indication for CSF examination to rule in or out an SAH. Since the negative predictive value of MR imaging for ruling out SAH in case of a negative CT is unknown, there is no indication to routinely proceed to MR in patients with a negative CT. We also do not advocate to proceeding with CT-angiography or MR-angiography in case of a negative CT scan. Because 3% of the population has an intracranial aneurysm, one may run into the problem of finding an intracranial aneurysm in a patient with acute headache and a negative CT scan. In such instances, it is unknown whether the

aneurysm is an incidental finding, or the cause of a not yet detected SAH. Thus, it is pivotal to first making the diagnosis of SAH, and only if this is established to proceed for looking for the cause of the SAH.

In patients with an aneurysmal pattern of haemorrhage and a negative CT-angiogram repeated vascular imaging in indicated after one or two days. In most studies DSA was used for this repeated imaging. If this second imaging is still negative, CTA or DSA should be repeated after two weeks and three months.

In patients with a perimesencephalic pattern of haemorrhage and a negative CTA, nu further imaging is needed.

Recommendations:

1. In patients suspected to have a subarachnoid haemorrhage from a ruptured aneurysm, CT scanning of the brain is the first line examination.
2. If CT performed within 6 hours after the onset of headache and is read negative by a radiologist experienced in reading brain CT, CSF examination is not indicated. If CT is performed more than 6 hours after onset and negative, lumbar puncture should be performed more than 12 hours after headache onset, and CSF examined for bilirubin (Grade B).
3. In patients with SAH, CTA is a sensible first line examination to detect an aneurysm (Grade B). According to the local health care system it can be performed in either the local hospital or the neuro-intervention centre.
4. In patients with a perimesencephalic pattern of haemorrhage on CT within 3 days and a negative CTA, no further imaging is needed (Grade B).
5. In patients with an aneurysmal pattern of haemorrhage and a negative CTA, repeated vascular imaging (CTA or DSA) should be performed within one or two days. If this second imaging is again negative, a third imaging is indicated in the second week after SAH, and if negative again a fourth after 3 months (Grade C).

References

1. Perry JJ, Stiell IG, Sivilotti ML, Bullard MJ, Emond M, Symington C, et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study. BMJ. 2011;343:d4277.

2. Blok KM, Rinkel GJ, Majoie CB, Hendrikse J, Braaksma M, Tijssen CC, et al. CT within 6 hours of headache onset to rule out subarachnoid hemorrhage in nonacademic hospitals. Neurology. 2015;84(19):1927-32.

3. Horstman P, Linn FH, Voorbij HA, Rinkel GJE. Chance of aneurysm in patients suspected of SAH who have a 'negative' CT scan but a 'positive' lumbar puncture. J Neurol. 2012;259(4):649-52.

4. Westerlaan HE, van Dijk MJ, MC J-vdW, de Groot JC, Groen RJM, Mooij JJ, et al. Intracranial Aneurysms in Patients with Subarachnoid Hemorrhage: CT Angiography as a Primary Examination Tool for Diagnosis--Systematic Review and Meta-Analysis. Radiology. 2011;258(1):134-45.

5. Jethwa PR, Punia V, Patel T, Gandhi CD, Prestigiacomo CJ. Digital Substraction Angiography in CT Angiography Negative Spontaneous Subarachnoid Hemorrhage: A Cost-Effectiveness Analysis. Neurosurgery. 2012;71(2):E548-E9.

6. Philipp LR, McCracken DJ, McCracken CE, Halani SH, Lovasik BP, Salehani AA, et al. Comparison Between CTA and Digital Subtraction Angiography in the Diagnosis of Ruptured Aneurysms. Neurosurgery. 2017;80(5):769-77.

7. Yang ZL, Ni QQ, Schoepf UJ, De Cecco CN, Lin H, Duguay TM, et al. Small Intracranial Aneurysms: Diagnostic Accuracy of CT Angiography. Radiology. 2017:162290.

8. Westerlaan HE, Gravendeel J, Fiore D, Metzemaekers JD, Groen RJM, Mooij JJ, et al. Multislice CT angiography in the selection of patients with ruptured intracranial aneurysms suitable for clipping or coiling. Neuroradiology. 2007;49(12):997-1007.

9. Velthuis BK, van Leeuwen MS, Witkamp TD, Ramos LMP, Berkelbach van der Sprenkel JW, Rinkel GJE. Surgical anatomy of the cerebral arteries in patients with subarachnoid hemorrhage: comparison of computerized tomography angiography and digital subtraction angiography. J Neurosurg. 2001;95(2):206-12.

10. Ruigrok YM, Rinkel GJE, Buskens E, Velthuis BK, van Gijn J. Perimesencephalic hemorrhage and CT angiography: A decision analysis. Stroke. 2000;31(12):2976-83.

11. Delgado Almandoz JE, Jagadeesan BD, Refai D, Moran CJ, Cross DT, III, Chicoine MR, et al. Diagnostic yield of computed tomography angiography and magnetic resonance angiography in patients with catheter angiography-negative subarachnoid hemorrhage. J Neurosurg. 2012;117(2):309-15.

12. Kalra VB, Wu X, Forman HP, Malhotra A. Cost-Effectiveness of Angiographic Imaging in Isolated Perimesencephalic Subarachnoid Hemorrhage. Stroke. 2014.

13. Kalra VB, Wu X, Matouk CC, Malhotra A. Use of Follow-Up Imaging in Isolated Perimesencephalic Subarachnoid Hemorrhage: Meta-Analysis. Stroke. 2014.

14. Heit JJ, Pastena GT, Nogueira RG, Yoo AJ, Leslie-Mazwi TM, Hirsch JA, et al. Cerebral Angiography for Evaluation of Patients with CT Angiogram-Negative Subarachnoid Hemorrhage: An 11-Year Experience. AJNR Am J Neuroradiol. 2015.

15. Agid R, Andersson T, Almqvist H, Willinsky RA, Lee SK, terBrugge KG, et al. Negative CT Angiography Findings in Patients with Spontaneous Subarachnoid Hemorrhage: When Is Digital Subtraction Angiography Still Needed? AJNR Am J Neuroradiol. 2010;31(4):696-705.

16. Delgado Almandoz JE, Jagadeesan BD, Refai D, Moran CJ, Cross DT, III, Chicoine MR, et al. Diagnostic yield of repeat catheter angiography in patients with catheter and computed tomography angiography negative subarachnoid hemorrhage. Neurosurgery. 2012;70(5):1135-42.

17. Delgado Almandoz JE, Kadkhodayan Y, Crandall BM, Scholz JM, Fease JL, Anderson RE, et al. Diagnostic yield of delayed neurovascular imaging in patients with subarachnoid hemorrhage, negative initial CT and catheter angiograms, and a negative 7 day repeat catheter angiogram. J Neurointerv Surg. 2013.

Session 2 - Talk 2) ICH - Which diagnostic test, and when?

Speaker: *Prof. Dr. Charlotte Cordonnier*

Background:

Acute non traumatic intracerebral haemorrhage (ICH) is the most devastating type of stroke with a poor prognosis and few proven treatments. One in three patients die within the first month after onset. Survivors have severe residual disability and are at high risk of recurrent ICH, other serious vascular events, and neurological complications such as epilepsy and dementia (1). Rapid brain imaging (either CT or MR) must be performed to assess volume and location of ICH, any intraventricular haemorrhage (IVH) extension, and where the presence of subarachnoid haemorrhage can suggest an aneurysm or cerebral amyloid angiopathy (CAA) as the underlying vessel disease. An underlying vascular lesion, such as an aneurysm or arteriovenous malformation, occurs in approximately 15% of adults with ICH. (2) The decision to perform vascular imaging - CT or MRI angiography (CTA, MRA) and conventional digital subtraction angiography - can be made on the probability of finding a structural lesion using simple criteria: patient age, ICH location, and presence of cerebral small vessel disease (3, 4). Diagnostic performance of CTA in the setting of ICH remains insufficient (3). In CTA negative cases, without any clear diagnosis brought by MRI, conventional DSA needs to be performed when the benefit/risk ratio of DSA is acceptable. ICH is an heterogeneous disease. There is no such thing as primary intracerebral haemorrhage in the same way that there is no such thing as primary cerebral infarction (1). Clinicians should investigate ICH patients as thoroughly as they do for ischaemic strokes. The underlying cause may impact the treatment strategy in emergency, and may also be indicative of future risk of bleeding or cognitive decline.

Recommendations:

1. ICH is a heterogeneous disease and clinicians should identify the underlying cause of the bleeding **(Grade C).**
2. At admission: CT angiography spot sign predicts haematoma growth but whether treatments tailored to this information may improve outcome remains uncertain **(Grade C).**
3. At admission: vessel imaging should be performed to detect an underlying cause: CTA/CTV or MRA/MRV in patients in whom early intervention is considered **(Grade C).**
4. In patients without identified vascular malformations, brain parenchyma should be explored to see markers of the disease, ideally with MRI **(Grade C).**
5. In the absence of markers of deep perforating vasculopathy or CAA, even in CTA negative patients: conventional DSA should be performed if the benefit/risk ratio of the DSA is acceptable. Conventional DSA should be performed between 2 and 6 months after ICH **(Grade C).**

References

1. Cordonnier C, Demchuck A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. Lancet 2018;392:1257–1268.
2. Delgado Almandoz JE, Schaeger PW, Forero NP, Falla JR, Gonzalez RG, Romero JM. et al. Diagnostic accuracy and yield of multidetector CT angiography in the evaluation of spontaneous intraprenchymal cerebral haemorrhage. Am J Neuroradiol 2009;30:1213–21.

3. Van Asch C, Velthius BK, Rinkel GJ, de Kort GA, Witkamp TD, de Ridder JC et al. Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study.BMJ 2015 Nov 9;351:h5762.
4. Hilkens NA, van Asch CJJ, Werring DJ, Wilson D, Rinkel GJE, Algra A et al. Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: the DIAGRAM prediction score. JNNP 2018; 89(7):674-679.

Session 2 -Talk 3) TICH-2: what lessons have we learned?

Speaker: *Prof. Dr. Nikola Sprigg*

Background:

Reducing hematoma expansion in ICH is based on the concept of preventing deterioration to promote better outcome. In the TICH-2 trial[1] 2325 patients with ICH were included and randomized to a bolus of tranexamic acid (1 g) followed by an 8-hour infusion (1 g). There were no differences between treatment groups' mRS at 3 months, nor in the subpopulation with a spot sign on CT-angiography. However, hematoma volume and 7-days mortality were slightly, but significantly lower in the intervention group. There were no safety issues observed, rates of SAE was lower in the intervention group. TICH-2 was completed within the timeframe and matched the disease population well as to age and sex, however, hematoma volumes were relatively small (mean app. 13 mL), median time from onset to inclusion 3.6 hours, systolic blood pressure mean app. 173 mmHg.

A number of factors are recognized to be likely to affect potential treatment benefit in relation to reduction of hematoma expansion. Small hematomas are less likely to expand, the time window for intervention may be as short as below 3 hours from symptom onset and blood pressure reduction to 140 mmHg or below reduces hematoma expansion and improves outcome. Further, there is little evidence to support the trialist in choosing an investigational medical product or its dosing for this indication as to highest likely benefit, though the safety profile of the chosen drug and dosing is favourable and well described.

Consensus statement:

New treatment options in acute ICH are urgently needed. Pre-clinical and explorative studies may ensure more certainty on the choice of IMP as well as dosing.

Trials addressing prevention of hematoma expansion must match the epidemiology of the disease in question, to ensure feasibility and allowing for recruitment of the needed sample size. Further, factors of prognostic importance including blood pressure must be controlled as part of the protocol, and inclusion windows should not exceed 3 hours. Benefit is most likely to be achieved in patients with medium seized hematomas.

Recommendations:

1. Inclusion window in acute ICH trials aiming at preventing hematoma expansion should be as short as possible and no longer than 4.5 hours from ictus **(Grade C).**
2. As part of future trial protocols, blood pressure should be controlled (≤ 140 mmHg systolic BP) **(Grade C).**
3. Future studies in ICH should include large number of patients, have no upper age limit and include proportional number of women **(Grade C).**

References

1. Sprigg N, Flaherty K, Salman RA, Bereczki M, Beridze M, Christensen H et al. Tranexamic acid for hyperacute primary intracerebral haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. Lancet. 2018;391:2107-2115

Session No 3: Blood pressure and glucose control after stroke

Chair: Simona Sacco (L'Alquila), Else Charlotte Sandset (Oslo). Secretary: Marius Matusevicius (Stockholm).

The following Consensus Statement was (if approved) adopted by the 12th ESO Karolinska Stroke Update meeting on November 12th/13th, 2018.

The consensus statement was proposed by a writing committee (in alphabetical order: Marius Matusevicius, Dr Simona Sacco, Dr Else Charlotte Sandset, Dr Thorsten Steiner, and Dr Georgios Tsivgoulis) and proposed by the chairs of the session, Dr Simona Sacco (Italy) and Dr Else Charlotte Sandset (Norway) and the session secretary Marius Matusevicius (Sweden), together with the speakers of the session, Dr Georgios Tsivgoulis (Greece), and Dr Thorsten Steiner (Germany). The statement was then finally approved by the participants of the meeting, after listening to the different presentations.

Issues for the 2018 consensus session:

1. Does blood glucose influence outcome in acute ischemic or hemorrhagic stroke, and how should it be managed?
2. Should blood pressure be lowered in the chain of treatment in patients with acute ischemic stroke and high blood pressure?
3. Should blood pressure be elevated in the chain of treatment in patients with acute ischemic stroke and high blood pressure?
4. What is the optimal blood pressure in acute intracerebral hemorrhage?
5. Blood pressure lowering in acute intracerebral hemorrhage: what is the influence of time, hematoma volume, choice of agent, and previous hypertension?

Session 3 - Talk 1) Glucose, does it matter?

Speaker: *Georgios Tsivgoulis*

Background:

Does the acute blood glucose value influence the outcome of patients with acute ischemic and hemorrhagic stroke?

Hyperglycemia presence during the first 24 hours from stroke onset is possibly attributed to stress mechanisms and to uncontrolled underlying diabetes mellitus, and has been independently associated with less favorable neurological or functional outcomes and increased mortality risk for patients with acute ischemic stroke (AIS) or intracerebral hemorrhage (ICH)[1-4]. In addition, glucose levels lower than 67mg/dL within the first 24 hours of ictus have been related to adverse functional outcomes in patients with acute stroke[5].

Numerous evidence from observational studies also suggest that increased serum glucose prior to the administration of intravenous thrombolysis (IVT) for patients with AIS is an independent predictor for symptomatic intracerebral hemorrhage (sICH) and unfavourable clinical outcomes following tissue plasminogen activator (tPA) infusion[6-9]. Likewise, admission hyperglycemia was independently associated with adverse outcomes in AIS patients with large vessel occlusion (LVO) treated with mechanical thrombectomy (MT)[10-12], in particular in cases of incomplete reperfusion[12] or good collaterals following endovascular reperfusion procedures[13].

How should blood glucose be values managed?

There is no randomized controlled clinical trial (RCT) to date that reports improved outcomes in AIS patients with hyperglycemia receiving glycemic control in the acute phase[14-16], while a Cochrane meta-analysis of 11 RCTs using insulin infusion to control hyperglycemia in acute stroke further highlights the lack of any clinical efficacy with an additional increased risk for hypoglycemic episodes (Number Needed to Harm: 9)[17]. However, current guidelines from the American Heart Association/ American Stoke Association (AHA/ ASA) on AIS management suggest that it seems reasonable to treat hyperglycemia within the first 24 hours to achieve blood glucose levels in a range of 140 to 180 mg/dL[18]. For patients with acute ICH, currently available AHA/ASA guidelines suggest that hyperglycemia should be avoided, without providing any specific recommendations for an optimal therapeutic range[19]. Recent ESO guidelines suggest against the routine use of tight glycaemic control with intravenous insulin as a means to improve outcomes in patients with AIS or ICH[20]. They also highlight that the currently available data about management of glycemia in acute stroke are limited and the strengths of the recommendations are therefore weak[20]. Finally, the European recommendations advocate that hyperglycemia in acute stroke patients could be treated as any other hospitalized patient using intravenous insulin therapy titrated to achieve a glucose level between 140-180mg/dL (7.8-10mmol/L)[20]. They also advocate against using Subcutaneous sliding-scale insulin, because it is neither evidence-based nor effective in glucose control in critically ill patients[20].

Another important consideration is that current international guidelines on acute stroke management[18-20] do not provide separate recommendations for patients receiving systemic or endovascular reperfusion treatments. Taking into account the results of the aforementioned

observational studies[9, 10] and the available prediction scores on the outcomes following IVT treatment [21, 22], the hypothesis that more intensive blood glucose control (<140 mg/dL; 7.8mmol/L) could provide benefit for the subgroup of AIS patient receiving IVT and/or MT remains unanswered.

How intensive should glucose be monitored?

Although AHA/ASA guidelines advocate closely monitoring to prevent hypo- and hyperglycemia in patients with either AIS or ICH (Class of Recommendation: IIa, Level of Evidence: C), they do not provide further recommendations on the time intervals or the monitoring method that should be employed[18, 19]. Elevated glycemic variability is an established predictor of increased mortality in critically-ill patients[22]. Moreover, there are emerging data indicating that glycemic variability may be adversely associated with functional outcomes and survival in acute stroke [23]. However, the potential therapeutic effect of a constant and optimal euglycemia through continuous glycemic control monitoring in acute IS and ICH patients has not been formally assessed in the settings of a RCT.

Recommendations:

- Hypo- and hyperglycemia in the acute phase of both ischemic and haemorrhagic stroke are associated with adverse outcomes **(Grade C).**

- Tight glycemic control with intravenous insulin does not improve stroke outcomes and is associated with increased risk of hypoglycemia **(Grade A).**

- Hyperglycemia in acute (<48hrs) stroke patients may be treated as any other hospitalised patient with a therapeutic target of 140-180mg/dL (7.8-10 mmol/L) using intravenous insulin therapy. Subcutaneous sliding-scale insulin should be avoided **(Grade C).**

- Hyperglycemia is associated with adverse outcomes in AIS patients treated with IVT and/or MT and should be corrected with a therapeutic target < 140 mg/dL (7.8 mmol/L) before and after treatment with acute reperfusion therapies **(Grade C).**

- Hypoglycemia (< 67mg/dL or 3.7mmol/L) in AIS or acute ICH should be actively treated **(Grade C).**

Session 3 - Talk 2) Blood pressure in the chain of ischemic stroke

Speaker: *Else Charlotte Sandset*

Background:

Up to 75% of patients have blood pressure >140 mmHg in the acute phase of AIS[24]. High and low blood pressure in the acute phase is associated with stroke recurrence, death and poor functional outcome[24]. Despite several large clinical trials, there is equipoise regarding the management of blood pressure in the chain of treatment of patients with acute ischemic stroke[25].

To date most trials of blood pressure lowering in the acute phase have included patients with either ICH or AIS, and patients have been enrolled up to 72 hours after symptom onset.

There are 4 large trials contributing the majority of the patients:

The China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) randomized 4071 patients with minor ischemic stroke who were not thrombolysed and blood pressure between 140 – 220 mmHg to antihypertensive versus no antihypertensive treatment. Blood pressure was reduced from 167 to 145 mmHg within 24 hours in the intensive group and from 166 to 153 mm Hg in the control group. There was no difference in the primary of death or major disability at 3 months (RR 1.00, 95% CI 0.89 – 1.11)[26].

The Efficacy of Nitric Oxide in Stroke trial randomized 4011 patients with either ischemic stroke or ICH with 48 hours to treatment with transdermal glyceryl trinitrate (GTN) patch (5 mg per day) or to no GTN. In the subgroup 3348 patients with ischemic stroke there was no difference between active treatment or control in the primary endpoint of shift in the modified Rankin Scale (RR 0.98, 95% CI 0.93 – 1.03)[27].

The Scandinavian Candesartan Acute Stroke Trial included 2029 patients with either ischemic or hemorrhagic stroke with systolic blood pressure (SBP) over 140 mmHg within 30 hours of symptom onset. In the subgroup of 1733 patients with AIS, there were no differences between the groups in death or disability at 6 months (RR 1.04, 95% CI 0.91 – 1.20)[28].
A meta-analysis by Lee et al. 2015, including 13 randomized controlled trials with 12 703 patients found no effect on the risk of death or disability at 3 months or at the trial end point (RR 1.04; 95% CI 0.96 – 1.13).

Recommendation:

Within patients with AIS who do not receive recanalization therapy blood pressure should not be lowered unless very high blood pressure (>220/120 mm Hg). Treatment should be individualized and tailored according to previous hypertension and other comorbidities **(Grade B).**

Blood pressure lowering in patients receiving intravenous thrombolysis

Inclusion criteria in the trials of intravenous thrombolysis required blood pressure ≤ 185/110 mmHg before the start of treatment[29], and current guidelines recommend the use of blood pressure thresholds from the clinical trials[18].

Data from large international registries have found associations between high SBP, both at baseline[30] and after treatment[7], and sICH, and subsequent poor functional outcome[30-32].

There are no results large clinical trials assessing the effect of blood pressure lowering in the setting of IVT.

Recommendation*:*

In patients treated with IVT, we suggest to keep the blood pressure thresholds of the clinical trials: ≤ 185/110 mm Hg before treatment, and of ≤ 180/105 mm Hg for the first 24 hours after treatment **(Grade C).**

Intraarterial therapy

There are no large RCTs investigating the effect of blood pressure lowering in relation to intraarterial therapy for stroke.

In observational studies, high intraprocedural blood pressure, increases in blood pressure after thrombectomy[33] and large drops in blood pressure are associated with poor long-term functional outcome.

A secondary analysis of Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Stroke (MR CLEAN) found no interaction between pre-treatment SBP (<120 mm Hg vs >120 mm Hg) and the effect intraarterial therapy on functional outcome (p-value for interaction = 0.90), and SBP did not influence the occurrence of symptomatic intracranial haemorrhage (p = 0.80)[34].

In patients requiring intraprocedural anesthesia, a secondary analysis from MR CLEAN found associations between drops in blood pressure and worse functional outcome (aOR 0.95, 95% CI: 0.92 – 0.99 per 1 mm Hg decrease in mean arterial pressure).[35] Conversely, a secondary analysis of the Sedation vs Intubation for Endovascular Stroke Treatment (SIESTA) found no relationship between intra-procedural drops in blood pressure drops outcome[36].

Recommendation*:*

In patients treated with endovascular recanalization, we suggest to keep blood pressure pre-, intra- and post-procedural ≤185/110 mmHg. However, we suggest to pursue recanalization therapy irrespective of blood pressure in patients with large vessel occlusions and major neurological deficits **(Grade C).**

Should hypertension be induced in patients with ischemic stroke?

In selected patients, the rationale of inducing hypertension is to improve cerebral blood flow and enhance collateral circulation. In a trial of phenylephrine with 17 ischemic stroke patients with occlusion in the middle cerebral artery or distal internal carotid artery, and a > 20% diffusion/perfusion mismatch, NIHSS was significantly lower in the treatment group on day 3 compared to control (5.6±6.0 vs 9.7±8.0; p=0.02). No large randomized controlled trials have assessed the effects of blood pressure elevation in acute ischemic stroke.[37, 38]

Results from the Safety and Efficacy of Therapeutic Induced HYPERTENSION (SETIN-HYPERTENSION) were presented at ESOC 2018. In 153 patients with non-cardioembolic stroke ineligible for reperfusion, induced hypertension was associated with early neurologic improvement and 3 months functional independence (results are not yet published).

Recommendation:

In patients with large vessel occlusion, fluctuating symptoms, and low systolic blood pressure who are ineligible for recanalization therapy, it is reasonable to consider systolic blood pressure elevation to prevent early neurological deterioration **(Grade C).**

Session 3 - Talk 3) Blood pressure management during the chain of treatment in patients with ICH

Speaker: *Thorsten Steiner*

Background:

The objectives of blood pressure normalization are prevention of ICH ("primary" prevention) and hematoma expansion in acute ICH (acute secondary prevention) and prevention of recurrent ICH after acute spontaneous ICH (post-acute secondary prevention). Where there is no doubt about efficacy of primary and post-acute secondary prevention there still is a debate on whether lowering of blood pressure in acute ICH does prevent hematoma expansion and improves clinical outcome.

There are three large randomized controlled trials that addressed blood pressure lowering in acute ICH. The Intensive blood pressure reduction in acute cerebral hemorrhage trial (INTERACT) compared the effect of 2 target SBP thresholds on hematoma expansion, SBP <140 mmHg and 140< SBP <180 mmHg in 400 patients[39]. The trial demonstrated significant reduction of the primary endpoint of mean proportional hematoma growth: 36.3% (SBP <180-group mmHg) and 13.7% (SBP<140 mmHg) a difference of 22.6%, (95% CI 0.6-44.5%; p=0.04).

The INTERACT-2 trial compared the effect of the same two treatment thresholds on clinical outcome at day 90 in about 2700 patients.[40] The difference of the primary outcome - mRS 0-2 vs 3-6 – missed statistical significance: odds ratio (OR) for clinical benefit in favor of SBP < 140 mmHg was 0.87; 95% confidence interval (CI), 0.75 to 1.01; p=0.06. However, the pre-defined secondary categorial shift analysis showed a significantly greater disability at day 90 in the group with a target pressure of SBP < 180 mmHg (OR 0.87; 95% CI, 0.77 to 1.00; p=0.04). There was no difference in hematoma expansion.

The Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial used the thresholds of 110< SBP <139mmHg and 140< SBP <180mmHg in 1000 patients[41]. The results for the primary endpoint (mRS 0-3 vs. 4-6) was neutral: 38.7% (110< SBP <139mmHg): vs. 37.7% (140< SBP <180mmHg), relative risk (RR): 1.04; 95% CI, 0.85 to 1.27). Only "any renal adverse events" were significantly more frequent in patient who did receive intensive lowering of SBP.

A meta-analysis by Boulouis et al. including these three and two smaller RCTs (N<100) did not find a clinical effect intensive lowering of SBP but demonstrated an effect on hematoma expansion[42].

What is the optimal blood pressure in patients with acute ICH

The meta-analysis by Boulouis and co-workers demonstrates significant reduction of hematoma expansion with intensive blood pressure lowering, i.e. a threshold below 140 mmHg. In ATACH-2, the

risk of renal advers events was increased by intensive blood pressure lowering in the intensive treatment group (targed threshold of 110 mmHg). These date are supported by a recently published post-hoc analysis of ATACH-2 that revealed beneficial effects of lowering and maintaining SBP at 120-130 mmHg during the first 24 hours on clinical outcomes by suppressing hematoma expansion but was somewhat offset by cardio-renal complications[43]. A prospective cases series including 448 patients with acute ICH found a maximum SBP reduction of more than 90 mmHg to increase the risk of in-hospital acute kidney injury[44]. In this trial the target blood pressure threshold was <140mmHg. Consequently, the target pressure threshold of 140 mmHg needs to be elevated in patients with systolic blood pressure values above 230 mmHg.

Recommendation:

In patients with acute intracerebral haemorrhage we recommend to lower systolic blood pressure below 140 mmHg but to keep it above 110mmHg and to avoid SBP reduction of more than 90 mmHg to prevent acute kidney injury **(Grade B).**

What is the optimal timing of blood pressure lowering in acute ICH?

The main objective of blood pressure lowering in the acute phase of acute ICH is to prevent hematoma expansion, because hematoma expansion is the main predictor of unfavorable clinical outcome[45, 46]. The risk of hematoma expansion decreases over time[47]. The critical duration of onset to treatment (OTT) to reduce the chance of hematoma expansion with an effect on clinical outcome is probably as short as 2,5 to 3 hours[48]. The mean OTT in the meta-analysis of the five RCTs on acute blood pressure lowering in acute ICH was 5.7 hours, which may have been too long to demonstrate a clinical benefit of the intervention, because most of hematoma expansion may have already occurred at that time[42].

Recommendation:

In patients with acute intracerebral haemorrhage, we recommend to lower blood pressure as soon and fast as possible: The optimal onset to treatment (OTT) time to impact on clinical outcome is probably as short as 2.5 hours **(Grade C).**

Still, after this period, blood pressure should be kept <140mmHg, because hematoma expansion does occur even after this time **(Grade C).**

What is the influence of previous hypertension and choice of agent on blood pressure lowering in acute ICH?

Data from RCTs on the meaning of SBP reduction in acute ICH patients with and without chronic hypertension can be derived from the subgroup analysis of INTERACT-2: Patients with no known history of hypertension benefited significantly from intensive SBP reduction. Still, also patients with chronic hypertension did benefit from the intensive SBP reduction but the confidence interval crossed the margin of significance[39].

As said above, a clinical benefit from SBP reduction by prevention of hematoma expansion depends on a short OTT. Therefore, RCTs only allowed for fast acting intravenous antihypertensives.

Recommendation:

- In patients with acute intracerebral haemorrhage and previous hypertension recommend to lower blood pressure as soon and fast as possible **(Grade C).**

- The optimal OTT to impact on clinical outcome may be 2.5 hours, but blood pressure should be kept <140mmHg, because the risk of hematoma expansion exists even after this time **(Grade C).**

- We recommend the use of short-acting intravenous drugs to lower SBP in the acute phase of ICH **(Grade C).**

Is blood pressure lowering important in all patients or should we differentiate according to hematoma volume?

Hematoma expansion is a function of baseline volume. Data from the PREDICT-Study revealed that small intracerebral haemorrhages have a low spot sign prevalence and are less likely to expand[49]. It is important to weigh two risks against each other: The risk of hematoma expansion, if no BP reduction is applied in small hematomas and the risk of acute kidney injury, if SBP reduction is applied even in small hematomas. Finally, there still is a chance of hematoma expansion even in small ICH. This is the consequence of the PREDICT analysis and this also follows from the 3 large RCT on SBP reduction in acute ICH that also included small hematomas and demonstrated an overall reduction of hematoma expansion. Thirdly, the only one significant result from the meta-analysis by Boulouis et al. was the reduction of hematoma expansion through SBP reduction though the mean median volume from all studies was small i.e. about 14 ml[42].

Recommendation:

In patients with acute intracerebral haemorrhage and small bleeding volumes we recommend to lower blood as soon and fast as possible to a SBP below 140 mmHg and above 110 mmHg but to avoid SBP reduction of more than 90 mmHg to prevent acute kidney injury **(Grade C).**

References

1. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: A systematic overview. *Stroke*. 2001;32:2426-2432

2. Stollberger C, Exner I, Finsterer J, Slany J, Steger C. Stroke in diabetic and non-diabetic patients: Course and prognostic value of admission serum glucose. *Ann Med*. 2005;37:357-364

3. Saxena A, Anderson CS, Wang X, Sato S, Arima H, Chan E, et al. Prognostic significance of hyperglycemia in acute intracerebral hemorrhage: The interact2 study. *Stroke*. 2016;47:682-688

4. Fogelholm R, Murros K, Rissanen A, Avikainen S. Admission blood glucose and short term survival in primary intracerebral haemorrhage: A population based study. *J Neurol Neurosurg Psychiatry*. 2005;76:349-353

5. Ntaios G, Egli M, Faouzi M, Michel P. J-shaped association between serum glucose and functional outcome in acute ischemic stroke. *Stroke*. 2010;41:2366-2370

6. Mundiyanapurath S, Hees K, Ahmed N, Wahlgren N, Uhlmann L, Kieser M, et al. Predictors of symptomatic intracranial haemorrhage in off-label thrombolysis: An analysis of the safe implementation of treatments in stroke registry. *Eur J Neurol*. 2018;25:340-e311

7. Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Davalos A, et al. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe implementation of thrombolysis in stroke-monitoring study (sits-most). *Stroke*. 2008;39:3316-3322

8. Lin SF, Chao AC, Hu HH, Lin RT, Chen CH, Chan L, et al. Hyperglycemia predicts unfavorable outcomes in acute ischemic stroke patients treated with intravenous thrombolysis among a chinese population: A prospective cohort study. *J Neurol Sci*. 2018;388:195-202

9. Poppe AY, Majumdar SR, Jeerakathil T, Ghali W, Buchan AM, Hill MD, et al. Admission hyperglycemia predicts a worse outcome in stroke patients treated with intravenous thrombolysis. *Diabetes care*. 2009;32:617-622

10. Goyal N, Tsivgoulis G, Pandhi A, Dillard K, Katsanos AH, Magoufis G, et al. Admission hyperglycemia and outcomes in large vessel occlusion strokes treated with mechanical thrombectomy. *J Neurointerv Surg*. 2018;10:112-117

11. Lu GD, Ren ZQ, Zhang JX, Zu QQ, Shi HB. Effects of diabetes mellitus and admission glucose in patients receiving mechanical thrombectomy: A systematic review and meta-analysis. *Neurocrit Care*. 2018

12. Kim JT, Jahan R, Saver JL, Investigators S. Impact of glucose on outcomes in patients treated with mechanical thrombectomy: A post hoc analysis of the solitaire flow restoration with the intention for thrombectomy study. *Stroke*. 2016;47:120-127

13. Kim JT, Liebeskind DS, Jahan R, Menon BK, Goyal M, Nogueira RG, et al. Impact of hyperglycemia according to the collateral status on outcomes in mechanical thrombectomy. *Stroke*. 2018;49:2706-2714

14. Lindsberg PJ, Roine RO. Hyperglycemia in acute stroke. *Stroke*. 2004;35:363-364

15. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: The uk glucose insulin in stroke trial (gist-uk). *Lancet Neurol*. 2007;6:397-406

16. Bruno A, Kent TA, Coull BM, Shankar RR, Saha C, Becker KJ, et al. Treatment of hyperglycemia in ischemic stroke (this): A randomized pilot trial. *Stroke*. 2008;39:384-389

17. Bellolio MF, Gilmore RM, Ganti L. Insulin for glycaemic control in acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014:CD005346

18. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2018;49:e46-e110

19. Hemphill JC, 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2015;46:2032-2060

20. Fuentes B, Ntaios G, Putaala J, Thomas B, Turc G, Díez-Tejedor E. European stroke organisation (ESO) guidelines on glycaemia management in acute stroke. *European Stroke Journal*. 2018;3:5-21

21. Strbian D, Meretoja A, Ahlhelm FJ, Pitkaniemi J, Lyrer P, Kaste M, et al. Predicting outcome of iv thrombolysis-treated ischemic stroke patients: The dragon score. *Neurology*. 2012;78:427-432

22. Krinsley JS. Glycemic variability: A strong independent predictor of mortality in critically ill patients. *Crit Care Med*. 2008;36:3008-3013

23. Kim YS, Kim C, Jung KH, Kwon HM, Heo SH, Kim BJ, et al. Range of glucose as a glycemic variability and 3-month outcome in diabetic patients with acute ischemic stroke. *PLoS One*. 2017;12:e0183894

24. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA, Group ISTC. Blood pressure and clinical outcomes in the international stroke trial. *Stroke*. 2002;33:1315-1320

25. Sandset EC, Sanossian N, Woodhouse LJ, Anderson C, Berge E, Lees KR, et al. Protocol for a prospective collaborative systematic review and meta-analysis of individual patient data from randomized controlled trials of vasoactive drugs in acute stroke: The blood pressure in acute stroke collaboration, stage-3. *Int J Stroke*. 2018;13:759-765

26. He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: The catis randomized clinical trial. *JAMA*. 2014;311:479-489

27. Investigators ET, Bath PM, Woodhouse L, Scutt P, Krishnan K, Wardlaw JM, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (enos): A partial-factorial randomised controlled trial. *Lancet*. 2015;385:617-628

28. Sandset EC, Bath PM, Boysen G, Jatuzis D, Korv J, Luders S, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (scast): A randomised, placebo-controlled, double-blind trial. *Lancet*. 2011;377:741-750

29. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317-1329

30. Bangalore S, Schwamm L, Smith EE, Hellkamp AS, Suter RE, Xian Y, et al. Blood pressure and in-hospital outcomes in patients presenting with ischaemic stroke. *Eur Heart J*. 2017;38:2827-2835

31. Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Davalos A, et al. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe implementation of thrombolysis in stroke-monitoring study (sits-most). *Stroke*. 2008;39:3316-3322

32. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: Retrospective analysis from safe implementation of thrombolysis in stroke-international stroke thrombolysis register (sits-istr). *Stroke*. 2009;40:2442-2449

33. Goyal N, Tsivgoulis G, Pandhi A, Dillard K, Alsbrook D, Chang JJ, et al. Blood pressure levels post mechanical thrombectomy and outcomes in non-recanalized large vessel occlusion patients. *J Neurointerv Surg*. 2018;10:925-931

34. Mulder M, Ergezen S, Lingsma HF, Berkhemer OA, Fransen PSS, Beumer D, et al. Baseline blood pressure effect on the benefit and safety of intra-arterial treatment in mr clean (multicenter randomized clinical trial of endovascular treatment of acute ischemic stroke in the netherlands). *Stroke*. 2017;48:1869-1876

35. Treurniet KM, Berkhemer OA, Immink RV, Lingsma HF, Ward-van der Stam VMC, Hollmann MW, et al. A decrease in blood pressure is associated with unfavorable outcome in patients undergoing thrombectomy under general anesthesia. *J Neurointerv Surg*. 2018;10:107-111

36. Schonenberger S, Uhlmann L, Ungerer M, Pfaff J, Nagel S, Klose C, et al. Association of blood pressure with short- and long-term functional outcome after stroke thrombectomy: Post hoc analysis of the siesta trial. *Stroke*. 2018;49:1451-1456

37. Hillis AE, Ulatowski JA, Barker PB, Torbey M, Ziai W, Beauchamp NJ, et al. A pilot randomized trial of induced blood pressure elevation: Effects on function and focal perfusion in acute and subacute stroke. *Cerebrovasc Dis*. 2003;16:236-246

38. McManus M, Liebeskind DS. Blood pressure in acute ischemic stroke. *J Clin Neurol*. 2016;12:137-146

39. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (interact): A randomised pilot trial. *Lancet Neurol*. 2008;7:391-399

40. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *The New England journal of medicine*. 2013;368:2355-2365

41. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *The New England journal of medicine*. 2016;375:1033-1043

42. Boulouis G, Morotti A, Goldstein JN, Charidimou A. Intensive blood pressure lowering in patients with acute intracerebral haemorrhage: Clinical outcomes and haemorrhage expansion. Systematic review and meta-analysis of randomised trials. *J Neurol Neurosurg Psychiatry*. 2017;88:339-345

43. Toyoda K, Koga M, Yamamoto H, Foster L, Palesch YY, Wang Y, et al. Clinical outcomes depending on acute blood pressure after cerebral hemorrhage. *Ann Neurol*. 2019;85:105-113

44. Burgess LG, Goyal N, Jones GM, Khorchid Y, Kerro A, Chapple K, et al. Evaluation of acute kidney injury and mortality after intensive blood pressure control in patients with intracerebral hemorrhage. *Journal of the American Heart Association*. 2018;7

45. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175-1181

46. Gregson BA, Broderick JP, Auer LM, Batjer H, Chen XC, Juvela S, et al. Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage. *Stroke*. 2012;43:1496-1504

47. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the ct-angiography spot sign (predict): A prospective observational study. *Lancet Neurol*. 2012;11:307-314

48. Mayer SA, Davis SM, Skolnick BE, Brun NC, Begtrup K, Broderick JP, et al. Can a subset of intracerebral hemorrhage patients benefit from hemostatic therapy with recombinant activated factor vii? *Stroke*. 2009;3:833-840

49. Dowlatshahi D, Yogendrakumar V, Aviv RI, Rodriguez-Luna D, Molina CA, Silva Y, et al. Small intracerebral hemorrhages have a low spot sign prevalence and are less likely to expand. *Int J Stroke*. 2016;11:191-197

Session 4: Update on Work-up and secondary prevention issues 1

Chair: Andreas Charidimou (Boston), George Ntaios (Larissa). Secretary: Tiago Moreira (Stockholm).

Consensus Statement
The Consensus Statement was prepared by a writing committee (George Ntaios, Haralampos Milionis, Marta Rubiera, Robert Hart, Andreas Charidimou, Tiago Moreira) and proposed by the chairs of the session, Andreas Charidimou (Boston, USA), George Ntaios (Larissa, Greece), and the session secretary, Dr Tiago Moreira (Stockholm, Sweden), together with the speakers of the session, George Ntaios, Haralampos Milionis (Ioannina, Greece), Marta Rubiera (Barcelona, Spain), Robert G. Hart (Hamilton, Canada).

Session 4 - Talk 1) What is good clinical practice in work up for suspected cardio-embolic cases? Echo and monitoring in all patients?

Speaker: *Marta Rubiera*

Background:

According to the guidelines for management of ischaemic stroke and transient ischaemic attack 2008, the bulk of the major cardioembolic sources of ischemic stroke can be diagnosed with a basic examination. A good medical history, physical examination, laboratory testing, a 24 hour 12-lead electrocardiogram (ECG) and transthoracic echocardiogram (TTE) would detect a permanent atrial fibrillation (AF), recent myocardial infarction, severe mitral stenosis, left ventricular thrombus or severe dilated myocardiopathy with a left ejection fraction <30%. In the case of a suspected

mechanical valvar thrombosis, endocarditis, thrombus in the left atrial appendage (LAA) or some cardiac tumours, a transesophageal echocardiogram (TEE) would be needed.[1-3]
However, the main diagnosis challenge comes from the embolic strokes of undetermined source (ESUS). The concept of ESUS was established in 2014 to provide a positively-described, well defined subgroup of cryptogenic strokes with a plausible thromboembolic origin.[4] Because the term cryptogenic stroke is variably defined and, for example, can include a patient with two causes (e.g. atrial fibrillation and severe carotid stenosis), we prefer the clearly defined construct of ESUS to identify patients who should be screened. It requires a basic complete diagnostic work-up such as mandatory neuroimaging studies (CT and/or MRI) to rule-out a lacunar stroke and vascular studies (carotid and transcranial ultrasound, CTA or MRA) to discard a significant atherosclerotic source of the embolic stroke. Finally, to rule-out the major cardioembolic sources, the cardiac work-up for ESUS involves at least an ECG, a 24 hours-ECG monitoring and a TTE.[4]

A) How long and by which technique should we monitor for paroxysmal AF?
Detection of a paroxysmal AF can be performed by single ECG, 24-, 48-, and 7-days Holter-ECG, multiple-repetitive explorations, or continuous ECG-monitoring during in hospital stay, or ambulatory. Recently, triggered-loop recorders and implantable devices have simplified ambulatory prolonged ECG monitoring, and "smart" wrist watch technologies are being explored. It was previously hypothesized that repetitive ECG recordings mildly increase the probability of silent AF detection. Accordingly, results from the CRYSTAL-AF[5] and EMBRACE[6] studies have shown that a prolonged ECG-monitoring by different techniques increases the detection of covert AF by at least 11% as compared with the 24h-monitoring. CRYSTAL-AF used an insertable cardiac monitor up to 12 months while EMBRACE used an ambulatory event-triggered loop-recorder for 30 days. CRYSTAL-AF showed that the diagnosis of silent AF increased progressively with time, with a 9% of AF detection after 6 months of monitoring, and a 12% after 12 months (as compared with 1.4% and 2% in controls, respectively). EMBRACE, with 30-days monitoring, yielded similar rates of AF detection (16% of AF as compared with 3.2% in controls). After the results of these trials, the current guidelines from the American Heart Association[2] state that continuous monitoring up to 30 days is reasonable **(Grade A)** in patients with embolic stroke and absence of other plausible etiologies, to increase covert AF detection. However, it remains to be firmly established that the increased detection of brief episodes of AF will lead to a reduction in stroke recurrence after adequate treatment **(Grade C).**

B). How should we select patients for specific test: prolonged ECG-monitoring, TEE, cardiac MR?
Despite the basic diagnostic requirements to define an ESUS, a more complete diagnostic work-up could detect the actual etiology in a substantial proportion of ESUS patients. It may be possible that the majority of ESUS patients have one or more from 3 potential thromboembolic sources: covert AF, non-stenosing atherosclerosis in the aortic arch or extra- / intra-cranial feeding arteries and paradoxical embolism through a patent foramen ovale (PFO).[7] Other potential etiologies include a congenital or acquired (i.e neoplastic) prothrombotic state, non-AF left atrial arrythmias or left atrial disease, or left ventricular myocardiopathy with an ejection fraction > 30%. How to select the adequate work-up in each ESUS patient may be challenging.
In the case of covert AF, patient selection should be recommended for longer ECG ambulatory monitoring (> 30 days) or implantable devices in terms of efficiency. Clinical data may influence this selection: in the general population, AF is frequently associated with hypertension, chronic heart failure, and valvular or ischaemic heart disease, and is an important sequela of cardiothoracic surgery. [8, 9] In stroke patients, covert AF is more frequently found in older patients, and those with the more severe baseline stroke (higher NIHSS or infarct volume in the neuroimaging).[10] In fact, stratification risk scores for AF have been developed based on these variables, with good predictive results.[11]
Auxiliary laboratory test such us increased levels of brain natriuretic protein (BNP) and the N-terminal pro-BNP[12], Holter-ECG findings such us atrial ectopic activity (EMBRACE) or subclinical atrial

tachyarrhythmias (ASSERT study)[13] and echocardiographic signs like left atrium enlargement, left ventricular diastolic dysfunction, spontaneous left atrium or LAA echo-contrast ("smoke") or low LAA emptying velocities[14] have been associated with covert AF. We recommend performing these tests in ESUS patients to identify those with the higher yield for prolonged ECG monitoring of implantable devices **(Grade C).**

In young patients with embolic stroke of undetermined etiology despite adequate diagnostic work-up, a paradoxical embolism via PFO is a frequent candidate for stroke etiology. However, considering that PFO is a common anatomical variant found in the general population, searching for PFO in all ESUS patients does not seem reasonable. A simple, cheap, non-invasive and almost widely available screening method for PFO is the right-to-left shunt detection by the bubble test-transcranial Doppler, which has sensitivity above 90% when compared with TEE.[15] If the case of a positive result, TEE should be performed to confirm the presence of a PFO, detect other potentially associated atrial septal abnormalities and help in the selection of PFO-closure candidates. [10]
Older patients, with vascular risk factors and small multiple ischemic lesions on MRI are the most probably candidates of a non-stenosing atherosclerotic aortic, extracranial or intracranial embolic sources.[13] The aortic arch atheroma (AAA) is a well-established, probably under-diagnosed cause of ESUS.[16] Thoracic computerized tomography angiography (CTA) and TTE can be considered as screening diagnostic test for AAA, but the gold-standard is still TEE.[17] To define if the AAA is the actual embolic source of a determined stroke is not easy, as it is a common found in autopsies of stroke-free older patients with vascular risk factors. TEE-findings suggestive of symptomatic AAA are protruding plaques with thickness >=4 mm, ulceration and more definitively causative are mobile thrombus adhering to the AAA.[18]
Less frequent stroke etiologies require more sophisticated diagnostic tools, like cardiac MR, for the detection of structural myocardiopathies or intracardiac tumours, thrombophilia test for congenital pro-coagulant states or even whole-body CT or Positron Emission Tomography looking for occult neoplasms.

Recommendations:

- A good medical history, physical examination, laboratory testing, a 24 hour 12-lead electrocardiogram (ECG) and transthoracic echocardiogram (TTE) are the mainstays of cardioembolic source detection **(Grade A).**
- Screening of patent foramen ovale (PFO) with bubble test-transcranial Doppler or transesophageal echocardiogram (TEE) is recommended in patients with embolic stroke of undetermined etiology despite recommended diagnostic-work up, who would be eligible for PFO closure **(Grade A).**
- Screening of aortic arch atheroma (AAA) with computer tomography angiography (CTA) or TTE is recommended in embolic strokes of undetermined source (ESUS); however, TEE is still the gold-standard for AAA evaluation **(Grade C).**
- Detection of some minor structural abnormalities on TEE has uncertain therapeutic implications **(Grade C).**
- Continuous monitoring of heart rhythm up to 30 days is reasonable in patients with embolic stroke of undetermined etiology despite recommended diagnostic-work up to increase covert atrial fibrillation detection (**Grade A).** However, it remains to be firmly established that the increased detection of brief episodes of AF will lead to a reduction in stroke recurrence after adequate treatment **(Grade C).**
- Covert AF can be associated with increased brain natriuretic peptide (BNP) and N-terminal-pro-BNP in laboratory tests; atrial ectopic activity, subclinical atrial tachyarrhythmias in Holter-ECG; left atrium enlargement, left ventricular diastolic dysfunction, spontaneous left atrium or left atrial apex (LAA) echo-contrast and low LAA emptying velocities in TTE/TEE. These findings should encourage long-term monitoring in ESUS patients **(Grade C)**

Session 4 - Talk 2) How to choose secondary prevention in Embolic Stroke of Undetermined Source (ESUS)

Speaker: *Robert Hart*

Background:

The construct of embolic stroke of undetermined source (ESUS) was proposed in 2014 to identify cryptogenic ischemic stroke patients with features supporting an embolic mechanism after required, specific diagnostic evaluation.[4] ESUS patients comprise 15-20% of ischemic stroke patients and include heterogeneous sources, often multiple, of embolism.[19] For ESUS patients, it was hypothesized that oral anticoagulants would be more efficacious than antiplatelet therapies for secondary stroke prevention, the latter recommended by most guidelines.[4]

Two large, international double-blinded randomized trials compared non-vitamin-K-antagonist oral anticoagulants (NOAC) with aspirin for secondary prevention.[20-23] Both trials failed to demonstrate superiority of NOAC over aspirin for secondary stroke prevention. Consequently, antiplatelet therapy remains the mainstay antithrombotic therapy for secondary stroke prevention for most patients with ESUS. Subgroup analyses of these two trials are underway seeking to define ESUS who might benefit from anticoagulation, but these would be regarded a hypothesis-generating and should not, by themselves, alter clinical management.

Patients with ESUS and patent foramen ovale (PFO) were included in the two large ESUS RCTs. Subsequently, there has been consistent evidence supporting the efficacy of PFO closure for stroke prevention for selected patients who are under age 60 years.[24] Hence, management of ESUS patients who are under age 60 years with PFO who would have been eligible for inclusion in these trials should consider closure based on individualized assessment.

Specific issues:

1. Is there any role for anticoagulation for secondary stroke prevention in ESUS patients?
Not at present.

2. In the absence of substantial ischemic stroke reduction by rivaroxaban (NAVIGATE ESUS) or dabigatran (RE-SPECT ESUS) vs. aspirin, is ESUS a therapeutically relevant target?
ESUS is not a therapeutic target for anticoagulation alone, but it may be premature to abandon ESUS as a potential therapeutic target. The ESUS definition reproducibly identifies 15-20% of ischemic stroke patients who are relatively young and have high (~5%/yr) stroke recurrence despite guideline-recommended interventions. It identifies a substantial subgroup of ischemic stroke patients with a large unmet need. Some tweaking of the ESUS definition in the wake of insights from subgroup analyses of the large recent trials may be useful. Testing “broad spectrum”, combined antithrombotic therapy (low-dose NOAC plus aspirin) that has resulted in large reductions in stroke in other populations should be tested in ESUS patients.[25]

Recommendations:

- The best current secondary prevention in ESUS patients is antiplatelet treatment **(Grade A).** ***(pending publication of the RE-SPECT ESUS trial)***

- ESUS patients are relatively young and have 5% yearly stroke recurrence despite guideline-recommended therapy and thus represent a substantial unmet need in secondary stroke prevention **(Grade C).**
- Subgroups of ESUS patients who may benefit from anticoagulation have not yet been validated by clinical trials **(Grade C).**

Session 4 - Talk 3) What secondary prevention in multiple stroke etiologies?

Speaker: *George Ntaios*

Background:

Stroke is a syndrome, not a disease. Numerous pathologies may lead to an ischemic stroke, arising from the arteries, the heart or the venous circulation[26].
Frequently, more than one stroke-related pathologies coexist in patients with ischemic stroke, especially if we consider also stroke-related pathologies which are currently assumed to confer a lower risk for stroke like atrial cardiopathy, non-stenotic carotid plaques, cancer, patent foramen ovale, valvular heart disease and left ventricular disease[26]. In such patients, it may be challenging and unreliable to assume which one of the existing stroke-related pathologies was the actual cause of stroke. Pointing towards the same direction, about 50% of stroke recurrences are attributed to an etiology which is different from the etiology of the index stroke[27].
It seems likely that patients with more than one stroke-related pathologies may be in higher risk for stroke recurrence[28]. In this context, it could be hypothesized that more aggressive strategies of secondary prevention (e.g. more aggressive antithrombotic treatment) may be warranted in this patient group; however, a possible effect on stroke risk reduction could be counterbalanced by an increase in bleeding events. The related evidence is scarce and therefore, any recommendations and guidelines about secondary stroke prevention in this patient group rely largely on expert opinion rather than hard evidence.
In conclusion, there is an unmet need for more evidence in this topic. Well-designed, adequately-powered randomized clinical trials are warranted to address the issue of secondary prevention strategies in patients with concomitant stroke-related pathologies.

Recommendations:

- Patients with multiple stroke etiologies represent a significant proportion of the embolic stroke population. The optimal strategy for secondary prevention in these patients is uncertain **(Grade C).**

Session 4 - Talk 4) Lipids and stroke: Statins, PCSK9 inhibitors, and LDL-levels; and whom not to treat?

Speaker: *Haralampos Milonis*

Background:

Low-density lipoprotein (LDL) cholesterol has been validated as a modifiable risk factor for atherosclerotic vascular disease (AVD) since at least three decades but its association with stroke has

been long disputed. In addition, the implementation of intensive lipid-lowering therapy after stroke has been slow compared with coronary heart disease (CHD). The heterogeneity of the underlying pathogenetic mechanisms of stroke has been mostly incriminated.

A. In the primary prevention of stroke, who gets the most benefit by statin treatment?

Statin treatment remains the mainstay of lipid-lowering therapy in primary and secondary prevention of AVD. Statins have been shown to reduce the risk of stroke in individuals in primary prevention, especially in patients at increased risk for AVD events.[29] In the Collaborative Atorvastatin Diabetes Study (CARDS), atorvastatin treatment in patients with type 2 diabetes mellitus plus at least one AVD risk factor was associated a 50% reduction in non-hemorrhagic stroke (95% confidence interval, CI: 9–72%, p=0.024).[30] Likewise in patients at high AVD risk in the Heart Protection Study (HPS), simvastatin treatment resulted in a reduction by 28% (95% CI, 19–37; p<0.0001) in ischemic strokes.[31]

B. Is there a LDL-C cut-off value to prevent stroke in high-risk patients with a history of atherosclerotic vascular disease (AVD)?

Patients with a history of myocardial infarction, regardless of type, experience increased risk of stroke over time.[32] There is ample evidence that statin treatment reduces the risk of stroke in patients with CHD patients.[33] Treatment targets of LDL cholesterol for the prevention of AVD, including ischemic stroke, have continuously decreased to a cut-off value as low as 70 mg/dl (1.8 mmol/L);[34] however, these targets may practically be hard to attain. To this, ezetimibe, an inhibitor of cholesterol absorption, reduces LDL cholesterol by 15-20% on top of statin treatment, while novel treatment modalities, such as proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors may further lower LDL cholesterol by as much as 60%.[35]

In the *IMProved* Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT), the addition of ezetimibe to simvastatin in stabilized patients with acute coronary syndromes was associated with a 21% reduction in ischemic stroke risk.[36] Similarly, in the FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) trial, the addition of evolocumab resulted in 25% lower risk of ischemic stroke and 25% lower risk of all strokes in AVD patients.[37] The same magnitude of benefit (27% lower risk of ischemic stroke) was reported with alirocumab in ACS patients in the ODYSSEY OUTCOMES trial.[38]

C. Is high-intensity lipid-lowering treatment to reduce recurrent stroke applicable in ischemic stroke survivors?

Patients with a history of stroke are at increased risk for future cardiovascular events and death in the years following stroke.[39] In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial 4,731 patients with history of non-cardioembolic stroke or TIA (<6 months) were randomized to high-intensity statin treatment (i.e atorvastatin 80 mg / day) or placebo. After 4.9 years of follow-up, ''intensive" lipid-lowering resulted in a 16% relative reduction in the risk of stroke, 35% reduction in major coronary events, and 42% reduction in all coronary events despite a small increase in the risk of hemorrhagic stroke. Major statin trials involving stroke survivors have also shown that the absolute benefit regarding recurrence of ischemic stroke seems to be related to the LDL cholesterol levels attained.

In a subgroup analysis of the IMPROVE-IT in patients with prior ACS and a history of stroke (n=641) prior to randomization the combination of statin with ezetimibe was associated with a 40% reduction of stroke risk (hazard ratio, HR 0.60, 95% CI 0.38-0.95; p =0.03).[36]

Of note, in patients with previous history of stroke in the FOURIER trial (n=5,337), treatment with evolocumab had a similar effect to that for patients with other forms of AVD (HR 0.85, 95% CI: 0.72-1.00).

D. Does aggressive lipid-lowering increase the risk of hemorrhagic stroke?

Available data from RCTs with statins as monotherapy or in combination with ezetimibe and/or PCSK9 inhibitors do not indicate that intensive LDL cholesterol-lowering is a risk factor for hemorrhagic stroke.

Conclusion:

- Statin treatment decreases the risk of ischemic stroke in primary prevention, primarily in patients at increased AVD risk such as diabetics and individuals with multiple vascular risk factors.
- High intensity lipid lowering therapy with statins reduces the risk of stroke in patients with established CHD or ACS.
- The addition of ezetimbe or/and PCSK9 reduces the risk of stroke in patients with prior ACS or stabilised CHD.
- Aggressive lipid lowering therapy with statins plus/minus ezetimibe reduces the risk of stroke in stroke survivors in a LDL-C dependent manner.
- PCSK9 inhibitors represent a therapeutic option on top of statin plus/minus ezetimibe therapy to achieve very low LDL cholesterol target levels; alirocumab and evolocumab reduce the risk of ischemic stroke in patients with AVD or ACS, while evolocumab has been reported to reduce AVD risk in patients with a previous history of stroke.

Recommendations:

- We recommend that statins be used as a part of standard secondary prophylactic treatment after an ischemic stroke or a transient ischemic attack (TIA). Most benefit was observed with atorvastatin 80 mg **(Grade A)**. Aggressive Intensive lipid lowering therapy with statins plus/minus ezetimibe reduces the risk of stroke in stroke survivors in a LDL-C dependent manner **(Grade A).**
- PCSK9 inhibitors represent a therapeutic option on top of statin plus/minus ezetimibe therapy to achieve very low LDL cholesterol target levels **(Grade B).** The addition of evolocumab was shown to reduce the risk of ischemic stroke in patients with stabilized cardiovascular disease and the addition of alirocumab reduced the risk of ischemic stroke in patients with acute coronary syndrome **(Grade A).**
- Evolocumab has been reported to reduce AVD risk in patients with a previous history of stroke **(Grade B).**
- The use of statins in secondary prevention of ischemic stroke caused by less frequent non-atherosclerotic etiologies such as arterial dissection and PFO requires further investigations.
- Lipid lowering treatment with statins in combination with lifestyle changes is recommended is the mainstay for primary prevention of ischemic stroke in patients who have high 10-year risk for cardiovascular events. The patients with diabetes and patients with multiple risk factors appear to benefit the most **(Grade A).** The drug-class and the intensity of the lipid-lowering treatment as well as the treatment goals are thus dependent on patient characteristics (**Grade A).**

- Statins should be used with caution in patients with previous spontaneous ICH **(Grade C).** Using high-dose statin regimens in patients with ICH should be decided on an individual patient basis. In a subgroup of patients with cerebral amyloid angiopathy-related lobar ICH, statin use should probably be reserved for compelling indications **(Grade C).**
- There is no evidence from RCTs to support the routine use of statins in the acute phase of stroke (first 2 weeks). However, observational studies do not show an increase in symptomatic ICH in patients previously treated with statins or to whom statin was given within 3 days after stroke. Statin treatment is thus recommended to start before discharge from hospital after an AIS or at least during follow-up **(Grade C).**

References

1. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2018; 49: e46-e110.
2. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014; 45: 2160-236.
3. European Stroke Organisation Executive C and Committee ESOW. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008; 25: 457-507.
4. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014; 13: 429-38.
5. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014; 370: 2478-86.
6. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014; 370: 2467-77.
7. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology*. 2013; 81: 619-25.
8. Ommen SR, Odell JA and Stanton MS. Atrial arrhythmias after cardiothoracic surgery. *N Engl J Med*. 1997; 336: 1429-34.
9. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB and Lip GY. Assessment of the CHA2DS2-VASc Score in Predicting Ischemic Stroke, Thromboembolism, and Death in Patients With Heart Failure With and Without Atrial Fibrillation. *JAMA*. 2015; 314: 1030-8.
10. Ryoo S, Chung JW, Lee MJ, et al. An Approach to Working Up Cases of Embolic Stroke of Undetermined Source. *J Am Heart Assoc*. 2016; 5: e002975.
11. Brunner KJ, Bunch TJ, Mullin CM, et al. Clinical predictors of risk for atrial fibrillation: implications for diagnosis and monitoring. *Mayo Clin Proc*. 2014; 89: 1498-505.
12. Yang H, Nassif M, Khairy P, et al. Cardiac diagnostic work-up of ischaemic stroke. *Eur Heart J*. 2018; 39: 1851-60.
13. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012; 366: 120-9.
14. Kim TS and Youn HJ. Role of echocardiography in atrial fibrillation. *J Cardiovasc Ultrasound*. 2011; 19: 51-61.
15. Katsanos AH, Psaltopoulou T, Sergentanis TN, et al. Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: A systematic review and diagnostic test accuracy meta-analysis. *Ann Neurol*. 2016; 79: 625-35.
16. Amarenco P, Cohen A, Hommel M, Moulin T, Leys D and Bousser MG. Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. *N Engl J Med*. 1996; 334: 1216-21.

17. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW and Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. *J Am Coll Cardiol*. 1998; 31: 1622-6.
18. Tunick PA and Kronzon I. Atheromas of the thoracic aorta: clinical and therapeutic update. *J Am Coll Cardiol*. 2000; 35: 545-54.
19. Hart RG, Catanese L, Perera KS, Ntaios G and Connolly SJ. Embolic Stroke of Undetermined Source: A Systematic Review and Clinical Update. *Stroke*. 2017; 48: 867-72.
20. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for secondary stroke prevention in patients with embolic strokes of undetermined source: Design of the NAVIGATE ESUS randomized trial. *Eur J Stroke*. 2016; 1: 146-54.
21. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. *N Engl J Med*. 2018; 378: 2191-201.
22. Diener HC, Easton JD, Granger CB, et al. Design of Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS). *International journal of stroke : official journal of the International Stroke Society*. 2015; 10: 1309-12.
23. Diener H, Sacco RL, Easton J, et al. RE-SPECT ESUS: Dabigatran versus acetylsalicylic acid for stroke prevention in patients with embolic stroke of undetermined source. *11th World Stroke Congress*. Montreal, Canada: World Stroke Organization, 2018.
24. Ntaios G, Papavasileiou V, Sagris D, et al. Closure of Patent Foramen Ovale Versus Medical Therapy in Patients With Cryptogenic Stroke or Transient Ischemic Attack: Updated Systematic Review and Meta-Analysis. *Stroke*. 2018; 49: 412-8.
25. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med*. 2017; 377: 1319-30.
26. Ntaios G and Hart RG. Embolic Stroke. *Circulation*. 2017; 136: 2403-5.
27. Toni D, Di Angelantonio E, Di Mascio MT, Vinisko R, Bath PM and Group PRS. Types of stroke recurrence in patients with ischemic stroke: a substudy from the PRoFESS trial. *International journal of stroke : official journal of the International Stroke Society*. 2014; 9: 873-8.
28. Lehtola H, Airaksinen KEJ, Hartikainen P, et al. Stroke recurrence in patients with atrial fibrillation: concomitant carotid artery stenosis doubles the risk. *European journal of neurology : the official journal of the European Federation of Neurological Societies*. 2017; 24: 719-25.
29. Barkas F and Milionis H. Treating Dyslipidemia for the Primary and Secondary Prevention of Stroke. *Seminars in neurology*. 2017; 37: 286-93.
30. Hitman GA, Colhoun H, Newman C, et al. Stroke prediction and stroke prevention with atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetic medicine : a journal of the British Diabetic Association*. 2007; 24: 1313-21.
31. Collins R, Armitage J, Parish S, Sleight P, Peto R and Heart Protection Study Collaborative G. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004; 363: 757-67.
32. Polonski L, Gasior M, Gierlotka M, et al. A comparison of ST elevation versus non-ST elevation myocardial infarction outcomes in a large registry database: are non-ST myocardial infarctions associated with worse long-term prognoses? *International journal of cardiology*. 2011; 152: 70-7.
33. Amarenco P and Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *The Lancet Neurology*. 2009; 8: 453-63.
34. Authors/Task Force M, Catapano AL, Graham I, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the

special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis*. 2016; 253: 281-344.
35. Milionis H, Barkas F, Ntaios G, et al. Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors to treat hypercholesterolemia: Effect on stroke risk. *European journal of internal medicine*. 2016; 34: 54-7.
36. Bohula EA, Wiviott SD, Giugliano RP, et al. Prevention of Stroke with the Addition of Ezetimibe to Statin Therapy in Patients With Acute Coronary Syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation*. 2017; 136: 2440-50.
37. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *The New England journal of medicine*. 2017; 376: 1713-22.
38. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018; 379: 2097-107.
39. Dhamoon MS, Tai W, Boden-Albala B, et al. Risk of myocardial infarction or vascular death after first ischemic stroke: the Northern Manhattan Study. *Stroke*. 2007; 38: 1752-8.

Session 5: Update on secondary prevention issues 2

Chair: Danilo Toni (Rome) and Christian Pristipino (Rome). Secretary: Maria Lantz (Stockholm).

The following Consensus Statement was (if approved) adopted by the 12th ESO Karolinska Stroke Update meeting on November 12th/13th, 2018.

The consensus statement was proposed by the chairman of the session, Professor Danilo Toni, Italy and Dr Christian Pristipino, Italy, and the session secretary Dr Maria Lantz, Sweden, together with the speakers of the session. The statement was then finally approved by the participants of the meeting, after listening to the different presentations.

The speakers in this session were Dr Christina Sjöstrand, Sweden, Dr Christian Pristipino, Italy, Dr Grethe Andersen, Denmark and Dr Peter Schellinger, Germany.

Issues for the 2018 consensus session:

1. Does percutaneous closure of PFO vs antiplatelet therapy reduce the risk of stroke recurrence?
2. Does percutaneous closure of PFO vs oral anticoagulants reduce the risk of stroke recurrence?
3. Does oral anticoagulant therapy vs antiplatelet therapy reduce the risk of stroke recurrence?

4. In patients with non-valvular AF and previous ischemic stroke or TIA, does left atrial appendage closure reduce risk of recurrent stroke or thromboembolism compared to oral anticoagulant treatment?
5. In patients with non-valvular AF and previous ischemic stroke or TIA, does left atrial appendage closure lead to lower risk of serious adverse events compared to oral anticoagulant treatment?
6. In patients with non-valvular AF and previous ischemic stroke or TIA submitted to left atrial appendage closure, does antiplatelet treatment reduce risk of thrombus formation on the device compared to oral anticoagulant treatment?

Session 5 – Part 1) PFO-Closure

Speakers: *Christina Sjöstrand and Christian Pristipino*

Background:

Basing on the available literature, the Karolinska Consensus 2016 had released the following recommendations:

1. We recommend that percutaneous PFO closure should be offered to patients with cryptogenic stroke and a PFO provided that the PFO is likely stroke-related according to the RoPE score **(Grade A).**

2. Current evidence did not show any difference in outcome comparing oral anticoagulation and antiplatelet therapy for secondary stroke prevention in patients with PFO. We recommend future randomized trials comparing different antithrombotic/anticoagulant approaches in patients with cryptogenic stroke and PFO, especially trials that include the non-vitamin K antagonist (VKA) oral anticoagulants **(Grade B).**

3. Currently, the Risk of Paradoxical Embolism (RoPE) score represents the best tool to estimate the probability whether a discovered PFO is likely stroke-related or incidental. It is desirable that the ROPE score be validated in a prospective large cohort (Grade B).

Hence, the focus was on detecting the appropriate patient to be implanted using the ROPE score, though its validation on prospective cohorts of patients was not available.

Since then, three new trials, the CLOSE, the REDUCE, the DEFENSE-PFO trials, the long term follow up of the RESPECT trial and several meta-analyses have been published.

1) Does percutaneous closure of PFO vs antiplatelet therapy reduce the risk of stroke recurrence?

The Reduce trial[3], evaluated PFO closure with the Gore Helex (not available any more) or Gore Cardioform septal occluder plus antiplatelet therapy versus antiplatelet treatment alone in 664 patients with a cryptogenic ischaemic stroke. Atrial septal aneurysm (ASA) was present in 20% of patients undergoing closure (this data is not available for patient on medical therapy only) and a moderate-to large shunt was present in approximately 80% of patients in both arms. The incidence of new brain infarctions was significantly lower in the PFO closure group than in the antiplatelet-only group (5.7% vs. 11.3%; P = 0.04). Atrial fibrillation occurred in 6.6% of patients after PFO closure vs 0.4% ($p<0.001$).

The Close study[4] was a 3 arm randomised study. The 3 arms of the study were: 1) antiplatelet therapy plus trans-catheter PFO closure with any CE-mark of PFO closure device; 2) antiplatelet therapy alone; 3) anticoagulant therapy alone, with warfarin or direct oral anticoagulants. The study included 663 patients, with a cryptogenic ischaemic stroke and a PFO with an associated ASA or large interatrial shunt. ASA was present in approximately 32% of patients in both arms, a large shunt was present in approximately 72% of patients in both arms. The risk of recurrent stroke was significantly reduced in the PFO closure group as compared with the antiplatelet therapy alone group (97 % RR; HR 0.03; 95 % CI: 0.00–0.26; p<0.001). A significantly higher rate of new-onset paroxysmal atrial fibrillation in the PFO closure group compared to the antiplatelet only group was also reported (4.6 % versus 0.9 %; p<0.02).

The Defense-PFO study compared PFO closure with Amplatzer PFO Occluder or medical therapy alone as chosen by the caring physician (antiplatelet agents or warfarin) in 120 patients who experienced a cryptogenic ischaemic stroke and had a high risk PFO (ASA, PFO width >2 mm or moderate-to-large shunt). ASA was present in approximately 10% of patients in both arms, atrial septal hypermobility in 45% and a large shunt in 90% of patients. The primary endpoint was a composite of stroke, vascular death, or Thrombolysis In Myocardial Infarction (TIMI)–defined major bleeding during 2 years of follow-up, and occurred in 6 patients undergoing medical therapy only, and in none undergoing PFO closure (p=0.013). The study reports 2 cases of AF in the group undergoing closure and none in the medical therapy-group.

The Respect trial [8] compared the Amplatzer PFO Occluder with antiplatelet or anticoagulation as monotherapy or in different combinations in 980 patients with a cryptogenic stroke only. A similar proportion of patients with ASA (36.1 % vs 35.1 %) and presence of substantial shunting (77.9 % vs 74.1 %) was observed.

The primary analysis[8] showed similar results in the prevention of stroke in the 2 arms at an average of 3 years follow-up, with a per-protocol analysis suggesting benefit for PFO closure (HR 0.366, 95 % CI 0.141–0.955, p=0.032). However, In the long term follow-up report[6], published in 2017, the investigators reported that after 10 years, in an intention-to-treat analysis, PFO closure with the Amplatzer PFO Occluder resulted in a 62 % relative risk reduction (RRR) for recurrent ischaemic stroke compared to medical management (HR 0.38; 95 % CI: 0.18–0.79; 10-year event rates 2.3 % versus 11.1 %; p=0.007). The rates of atrial fibrillation, major bleeding, and death from any cause were comparable or lower in the device study arm.

- Only CLOSE and REDUCE trials directly compared percutaneous closure plus antiplatelet therapy vs. antiplatelet therapy alone. Both of them showed a statistically significant superiority of percutaneous closure on top of antiplatelet therapy versus antiplatelet therapy alone in preventing the recurrence of stroke[3,4]. In both studies, serious adverse events incidence was similar in the two arms, while a higher incidence of atrial fibrillation in the first 30 days was observed in patients undergoing closure (6.6% in REDUCE and 4.6% in CLOSE) as compared to patients on medical therapy only (0.4% in REDUCE and 0.9% in CLOSE)
- In two subgroup analyses of CLOSURE I and RESPECT studies considering only patients receiving antiplatelet therapy, the results were respectively a similar efficacy of both strategies and a statistically significant superiority of percutaneous closure on top of antiplatelet therapy versus antiplatelet therapy alone[5,6].
- Overall, all recent meta-analyses of the 6 randomised trials (enrolling patients aged 18-65 years old) are consistent with a superiority of percutaneous closure plus pooled medical therapy vs. pooled medical therapy alone in preventing the recurrence of stroke (NNT=37; 95%CI: 26 to 68), with a similar safety profile of the two strategies (serious adverse events

incidence) in the follow-up, except for a higher risk of early and transient atrial fibrillation after the procedure in patients undergoing percutaneous closure[1,2].

- A subgroup study-level meta-analysis of all antiplatelet-specific data shows a statistically significant superiority of percutaneous closure on top of antiplatelet therapy versus antiplatelet therapy alone (NNT=28) [1,2].
- The overall results of the meta-analysis of the 6 randomised trials are mainly due to the results on the antiplatelet subgroup. However, in a subgroup study-level meta-analysis, the superiority of percutaneous closure over medical therapy was observed only in patients with high risk PFO features (atrial septal aneurism or atrial septal hypermobility and/or moderate-severe shunt)[1,7]. This was true for both: A) the subgroup-analysis based on enrolment criteria in the different studies [studies enrolling patients unselected for PFO characteristics (CLOSURE I, PC and RESPECT trials) vs. studies enrolling patients with selected PFO characteristics (REDUCE, CLOSE and DEFENSE-PFO trials), NNT=21] and B) the network meta-analysis based on high- vs. low-risk PFOs sub-groups enrolled in the different studies (NNT=4; 95%CI:3 to15). Nonetheless, single individual high-risk features have not been assessed separately. Moreover, a selection bias is clearly evident since not all candidate high-risk factors have been addressed. Therefore, it is not possible to conclude for a precise high risk profile[1].

Recommendations:

In patients aged 18-60 years old with cryptogenic stroke/TIA and with high risk PFO features (moderate or severe shunt, ASA, atrial septal hypermobility) we recommend percutaneous closure plus medical therapy instead of antiplatelet therapy alone **(Grade A).**

In patients between 60 and 65 years percutaneous closure plus medical therapy instead of antiplatelet therapy alone can be offered **(Grade B).**

Percutaneous closure plus medical therapy can be considered in place of antiplatelet therapy alone also for patients aged <18 and >65 years old on an individual basis. **(Grade C).**

2) Does percutaneous closure of PFO vs oral anticoagulants reduce the risk of stroke recurrence?

- No randomised study directly compared percutaneous closure plus medical therapy vs. oral anticoagulant (OAC) therapy alone[1].
- A pre-specified inter-arm comparison of CLOSE study on 425 patients, showed a statistically non-significant lower incidence of recurrent stroke with percutaneous closure on top of medical therapy as compared to OAC therapy alone (0% vs 1.6%, p= 0.08)[7]
- A subgroup study-level meta-analysis of data on patients undergoing only OAC shows a similar risk of recurrent stroke in patients undergoing percutaneous closure on top of medical therapy and those undergoing OAC therapy alone. However, only 814/3216 patients (25%) could be analysed for the comparisons between percutaneous closure and OAC [1]

Recommendations:

Based on the few available data, percutaneous closure and OAC therapy seem to perform equally **(Grade C).** Therefore, while waiting for further evidence and based on the superiority of percutaneous closure over medical therapy as a whole, patient engagement in the choice becomes pivotal.

Adequately dimensioned randomised clinical trials addressing the comparison between percutaneous closure plus medical therapy versus OAC (vitamin-K antagonists or direct OAC) in carefully characterised patients with cryptogenic cerebrovascular accident and different risk characteristics, should be performed

3) Does oral anticoagulant therapy vs antiplatelet therapy reduce the risk of stroke recurrence?

Only one randomised trial, three adjusted and several non-adjusted observational comparisons are available[1].

- The randomised CLOSE trial showed a statistically non-significant reduction of stroke with OAC as compared to antiplatelet therapy [4]. However, a single trial enrolling only 300 patients reporting outcomes with wide confidence intervals cannot be considered conclusive.
- The most recent meta-analysis of these data, showed a lower risk of recurrent stroke in patients with cryptogenic stroke treated with OAC as compared to those treated with antiplatelet therapy (OR=0.88; 95%CI: 0.83-0.92) with an excess risk of bleeding (OR=4.57; 95%CI: 2.10-9.93)[1].
- The certainty of evidence is very low, because the results are mainly derived from non-randomised comparisons, and the included randomised trial, enrolling only approximately 300 patients, reported wide confidence intervals in effect estimates. Therefore, further RCTs will probably impact on effect estimates[1].
- Almost all the evidence is about vitamin K inhibitors.

Recommendations:

In patients in whom a medical therapy only is chosen, we recommend to choose the specific drugs weighing the individual risk of bleeding against the risk of PFO-related stroke recurrence, in close connection with the patient. Long-term OAC with vitamin K antagonists may be preferred if: a) the patient has a low haemorrhagic risk, b) a probable good therapeutic compliance is foreseen, and c) a proper anticoagulant monitoring can be guaranteed **(Grade B).**

We recommend performing adequately dimensioned head-to-head randomised clinical trials addressing the comparison between single antiplatelet drugs versus OAC (vitamin-K antagonists or DOAC) in patients in which percutaneous closure has been excluded.

References

1. Pristipino C, Sievert H, D'Ascenzo F, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *Eur Heart J*. October 2018. doi:10.1093/eurheartj/ehy649.

2. Pristipino C, Sievert H, D'Ascenzo F, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *EuroIntervention*. 2018. doi:10.4244/EIJ-D-18-00622.

3. Søndergaard L, Kasner SE, Rhodes JF, et al. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. *N Engl J Med*. 2017;377(11):1033-1042.

doi:10.1056/NEJMoa1707404.

4. Mas J-L, Derumeaux G, Guillon B, et al. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. *N Engl J Med*. 2017;377(11):1011-1021. doi:10.1056/NEJMoa1705915.

5. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med*. 2012;366(11):991-999. doi:10.1056/NEJMoa1009639.

6. Saver JL, Carroll JD, Thaler DE, et al. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. *N Engl J Med*. 2017;377(11):1022-1032. doi:10.1056/NEJMoa1610057.

7. Turc G, Calvet D, Guérin P, et al. Closure, Anticoagulation, or Antiplatelet Therapy for Cryptogenic Stroke With Patent Foramen Ovale: Systematic Review of Randomized Trials, Sequential Meta-Analysis, and New Insights From the CLOSE Study. *J Am Heart Assoc*. 2018;7(12):e008356. doi:10.1161/JAHA.117.008356.

8. Carroll JD, Saver JL, Thaler DE, et al. Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke. *N Engl J Med*. 2013;368(12):1092-1100. doi:10.1056/NEJMoa1301440.

Session 5 – Part 2) LAA Occlusion

Speakers: *Grethe Andersen and Peter Schellinger.*

Background:

Previous consensus from Karolinska Stroke Update 2012

Based on the available literature, the Karolinska Consensus 2012 released the following considerations: Cardioembolic stroke is frequent and its incidence is increasing with age, in particular over the age of 80 years old. Cardioembolic stroke results in more disability and a higher mortality. Stroke prophylaxis in patients older than 80 years is often complex, due to concomitant large artery disease, which might need ASA treatment, decreased kidney function, risk for interaction and/or less compliance, higher risk of ICH. New OACs are promising, but bleeding problems are not eliminated. LAA occlusion might be an alternative to be considered when long term OAC is contraindicated.

1) In patients with non-valvular AF and previous ischemic stroke or TIA, does left atrial appendage closure reduce risk of recurrent stroke or thromboembolism compared to oral anticoagulant treatment?

LAA occlusion

Stroke is the most debilitating consequence of NVAF. Cardioembolic stroke due to NVAF occur with increasing frequency in the aging stroke population and is the cause of AIS in 1 of 3 in patients aged more than 80 years. These stroke types are often more severe, and patients may be multimorbid or at a high risk of hemorrhagic stroke as well due to hypertensive angiopathy or cerebral amyloid angiopathy (1).

In half cases of stroke due to NVAF the NVAF is new. Secondary preventing of stroke is of utmost importance. Risk of both AIS and ICH is increased in stroke populations compared to primary stroke prevention in NVAF and are high risk patients on both CHA_2DS_2-VASc and HAS-BLED scores (1). Guidelines recommend oral anticoagulation (class 1A), and although ischemic stroke prevention are equal - NOAC is **favoured** over VKA as NOAC has significantly reduced major bleedings compared to VKA (2). There is an increasing use of NOAC´s in case of new NVAF onset, but national registration studies show that 30% of patients with NVAF at risk of thromboembolism are not properly anticoagulated (3). Furthermore, a recent Danish study show that more than 20% of patients initiating NOAC therapy will discontinue treatment within 2 years (4). Bleeding events and fear thereof may be attributing to these results. Although NOAC has improved secondary prophylaxis in NVAF, bleeding problems are not eliminated. LAAO is designed to eliminate the emboli originating from the left atrial appendage that constitute 90% of all thromboembolic events in NVAF. Over the years several devices for LAA closure has been developed, although only the WATCHMAN device has been evaluated in randomized controlled trials.

PROTECT-AF was a randomized proof of concept study comparing LAAO (Watchman device) and VKA in NVAF with composite primary endpoint of stroke, systemic emboli and CV death. The study included 707 patients in a 2:1 ratio to intervention or treatment with OAC. Only 18% of the patients had a previous stroke/TIA. The study was first published in 2009 and final follow-up results published in 2014 (5,6). Final results were **analysed** according to intention to treat principle and showed LAAO to be equal to VKA in ischemic stroke prevention but superior to VKA in preventing ICH (85% reduction) and CV death (60% reduction).

In PROTECT-AF the procedure complications were unacceptably high, with number needed to harm (NNH) of 20 for pericardial effusion, 50 for emergency open heart surgery, and 100 for periprocedural stroke. The study was therefore followed by the PREVAIL study (7) to elaborate on safety. The VKA arm in the PREVAIL study showed exceptionally low ischemic stroke rate (0.3%), a rate far below that in any other prior trial. For the first coprimary endpoint, a composite of stroke, systemic embolism and cardiovascular/unexplained death, non-inferiority could not be demonstrated. The second coprimary endpoint, stroke or systemic embolism >7 days post randomization, showed non-inferiority but not superiority, compared with warfarin, however the study was not powered to show efficacy. Regarding safety, the PREVAIL study showed improved operator skills and a decrease in perioperative ischemic stroke events, going down from 8.7% in PROTECT-AF to 4.2% in PREVAIL. Continually, LAAO has been refined and operator experience has increased with an even lower peri-procedural complication rate (2-3%) and better devices have been developed (7-12). Nevertheless, LAAO remain confined to patients ineligible to oral anticoagulation in clinical practice. This is merely a consequence of the lack of randomized studies comparing LAAO with NOAC.

A recent patient-level metanalysis of PROTECT and PREVAIL studies include all randomized patients including both the high peri-procedure ischemic stroke rate in PROTECT-AF and the very low ischemic stroke rate in PREVAIL. This analysis of all randomized patients shows a similar overall rate of stroke or systemic emboli when LAAO was compared to VKA. This was due to more ischemic strokes which was balanced by a significant reduction in hemorrhagic strokes. Cardiovascular death or unexplained death was also significantly reduced (13).

Stroke outcome beyond the RCT´s.

Non-randomized large post-marketing registries and real-world studies of LAAO consistently show lower ischemic stroke rates compared to untreated patients. (CAP, CAP2, EWOLUTION using Watchman device - and ACP and Amulet registries using Amplatzer Cardiac Plug and the Amulet device (8-12)) all including more than 1000 patients (ischemic stroke rates down to 1.1% to 2.3%). In comparison to the randomized trials the population included in the EWOLUTION registry to a higher degree had a previous history of stroke/TIA and 73% of the patients were deemed unsuitable for anticoagulation. One-year mortality rate was 9.8%. The ischemic stroke rate was 1.1%, and the relative risk reduction compared to estimated historical data was 84%. Also, major bleeding was reduced by 50%, from 5% to 2.5%, compared with expected rates according to HASBLED scores.

Answer to PICO Q1:

LAAO has a similar rate of recurrent stroke or thromboembolism as compared to oral anticoagulant in patients with NVAF. There is a non-significant increase in ischemic strokes but significantly reduced hemorrhagic strokes and an overall lower cardiovascular death. However, in clinical practice different devices are used for LAAO, while randomized data only exist for the WATCHMAN device. In studies of other devices an outcome of stroke has been compared to $CHADS_2$- expected stroke rates. Also, in randomized trials only a minor portion of patients (18%) had the procedure performed as secondary prophylaxis due to prior TIA/stroke. Considering the above there is only limited randomized data for the use of LAAO in secondary prophylaxis.

2) In patients with non-valvular AF and previous ischemic stroke or TIA, does left atrial appendage closure lead to lower risk of serious adverse events compared to oral anticoagulant treatment?

Mortality was not the primary outcome of the PROTECT-AF and PREVAIL studies, but part of the composite endpoint, and the 50% mortality reduction was driven by reduced hemorrhagic strokes. The major advantage of LAAO over OAC is a lower bleeding risk over time and probably the explanation why LAAO is becoming an attractive alternative to OAC in high-risk of bleeding NVAF patients (2,13). It is conceivable that the net clinical benefit of LAAO over OAC may increase even more with longer time follow-up, because bleeding events will continue with OAC. However, there are no available data comparing LAA closure with NOACS, which are associated with a substantially lower bleeding rate in patients with atrial fibrillation. LAAO converts the need for OAC to long-term antithrombotic treatment with aspirin and/or clopidogrel.

Other safety concerns are procedural complications (7,11,14): most prevalent was cardiac tamponade, but this was reduced from 4.3% to 1.9% in CAP and CAP2 registries and even further down to 0.3% in real world registries. As already argued, as more experienced specialists were trained the learning curve improved. Post-marketing registries show other serious adverse events: procedure related stroke with rates from 0.18%-1.24% and device embolization 0.1%-0.77%. Newer devices like the Amplatzer Amulet device show lowering of peri-procedure complications and the Watchman Flex device is underway. Taken all together the safety issues seem comparative and at an acceptable rate and not higher than in other commonly performed percutaneous interventions such as NVAF catheter ablation. Post-procedural device thrombus occurs in 2%-5% (7,11,14) and demands transient OAC treatment for 2-6 weeks. OAC was therefore standard medical treatment in the randomized trials. Finally, whereas LAAO side-effects are mostly procedural-related and manageable

with few lasting long-term sequelae, OAC bleeding are unpredictable in timing and has the disadvantage of ongoing bleeding risk with continued drug exposure in an aging stroke population.

Answer to PICO Q2:

Earlier studies had a high degree of procedure related SAEs. With an improved learning curve, LAAO after stroke or TIA in patients with NVAF now have a low peri-procedural complication rate that most often are without lasting sequelae and a significantly lower rate of long-term serious adverse events measured as ICH and CV death compared to OAC. However, data are mainly from registries and real-life data, and there is limited evidence from randomized studies.

3) In patients with non-valvular AF and previous ischemic stroke or TIA submitted to left atrial appendage closure, does antiplatelet treatment reduce risk of thrombus formation on the device compared to oral anticoagulant treatment?

A single **centre** study has shown promising results from an alternative standard antithrombotic treatment first 6 months without a higher frequency of device thrombus formation compared to RCT (15). Device thrombus formation that results in stroke or TIA are extremely infrequent (0.5%). Thrombus formation is treated with transient OAC under close TEE evaluation. This makes LAAO attractive also for patients with very high bleeding risks on OAC, as OAC is only used in the few cases of thrombus formation, and not as standard treatment. However, LAA occlusion have not yet been compared to NOAC, which have a lower risk of bleeding compared to OAC with warfarin.

Answer to PICO Q3:

Antithrombotic treatment has not been compared to OAC to prevent device thrombus formation, but an observational single **centre** study using post-procedure antithrombotic therapy shows similar magnitude of device thrombus formation as compared to studies using standard transient OAC.

Consensus Statement:

The presently available data from randomized controlled trials do not allow to provide a recommendation on LAA closure in patients with non-valvular AF and previous ischemic stroke or TIA, as an alternative to oral anticoagulant therapy.

Recommendations:

- Patients with non-valvular AF and previous ischemic stroke or TIA with high risk of bleeding or other contraindications to OAC should be included in randomised controlled trials if possible **(Grade C).**

- Waiting for RCTs, LAA closure might be considered in selected patients with absolute contraindications to OAC/DOAC **(Grade C).**

- LAA closure is safer than OAC in terms of risk of bleeding in the long term, but is less safe in term of short-term complications.

- In case of LAA closure in patients at very high risk of intra- and/or extra-cranial bleeding, post-procedural aspirin as single antithrombotic therapy for at least 6 months or lifelong may be used **(Grade C).**

References:

1. Johnsen SP et al. Preadmission oral anticoagulant treatment and clinical outcome among patients hospitalized with acute stroke and atrial fibrillation. A Nationwide Study. Stroke 2014;45:168-175.
2. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC Endorsed by the European Stroke Organisation (ESO). Eur Heart J. 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210.
3. Gadsbøll K, Staerk L, Fosbøl EL, et al. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. Eur Heart J. January 2017:ehw658. doi:10.1093/eurheartj/ehw658.
4. Hellfritzsch M, Husted SE, Grove EL, et al. Treatment Changes among Users of Non-Vitamin K. Antagonist Oral Anticoagulants in Atrial Fibrillation. Basic Clin Pharmacol Toxicol. 2017;120(2):187-194. doi:10.1111/bcpt.12664.
5. Holmes DR et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 2009;374:534-42.
6. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA. 2014;312(19):1988-1998. doi:10.1001/jama.2014.15192.
7. Holmes DR, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol. 2014;64(1):1-12. doi:10.1016/j.jacc.2014.04.029.
8. Reddy VY, Doshi SK, Kar S, et al. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. J Am Coll Cardiol. November 2017. doi:10.1016/j.jacc.2017.10.021.
9. Boersma LV, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. Eur Heart J. 2016;37(31):2465-2474. doi:10.1093/eurheartj/ehv730.
10. Boersma LV, Ince H, Kische S, et al. Efficacy and Safety of Left Atrial Appendage Closure with WATCHMAN in Patients with or without Contraindication to Oral Anticoagulation: 1-year follow-up outcome data of the EWOLUTION trial. Heart Rhythm. May 2017. doi:10.1016/j.hrthm.2017.05.038.
11. Tzikas A, Shakir S, Gafoor S, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. EuroIntervention. 2016;11(10):1170-1179. doi:10.4244/EIJY15M01_06.
12. Landmesser U, Schmidt B, Nielsen-Kudsk JE, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. EuroIntervention. June 2017. doi:10.4244/EIJ-D-17-00493.

13. Holmes DR et al. Left artial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation. A patient-level meta-analysis. JACC 2015;65:2614-23.
14. Reddy VY et al. The safety of percutaneous left atrial appendage closure: results from PROACT-AF and the continued access registry. Circulation 2011;123:417-424.
15. Korsholm K, Nielsen KM, Jensen JM, Jensen HK, Andersen G, Nielsen-Kudsk JE. Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant antithrombotic therapy. Eurointervention 2016; DOI:10.4244/RIJ-D-16-00726.
16. Schellinger PD, Tsivgoulis G, Steiner T, Kohrmann M: Percutaneous left atrial appendage occlusion for the prevention of stroke in patients with atrial fibrillation: Review and critical appraisal. J Stroke 2018;20:281-291.

Session 6: Clinical stroke trials

Chair: Hanne Christensen (Copenhagen) and Martin Köhrmann (Essen). Secretary: Konstantinos Kostulas (Stockholm).

The following Consensus Statement was (if approved) adopted by the 12th ESO Karolinska Stroke Update meeting on November 12th/13th, 2018.

The consensus statement was proposed by the chairman of the session, Hanne Christensen (Copenhagen) and Martin Köhrmann (Essen), and the session secretary Konstantinos Kostulas (Stockholm) together with the speakers of the session. The statement was then finally approved by the participants of the meeting, after listening to the different presentations. The speakers in this session were Hanne Christensen (Denmark), Martin Köhrmann (Germany) and Georgios Tsivgoulis (Greece).

Issues for the 2018 consensus session:

1. How do we increase the generalisability of future stroke trials especially as to women and the old?
2. Clinical end-point trials for prolonged cardiac monitoring in stroke.

Session 6 – Part 1) How do we increase the generalisability of future stroke trials especially as to women and the old?

Speaker: *Hanne Christensen*

Background:

Randomised controlled trials and systematic reviews remain the most reliable methods of assessing the effects of a medical intervention. There has been increasing focus on the internal validity to reduce bias in recent years leading to more focus on design and conduct of trials. However, for a trial to be clinically useful it also needs external validity, also termed applicability or generalizability[1].

In other words: the patients included into definitive trials should mirror the target population to ensure clinical relevance. This should be reflected in the characteristics of randomised patients, selection of patients and setting of the trial among other issues[2].

The applicability of inclusion criteria of clinical trials to an unselected cohort of patients with ICH was assessed based on data from the Lund Stroke Registry (2001-2007) reporting eligibility proportions ranging between 2% and 36%[3]. Further, patients not eligible for any trials had significantly more severe presentations and poorer outcome; no data on the influence of age and gender is shared.

Age and sex remain challenging in regards to external validity in many stroke trials in spite of the increasing bulk of evidence supporting the importance of these two factors[4]. Based on the Danish Stroke registry[5] the median age in all Danish stroke patients (TIA, ischemic stroke and intracerebral haemorrhage) was 72 years and 56% were women. Women are older at the time of stroke[6]. However, trials do not overall reflect this appropriately: Non-vitamin K antagonist oral anticoagulants (NOACs) were evaluated in seven RCTs, in which less than 40% of the people enrolled were women[7], while mean age in trials was 71.5 years; trials did not report any sex differences concerning safety or benefit of the intervention. In the recent WAKE UP trial, mean age was 65 years and 35% of patients were women[8].

As a response, healthcare authorities and scientific societies have already more than a decade ago started making recommendations to promote sex equality in clinical research with specific focus on inclusion of both men and women[9].

Narrow inclusion criteria can offer advantages including increased precision and reduced loss to follow up but the disadvantages include uncertainty about the extrapolarisation of results to a major part of the population in question[10]. In explorative trials looking for proof of concept this is of less importance, however in definitive trials this may for subgroups of the patient population lead to withholding treatment benefits or exposure to unacceptable risks. In stroke trials, this remains the case especially for older women.

A number of reasons for selective participation and exclusion in trials have been proposed[11], including medical reasons, where often specifically older patients are excluded due to age as an inclusion factor, comorbidity and/or pre-existing handicap. Those women with stroke are older than men, which may offer a partial explanation for the lower proportion of women in trials. Safety issues as well as the need to reduce factors that may blur benefit are the arguments for these restrictions to inclusion; however, this reduces the generalisability of trial results in a context of unselected stroke patients.

Consensus Statement:

More evidence is urgently required regarding the effects of treatment interventions (benefit and harm) in especially elderly women with stroke. Trial designs tend not to match the epidemiology of stroke leading to reduced external validity and lack of generalisability to a significant part of the stroke population.

Recommendation:

- Effects of age and sex should be reported in all trials **(Grade A).**
- Enrolment age limits for randomized controlled trials should be avoided, and enrolment should mirror the sex distribution of the disease being investigated **(Grade B).**
- Exclusion criteria for comorbidity and handicap should be designed to exclude only more extreme presentations or specific safety issues **(Grade B).**

References

1. External validity of randomised controlled trials: ”To whom do the results of this trial apply?” Rothwell PM. Lancet 2005;365:82-93.

2. Factors That Can Affect the External Validity of Randomised Controlled Trials. PLOS Clinical Trials 2006;1(1):e9. DOI 10.1371/journal.pctr.0010009

3. Applicability of Clinical Trials in an Unselected Cohort of Patients With Intracerebal Hemorrhage. Hansen BM, Ullman N, Norrving B, Hanley DF, Lindgren A. Stroke 2016;47:2634-2637.

4. Stroke in women - from evidence to inequalities. Cordonnier C, Sprigg N, Sandset EC, Pavlovic A, Sunnerhagen KS, Caso V, Christensen H; Women Initiative for Stroke in Europe (WISE) group. Nat Rev Neurol. 2017;13:521-532. doi: 10.1038/nrneurol.2017.95.

5. www.rkkp.dk

6. Stroke in women - from evidence to inequalities. Cordonnier C, Sprigg N, Sandset EC, Pavlovic A, Sunnerhagen KS, Caso V, Christensen H; Women Initiative for Stroke in Europe (WISE) group. Nat Rev Neurol. 2017;13:521-532. doi: 10.1038/nrneurol.2017.95.

7. Sharma, M., Cornelius, V. R., Patel, J. P., Davies, J. G. & Molokhia, M. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and metaanalysis. Circulation 132, 194–204 (2015).

8. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, et al. for the WAKE-UP Investigators. N Engl J Med 2018;379:611-22. DOI: 10.1056/NEJMoa1804355

9. National Institute of Health. Revitalization act. Public Law 103–143 (1993) Stramba-Badiale, M. et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. Eur. Heart J. 27, 994–1005 (2006).

10. Committee on Women’s Rights and Gender Equality. Draft report on promoting gender equality in mental health and clinical research. 2016/2096 (INI) (European Parliament, 2016)

11. Threats to applicability of randomised trials: exclusion and selective participation. Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C. J Health Serv Res Policy 1999:4:112-121.

Session 6 – Part 2) Clinical endpoints for prolonged cardiac monitoring in stroke

Speakers: *Martin Köhrmann and Georgios Tsivgoulis.*

Background:

Paroxysmal atrial fibrillation (PAF) is known to be prevalent in more than one-fourth of patients with recent ischemic stroke (IS).[1] Clinical trials have provided unflinching evidence that prolonged cardiac rhythm monitoring (PCM) of 30 days and beyond can uncover a substantial portion of IS patients with occult PAF that is otherwise not detected by conventional short-term monitoring.[2-4] American Heart Association / American Stroke Association (AHA/ASA) recommendations on secondary stroke prevention advocate (Class IIa; Level of Evidence C) that PCM for approximately 30 days is reasonable for AF screening within 6 months after a cryptogenic stroke (CS).[5] Recent AHA/ACC/HRS guidelines on Atrial Fibrillation recommend the use of implantable cardiac monitors (loop recorders) in patients

with cryptogenic stroke (Class of Recommendation: IIa, Level of Evidence: B) in whom external ambulatory monitoring is inconclusive to optimize detection of silent AF.[6] The European guidelines on AF management, published by the European Society of Cardiology and endorsed by the European Stroke Organization, consider that additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders is feasible to document silent AF (Class: IIa, Level of Evidence: B).[7] Taking into account that PAF is known to be associated with a 5-fold increase in the IS risk,[8] and that anticoagulation therapy compared to placebo can effectively reduce annual recurrent stroke risk by 8.4% in contrast to antiplatelet therapy that appears to reduce annual recurrent stroke risk by 2.5% (compared to placebo),[9,10] it becomes evident that the successful identification of occult PAF leading to prompt anticoagulant initiation would inevitably have a preventive impact on stroke recurrence. In addition, a meta-analysis of randomized-controlled clinical trials comparing directly the efficacy of anticoagulation to antiplatelet therapy in terms of primary and secondary stroke prevention in non-valvular atrial fibrillation patients reported that anticoagulation therapy was related to a 7% annual recurrent stroke risk reduction compared to antiplatelet therapy.[10]

The main question regarding all above facts is if they also apply to PAF detected by PCM. In addition, there is the notion that short episodes of PAF (some seconds to a few minutes) detected by PCM are not clinically relevant, and thus should not prompt any change in patient management.[11] In the same line there is also expressed concern regarding temporal relationship between PAF episodes detected by PCM and clinical events of thromboembolism[12]. Several trials show no temporal relationship of PAF and ischemic events,[13] and additionally PAF episodes detected by PCM very close to the onset to cerebrovascular events could be rather a result of cerebrovascular ischemia -due to stroke-induced sympathetic activation- than a true causal underlying mechanism.[14]

Both clinical trial and real-world evidence suggest that short duration PAF episodes represent only the minority of episodes detected by PCM.[2,15] Additionally, as already known from pacemaker studies, brief episodes of atrial tachycardia/ PAF have been associated with a double-risk of stroke or death during follow-up.[16] Interestingly, findings from a post-hoc analysis of Find-AF trial reported that 75% of the patients with AF detected after cerebral ischemia were also found to have AF during long-term follow-up, contradicting thus the argument of a temporal association between PAF detection and time from IS onset.[17] Duration of PAF is also not known to be associated with baseline stroke severity and early outcomes in patients with cryptogenic stroke (CS).[18] Moreover, PAF duration appears not to be implicated in the decision to initiate anticoagulation treatment in every-day clinical practice according to the results of a recent survey.[19]

PCM emerges as an invaluable diagnostic tool to identify the subgroup of patients with embolic strokes of undetermined source (ESUS) due to underlying AF, who will benefit from oral anticoagulation,[20] and distinguish them from other cases that further investigation and different management might be required.[21] The notion that paroxysmal AF does not represent the main underlying etiopathogenic mechanism of cerebral ischemia in ESUS patients[22] is in line with the recently reported NAVIGATE ESUS (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source) trial where the detection rate of symptomatic AF during an approximate 1-year follow-up period was only 3%.[23] Therefore, due to the utility of PCM in the identification of individuals who require anticoagulation and thus its direct impact in secondary stroke preventions it is logical to assume that PCM is a cost-effective approach, as already highlighted in different clinical settings by numerous studies.[24-26] In addition, the cost-effectiveness of PCM can be further improved by the careful selection of patients who have a higher likelihood of underlying AF,[27,28] with no contraindication to anticoagulant treatment and other stroke causes excluded after a comprehensive initial diagnostic work-up.[21] The

Detection of Silent Atrial Fibrillation aFter Ischemic StrOke (SAFFO study) guided by implantable loop recorder[29] and the atrial fibrillation detected by continuous electrocardiographic monitoring using implantable loop recorder to prevent stroke in individuals at risk (LOOP study)[30] are two ongoing multicenter, open-label, randomized clinical trials that aim to evaluate further the clinical impact and potential cost-effectiveness of PCM in secondary stroke prevention.

Consensus Statement:

More evidence from adequately powered randomized clinical trials with sufficient follow-up time are needed to further investigate the impact of PCM on secondary stroke prevention and other clinical endpoints.

Recommendations:

- PCM can identify a significant proportion of IS patients with occult PAF, not detected by conventional cardiac monitoring **(Grade A).**
- PCM may have a substantial impact in secondary stroke prevention, through the identification and prompt anticoagulant initiation in IS patients with occult PAF **(Grade C).**
- Selection of patients based on clinical and echocardiographic parameters may further enhance the diagnostic utility of PCM, and further increase its cost-effectiveness **(Grade C).**

References

1. Sposato LA, Cipriano LE, Saposnik G, Ruíz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2015;14:377-87.

2. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478-86.

3. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med 2014;370:2467-77.

4. Reiffel JA, Verma A, Kowey PR, et al. Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable Cardiac Monitors in a High-Risk Population: The REVEAL AF Study. JAMA Cardiol 2017;2:1120-1127.

5. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160-236.

6. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. Circulation. 2019CIR0000000000000665. doi: 10.1161/CIR.0000000000000665. [Epub ahead of print]

7. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-2962

8. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991; 22: 983-988.

9. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131:492-501.

10. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857-867

11. Swiryn S, Orlov MV, Benditt DG, et al. Clinical Implications of Brief Device-Detected Atrial Tachyarrhythmias in a Cardiac Rhythm Management Device Population: Results from the Registry of Atrial Tachycardia and Atrial Fibrillation Episodes. Circulation. 2016;134:1130-1140.

12. Lee R, Mittal S, et al. Utility and limitations of long-term monitoring of atrial fibrillation using an implantable loop recorder. Heart Rhythm. 2018;15:287-295.

13. Brambatti M, Connolly SJ, Gold MR, et al, Healey JS; ASSERT Investigators. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation. 2014;129:2094-2099

14. Katsanos AH, Korantzopoulos P, Tsivgoulis G, et al. Electrocardiographic abnormalities and cardiac arrhythmias in structural brain lesions. Int J Cardiol. 2013;167:328-34.

15. Ziegler PD, Rogers JD, Ferreira SW, et al. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population. Int J Cardiol. 2017;244:175-179.

16. Glotzer TV, Hellkamp AS, Zimmerman J, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). Circulation. 2003;107:1614-9.

17. Weber-Krüger M, Lutz C, Zapf A, et al. Relevance of supraventricular runs detected after cerebral ischemia. Neurology. 2017;89:1545-1552.

18. Liantinioti C, Tympas K, Katsanos AH, et al. Duration of paroxysmal atrial fibrillation in cryptogenic stroke is not associated with stroke severity and early outcomes. J Neurol Sci. 2017;376:191-195.

19. Rankin AJ, Tran RT, Abdul-Rahim AH, Rankin AC, Lees KR. Clinically important atrial arrhythmia and stroke risk: a UK-wide online survey among stroke physicians and cardiologists. QJM. 2014;107:895-902.

20. Verma N, Ziegler PD, Liu S, Passman RS. Incidence of atrial fibrillation among patients with an embolic stroke of undetermined source: Insights from insertable cardiac monitors. Int J Stroke 2018. DOI: 10.1177/1747493018798554 [Epud ahead of Print]

21. Katsanos AH, Bhole R, Frogoudaki A, et al. The value of transesophageal echocardiography for embolic strokes of undetermined source. Neurology 2016;87:988-95.

22. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13:429-38.

23. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. N Engl J Med. 2018;378:2191-2201.

24. Yong JH, Thavorn K, Hoch JS, et al. Potential Cost-Effectiveness of Ambulatory Cardiac Rhythm Monitoring After Cryptogenic Stroke. Stroke. 2016;47:2380-5.

25. Kamel H, Hegde M, Johnson DR, Gage BF, Johnston SC. Cost-effectiveness of outpatient cardiac monitoring to detect atrial fibrillation after ischemic stroke. Stroke. 2010;41:1514-20.

26. Diamantopoulos A, Sawyer LM, Lip GY, et al. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. Int J Stroke. 2016;11:302-12.

27. Kwong C, Ling AY, Crawford MH, Zhao SX, Shah NH. A Clinical Score for Predicting Atrial Fibrillation in Patients with Cryptogenic Stroke or Transient Ischemic Attack. Cardiology. 2017;138:133-140.

28. Ricci B, Chang AD, Hemendinger M, et al. A Simple Score That Predicts Paroxysmal Atrial Fibrillation on Outpatient Cardiac Monitoring after Embolic Stroke of Unknown Source. J Stroke Cerebrovasc Dis. 2018;27:1692-1696.

29. Toni D, Lorenzano S, Strano S; SAFFO Trial Investigators. Detection of Silent Atrial Fibrillation aFter Ischemic StrOke (SAFFO) guided by implantable loop recorder: multicentre Italian trial based on stroke unit network with paired cardio-arrhythmology units (Italian Neurocardiology Unit Network). Int J Stroke. 2016;11:361-7.

30. Diederichsen SZ, Haugan KJ, Køber L, et al. Atrial fibrillation detected by continuous electrocardiographic monitoring using implantable loop recorder to prevent stroke in individuals at risk (the LOOP study): Rationale and design of a large randomized controlled trial. Am Heart J. 2017;187:122-132.

Session 8: Post-stroke early mobilization

Chair: Niaz Ahmed (Stockholm).

The following Consensus Statement was (if approved) adopted by the 12th ESO Karolinska Stroke Update meeting on November 12th/13th, 2018.

The Consensus Statement was prepared by Katharina Sunnerhagen (Göteborg) and proposed by the chair of the session Dr. Niaz Ahmed (Stockholm).

The speaker in this session discuss the following question:

1. Should we avoid early mobilization after AVERT?

Speaker: Katharina Sunnerhagen (Göteborg)

Background:

An important contributor to the stroke unit has in descriptive studies been identified as early mobilization (EM): starting out of bed, sitting, standing and walking early after stroke. There is evidence of the negative effects of lack of physical activity in healthy people as well as of

immobilization on patients. However, there have been concerns about the potential harm of EM and, in particular, due to possible reduced cerebral blood flow caused by adopting an upright position too early. These concerns lead to the AVERT study (A Very Early Rehabilitation Trial and 2104 patients were recruited (and a 99 % 3 months follow-up)[1].
The results from that study was that t 3 months, fewer patients in the VEM group had a favorable outcome (mRS score of 0–2) than in the usual care (UC) group. A total of 480 (46%) VEM patients had a **favourable** outcome compared with 525 (50%) in the UC group. Subgroup analysis of the primary outcome showed a consistent pattern **favouring** UC across all the main subgroups. There was a suggestion of poorer outcomes with VEM (Very Early Mobilisation) in patients with severe stroke and intracerebral hemorrhage but these did not achieve statistical significance (test for interaction p > 0.05).

The issue is the content of the VEM. It had to begin within 24 hours of stroke onset; the focus had to be on sitting, standing and walking activities (i.e. out of bed). The VEM had to be delivered in at least three out-of-bed sessions per day in addition to UC level. Sessions lasted between 10-30 minutes.

The question of possible reduced cerebral blood flow caused by adopting an upright position too early as well as the countervailing risk of aspiration pneumonia have led to variation in head positioning in clinical practice. This was investigated in the HeadPoST trial[2] where the hypothesis was that outcomes in patients with acute ischemic stroke could be improved by positioning the patient to be lying flat (i.e., fully supine with the back horizontal and the face upwards) to increase cerebral perfusion. 11,093 persons were randomized and the intervention started on average 14 hours post stroke onset and lasted for 24 hours.

The lying flat group stayed flat and graded elevation of the head and mobilization with toilet privileges commenced after 24 hours. For the sitting-up position, the head of the patient was elevated to at least 30 degrees and were allowed toilet privileges outside the bed according to their level of mobility. The 3 months follow-up was around 88%.

Disability outcomes after acute stroke did not differ significantly between patients assigned to a lying-flat position for 24 hours and patients assigned to a sitting-up position with the head elevated to at least 30 degrees for 24 hours. These results indicate that the patient can safely have the head up and leave bed according to the level of mobility.

Recommendations:
- The evidence point to that early mobilization is safe is stroke patients but should not be too intense **(Grade B).**

- A progressive adaptation to activities of daily living, such as going to the toilet with assistance (if needed) or sitting in a chair to eat could be initiated within the first days of in-hospital stay **(Grade A).**

- Patients should be clinically observed and monitored closely and in case they present symptoms noted **(Grade C).**

- Early mobilization after a stroke should be adapted to patient's clinical and neurological situation **(Grade C).**

References:

1. Bernhardt J et al: Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet 2015 Jul 4;386(9988):46-55.
2. Anderson CS et al: Cluster-Randomized, Crossover Trial of Head Positioning in Acute Stroke. N Engl J Med. 2017 Jun 22;376(25):2437-2447.

Session 9: Oral anticoagulation and reversal agents after stroke

Chair: Joji Kuramatsu (Erlangen) and Thorsten Steiner (Frankfurt/Main). Secretary: Boris Keselman (Stockholm).

The following Consensus Statement was (if approved) adopted by the 12th ESO Karolinska Stroke Update meeting on November 12th/13th, 2018.

The Consensus Statement was prepared by a writing committee (Andreas Charidimou, Boris Keselman, Eleni Korompoki, Joji Kuramatsu, Jan Purrucker and Thorsten Steiner) and proposed by the chairs of the session: PD Dr. med. Joji Kuramatsu (Erlangen, Germany) and Prof. Dr. med. Thorsten Steiner (Frankfurt am Main, Germany) and the session secretary, Dr. Boris Keselman (Stockholm, Sweden), together with the speaker of the session, Dr. Andreas Charidimou (Boston, USA), Dr. Eleni Korompoki (Athens, Greece/London, UK) and Dr. Jan Purrucker (Heidelberg, Germany).

The speakers in this session discuss the following questions:

1. In patients with intracerebral haemorrhage (ICH) and oral anticoagulation, how is optimal reversal under vitamin K antagonists (VKA) or novel oral anticoagulants (NOAC) achieved to improve outcomes (mortality and functional outcome); specifically, in ICH to reduce haematoma growth?
2. In acute ischaemic stroke how is optimal reversal under VKA or NOAC achieved to minimize bleeding complications with revascularization therapies?
3. In patients after acute ICH with the indication for oral anticoagulation, does (re)initiation of oral anticoagulant therapy compared to no therapy or compared to antiplatelet therapy, improve outcomes (mortality, functional outcome, and rates of thromboembolic/haemorrhagic complications)?
4. In patients after a cerebral amyloid angiopathy (CAA)-related lobar ICH with concomitant indication for oral anticoagulation due to non-valvular atrial fibrillation (AF), how is optimal antithrombotic management achieved to improve outcomes (mortality, functional outcome, and rates of thromboembolic/haemorrhagic complications)?
5. In patients after acute ischaemic stroke with cerebral microbleeds (CMBs) on MRI and the concomitant indication for oral anticoagulation due to AF, how is optimal antithrombotic management achieved to improve outcomes (mortality, functional outcome, and rates of thromboembolic/haemorrhagic complications)?

Session 9 – Talk 1) Use of reversal agents for anticoagulation in the setting of acute stroke (ischemic stroke eligible to revascularization or intracerebral haemorrhage)

Speaker: *Jan Purrucker*

Q1: In patients with ICH and oral anticoagulation, how is optimal reversal under VKA or NOAC achieved to improve outcomes (mortality and functional outcome); specifically, in ICH to reduce haematoma growth?

Background:

In VKA-associated ICH, haematoma expansion is described to occur at a rate of 23 to 36% even within INR levels within the therapeutic range.[1,2] Importantly, in warfarin-related ICH, haematoma growths over a prolonged period, potentially exceeding 24 hours, if the coagulations status is not immediately normalized[1]. According to recent observational studies, haematoma expansion occurs with similar frequency in NOAC-ICH (34 to 38%).[3,4] Likewise, no difference in the dismal prognosis of oral anticoagulated patients suffering ICH was found between VKA and NOAC-cohorts. [1–3,5,6] The high rate of haematoma expansion along with the overall high mortality builds the rational for emergency reversal of anticoagulation in acute oral-anticoagulation-associated ICH, irrespective of the anticoagulant used. In addition, a multicentre observational study found an association of rapid INR reversal with a reduced rate of haematoma expansion.[2] Parallel lowering of systolic blood pressure below 160 mmHg provided an additional effect on reduction of hematoma expansion and mortality. Importantly, an advantage of normalization of coagulation was only observed if the target (INR < 1.3) was achieved within 4 h after admission – thus demanding a straightforward treatment approach like in acute ischaemic stroke.[2] Regarding reversal in **VKA-ICH**, the prospective randomized INCH trial included VKA-ICH patients with an INR ≥ 2.0 at admission and compared fresh frozen plasma (FFP) to prothrombin complex concentrate (PCC) (four-factor PCC, 30 IU/kg). Enrolment was stopped after 50 patients for safety concerns as a significantly larger proportion of PCC treated patients (18/27, 67%) compared with FFP (2/23, 9%) reached the target INR of < 1.3 after 3 h (primary endpoint; adj. odds ratio 30.6, 95% CI 4.7–197.9; p=0.0003) and safety endpoints were in disfavour of FFP. Haematoma expansion occurred significantly less frequent in the PCC group (44%) compared to FFP (59%).[7] Due to the short half-time of the administered coagulation factors, a long-term reversal can only be reached if anticoagulation by PCC is accompanied by Vitamin K.

In **NOAC-ICH**, no randomized controlled data regarding the superiority of a reversal agent were found, and data on the efficacy of available unspecific and specific agents are still limited.

For **unspecific reversal agents**, experimental data have shown normalization of coagulation measurements in rivaroxaban and edoxaban pre-treated healthy volunteers with high doses of PCC (50 IU/kg)[8–11], however, in apixaban treated volunteers, the investigated doses of 25–37.5 IU/kg led only to partial reversal (data on 50 IU/kg are not available).[12] Another study found 4-factor PCC reduced prothrombin time in rivaroxaban treated healthy volunteers more effectively than 3-factor PCC [13]. No relevant effects of PCC on coagulation after dabigatran pre-treatment were observed. The exact mechanism by which PCC reverses NOAC is not established. Two observational studies found no difference in hematoma expansion rates and functional outcome between PCC treated NOAC-ICH patients and those who did not received a reversal attempt [3,4]. Due to the observational study design, the lack of randomization, differences in baseline characteristics and the limited sample size, there is a clear need for further data. Reversal of the anticoagulatory effect of rivaroxaban and apixaban by recombinant FVIIa has been suggested ex-vivo.[14–16] However, in vivo studies on rFVIIa in NOAC-ICH are missing, and the known increase in arterial thromboembolic complications with use of rFVIIa warrant caution.[17]

With regard to **specific reversal agents**, for dabigatran, the humanized monoclonal antibody fragment idarucizumab was shown to reverse anticoagulation activity within minutes. It acts by binding dabigatran with high affinity, administered by a single bolus administration only (2 x 2.5 g intravenously). In the open-label non-randomized RE-VERSE AD study, full reversal of dabigatran was achieved in 100% of the enrolled cases with either uncontrolled bleeding (n=301) or need to undergo an urgent invasive procedure (n=202). The study included 53 patients with intracerebral bleeding, 3

of these patients (6%) experienced a thromboembolic event, all > 10 days after idarucizumab administration and mechanistically an intrinsic prothrombotic risk cannot be expected.[18]

For reversal of the factor Xa inhibitors rivaroxaban and apixaban, the specific agent andexanet alfa (Andexxa® (coagulation factor Xa (recombinant), has been approved in May 2018 by the FDA, but is still undergoing review in the EU. It has been tested in two phase 3 trials and is currently investigated in a phase 4 study.[19,20] The randomized controlled phase 3 trials (ANNEXA-A and -R) compared the efficacy of Andexanet alfa in healthy volunteers taking either apixaban or rivaroxaban.[19] Andexanet alfa reversed the anticoagulants effects after bolus administration and continued infusion, however, after cessation of the infusion a rapid rebound and elevations in d-dimer and prothrombin fragments 1 and 2 were observed. Preliminary results of the ongoing open-label single-group phase 4 study in patients with acute major bleeding largely confirmed the efficacy findings from the phase 3 trials.[20]

Recommendations

In acute ICH, reversal of anticoagulation should be started as soon as possible after diagnosis of ICH **(Grade B: VKA; Grade C: NOAC).**

In VKA-ICH, optimal reversal is achieved by immediate application of 4-factor PCC (30 IU/kg):

- If INR ≥ 2.0 **(Grade B).**
- If INR ≥ 1.3 but < 2.0, a dose reduction to 10-25 IU/kg (dose depending on the INR) can be considered **(Grade C).**

In VKA-ICH, the target INR after reversal is < 1.**3 (Grade B).**

In VKA-ICH, INR should be monitored serially to trigger possible rescue therapy (repeated PCC application) **(Grade C).**

In VKA-ICH, all reversal treatments should be accompanied by Vitamin K administration (10 mg, i.v.; repeated doses depending on results of sequential INR measurements) **(Grade C).**

In NOAC-ICH, reversal treatment should not be delayed by waiting for results of coagulation test (Grade C).

In dabigatran-ICH, reversal treatment should be carried out by immediate application of idarucizumab (Bolus 2x2.5 g i.v.) **(Grade C).**

In factor Xa inhibitor-ICH, reversal treatment should be carried out by immediate application of andexanet alfa if marketed or within a study **(Grade C).**

In factor Xa inhibitors-ICH (if andexanet is unavailable), reversal treatment should be carried out by immediate application of high-dose 4-factor PCC (50 IU/kg) **(Grade C).**

PCC is not recommended in patients with ICH under dabigatran therapy **(Grade C).**

In NOAC-ICH, serial plasma concentration measurement is recommended to account for potential rebound effects **(Grade C).**

Q2: In acute ischemic stroke how is optimal reversal under VKA or NOAC achieved to minimize bleeding complications with revascularization therapies?

Background:

Regarding **intravenous thrombolysis** (IVT) in patients receiving VKA, observational data point towards an increased risk of symptomatic intracerebral haemorrhage (sICH) if the INR exceeds 1.7.[21] Observational data in NOAC-treated patients are limited, data from the US-GWTG-stroke Registry identified 251 of 42887 treated with IVT despite known NOAC treatment comprising close to 80% of potentially eligible NOAC patients.[22] Despite the NOAC patients being found to be older and having suffered from more severe strokes, no difference in the unadjusted rates of sICH were found between NOACs, VKA and non-anticoagulated patients (sICH, 4.8%, 4.9%, and 3.9%, resp.).[22] A recent review identified 462 NOAC-patients treated with IVT only and reported a sICH rate of 4.3%, but data on NOAC-specific coagulation test results were only available in a minority of the patients.[23] Based on these studies, the actual risk of IVT in NOAC treated patients cannot be established, and a conservative approach seems justified in light of the INR-dependent increase in sICH risk seen in VKA patients. Thus, reversal of anticoagulation before IVT might be an option to minimize bleeding risk. For dabigatran treated patients, idarucizumab can be used on-label to reverse anticoagulation before thrombolysis. According to a recent systematic review, 55 cases of IVT after idarucizumab treatment were published (mostly moderately affected, NIHSS 5-15, 63%).[24] Symptomatic ICH occurred in 5% (3/55).[24] In VKA, a prospective study in whom 26 patients with a mean admission INR of 2.3 (+/- 0.6) received 4-factor PCC before IVT reported no case of sICH, but 2 cases of recurrent stroke (day 4 and 15).[25] No data were found regarding use of andexanet alfa before IVT in factor xa inhibitor treated patients.

Concerning **endovascular treatment** (EVT), no data can be drawn from the stent-retriever RCTs.[26–29] For VKA anticoagulated patients, a cohort study and meta-analysis found no significant increase in sICH with INR > 1.7 compared to those with INR ≤ 1.7.[30] Results were replicated in a single-centre analysis.[31] A retrospective cohort study on patients with NOACs (n=17) and time since last intake < 24h compared to VKA (INR > 2.0, n=29) treated with EVT (stentretriever, 67%) found no difference in the rate of haemorrhagic transformations.[32] In the prospective multicentre RASUNOA registry, no difference between NOAC treated patients receiving either IVT plus EVT (n=5) or EVT only (n=23) in terms of sICH was observed.[33] As in the stentretriever RCTs no increased bleeding risk was observed between EVT treated patients and controls; an inherent bleeding risk besides the periprocedural risks of vessel rupture seems non-existent.

Expert recommendations based on extrapolations from trial data in surgery patients suggests that 30 ng/ml is a critical **threshold** above which an increase in bleeding complications in urgent procedures/surgery might be expected.[34–36] Additionally, commonly available tests used for measuring NOAC concentrations might encounter performance problems in lower concentrations (< 30 ng/ml).[34] Importantly, a recent study found calibrated anti Xa tests to provide high sensitivity and specificity in case of rivaroxaban, but only very limited sensitivity in case of apixaban, leading to falsely “safe” classified cases (concentrations in spectrometry > 30 ng/ml, but tests indicates < 30 ng/ml).[37] **Point-of-care testing (POCT)** is established for VKA and the same INR thresholds apply. In NOACs, a single-centre study evaluated the use of the Hemochron® Signature Elite POCT device to determine NOAC concentrations < 30 ng/ml.[38] Both PT/INR and ACT+ test cards were influenced by rivaroxaban and dabigatran, but only insufficiently by apixaban. For rivaroxaban, PT/INR ≤ 1.0 correctly identified concentrations < 30 ng/ml with a specificity of 97% (95% CI, 89–100), with similar results for the ACT+ measurements (≤ 120 s, specificity 96% (87–99)).[38] For dabigatran, Hemochron®-

PT/INR ≤ 1.1 had a specificity of 99 (92–100), and ACT+ ≤ 100 s a specificity of 96 (87–99) do identify concentrations < 30 ng/ml.[38] According to data presented at the ESOC 2018, a Hemochron® PT/INR > 1.5 detects edoxaban concentrations > 30 mg/ml with a sensitivity of 99% and specificity of 98%.[39] Prospective data evaluating the safety of IVT in NOAC patients after POCT measurements are not yet available.

Recommendations:

Patients with acute ischemic stroke under VKA or NOAC treatment with proven large vessel occlusion should be offered IVT (if feasible) and endovascular treatment (thrombectomy) **(Grade C).**

In acute ischaemic stroke under VKA treatment and otherwise eligible for thrombolysis:

- In INR ≤ 1.7: IVT (alteplase) should be administered **(Grade C).**
- In INR > 1.7: The current evidence does not support a statement in favour for or against IVT after reversal with PCC **(Grade C).**

In acute ischaemic stroke under NOAC treatment and otherwise eligible for thrombolysis:

- Relevant drug concentrations in patients on NOACs must be assumed if
    - Global routine tests (activated Partial Thromboplastin Time [aPTT] and/or Prothrombin Time [PT]/INR) are above normal **(Grade C).**
    - If calibrated agent-specific tests or the Ecarin Clotting Time (dabigatran only) indicate concentrations > 30 ng/ml.
- Global routine tests (aPTT and PT/INR) within normal ranges do not exclude relevant drug concentrations and should not be used to guide therapy **(Grade C).**
- In case of dabigatran, administration of idarucizumab (Bolus 2x2.5 g intravenously) followed by IVT might be considered even without specific laboratory tests **(Grade C).**
- In case of factor Xa inhibitors, IVT might be considered without prior reversal if calibrated agent-specific tests indicate NOAC concentration < 30 ng/ml **(Grade C).**
- Point-of-care testing may accelerate IVT. The following thresholds indicating NOAC plasma levels < 30 ng/ml allowing for IVT are currently available for the Hemochron® Signature Elite device only **(Grade C).**
    - Dabigatran Hemochron® Signature Elite-PT/INR ≤ 1.1 or Hemochron® Signature Elite-ACT+ ≤ 100 s
    - Edoxaban Hemochron® Signature Elite-PT/INR ≤ 1.4
    - Rivaroxaban Hemochron® Signature Elite-PT/INR ≤ 1.0 or Hemochron® Signature Elite-ACT+ ≤ 120 s
    - For Apixaban, currently no reliable tests are available

Session 9 – Talk 2) Reinitiation of antithrombotics after ICH

Speaker: *Eleni Korompoki*

Q3: In patients after acute ICH with the indication for oral anticoagulation, does (re)initiation of oral anticoagulant therapy compared to no therapy or compared to antiplatelet therapy, improve outcomes (mortality, functional outcome, and rates of thromboembolic/haemorrhagic complications)?

Background:

For decision making on OAC resumption after ICH the risk of ICH recurrence needs to be carefully balanced against the risk of IS. At present, the application of established clinical stratification risk scores for thromboembolism (CHA_2DS_2Vasc) and bleeding (HAS-BLED score) is challenging in the setting of ICH as they share similar risk factors. Data from available observational studies suggest that the median annual event rate for IS in ICH survivors who did not resume OAC is around 8% while the median annual event rate of ICH recurrence while on OAC is almost 4.5%, which theoretically results in an absolute rate-difference of 3.5% per year.[2,40]

A recent systematic review and meta-analysis of eight observational retrospective studies evaluated the safety and efficacy of OAC resumption (mostly VKA) in 5306 patients with a history of intracranial haemorrhage and OAC resumption was associated with a significantly lower risk of thromboembolic events (pooled relative risk RR, 0.34; 95% CI, 0.25–0.45) without increased risk of recurrence (pooled RR, 1.01; 95% CI, 0.58–1.77).[41] A more recent meta-analysis of observational studies confirmed these results also reporting no increase in ICH recurrence (pooled RR 1.14, 95% CI 0.72 to 1.80; p=0.57), fewer thromboembolic events (pooled RR 0.31, 95% CI 0.23 to 0.42; p<0.001) with OAC resumption and further a reduced long-term mortality (pooled RR 0.27, 95% CI 0.20 to 0.37, p<0.001) in a sub-group of patients with AF as an indication for long-term OAC.[42] All previous studies were conducted on ICH populations with mixed indications for OAC resumption. A systematic review and meta-analysis of observational studies focusing specifically on ICH survivors with AF provided aggregate data on 2,452 patients (97% with VKA related ICH), derived from seven observational cohort studies.[43] Different treatment exposure strategies i.e. VKA, antiplatelets and no antithrombotics were considered after the index ICH using a 6-week landmark approach to reduce selection bias derived from the non-randomized allocation. This meta-analysis showed that anticoagulation with VKA is beneficial over no anticoagulation or antiplatelet agents for IS prevention (pooled Rate Ratio (RR)= 0.46, 95% CI: 0.29-0.72 p=0.008; or RR=0.45, 95 % CI 0.27-0.74, p=0.002) without a statistically significant increase of ICH recurrence (pooled RR=1.23, 95% CI: 0.80-1.87, p=0.53). Finally, VKA resumption compared to no antithrombotic treatment resulted in a significantly lower rate of IS (pooled RR=0.47, 95% CI 0.29-0.77, p=0.002) without increasing ICH recurrence (pooled RR=0,93, 95% CI 0.45-1.90, p=0.84). In this meta-analysis, the pooled annual event rate for IS was significantly lower in patients who resumed VKA (3.2% per 100 patient-years) compared to other treatment strategies (antiplatelets: 9.5 per 100 patient-years; no antithrombotics: 6.1 per 100 patient-years) although the pooled annual event rate for ICH survivors who resumed VKA was 0.4% to 0.9% higher compared to other treatments groups.

Reported outcomes on ICH survivors in particular were reinforced by an international collaborative individual patient data meta-analysis of three cohort studies including 1,012 ICH survivors with comorbid AF.[44] This is the only existed meta-analysis reporting hard outcomes in relation to ICH topography (lobar vs. nonlobar). The study also provided data on mortality and functional outcome after median follow-up 48.6 months. The median time for OAC resumption after non-lobar

haemorrhage was 35 (22-64) days and after lobar ICH 38 (29-72) days. The study showed that OAC resumption was associated with reduced mortality (adjusted HR 0.33, 95% CI 0.12-0.87 for lobar and aHR 0.30, 95% CI 0.10-0.91 for non-lobar ICH) and disability (aHR for favourable outcome 3.89, 1.26-11.98, p=0.019 for lobar and aHR 4.10, 1.24-13.57, p=0.022 for non-lobar ICH) independently of ICH location. Propensity-adjusted Cox models revealed no association between OAC resumption and early mortality within 90 days for either nonlobar ICH (hazard ratio [HR] 5 1.22, 95% CI 5 0.61–2.45, p = 0.58) or lobar ICH (OR 5 0.93, 95% CI 5 0.70–1.23, p = 0.62) In a follow-up study, the same population was used to analyse associations of OAC resumption with functional recovery at 1 year in relation to thromboembolic risk evaluated by the CHA_2DS_2Vasc Score. Results showed that OAC resumption was associated with an increased likelihood of functional recovery in all patients (odds ratio, 1.89; 95% CI, 1.32–2.70), but importantly with an increased likelihood in patients with $CHA_2DS_2Vasc > 4$.[45] Current view is that in the lack of strong evidence decision making should be individualized on the basis of blood pressure control, ICH location, underlying small vessel disease, suspected cerebral amyloid angiopathy, history of IS, comorbidities that increase thromboembolic and bleeding risk, need of concomitant antiplatelet therapy.[46–48] Data suggests that factors favouring OAC resumption in ICH survivors with AF include younger age, deep location, and notably well controlled hypertension. [46–48] Before resuming OAC all modifiable risk factors should be identified, evaluated and eliminated where possible (hypertension, alcohol abuse, renal dysfunction, liver dysfunction, reconsideration for need of concomitant therapy with antiplatelets).[46,47] For those patients perceived to be at a particular high risk of ICH recurrence alternative therapeutic strategies may be considered.[46–48]

The currently available evidence for OAC in ICH patients with AF is largely based on anticoagulation with VKA. However, available data suggest that NOAC, with at least equal efficacy and better safety for stroke prevention may provide a better alternative compared to VKA. NOACs consistently reduced the risk of ICH by 50% in large RCTs of stroke prevention in AF patients.[49,50] However, ICH patients were excluded from all previous randomized controlled stroke prevention trials. In addition, the largest observational data set suggested that among patients with OAC-ICH, prior use of NOAC compared to warfarin was associated with reduced risk of in-hospital mortality, but other adjusted analyses showed similar outcomes.[3,4,51]

With regards to the optimal timing of OAC resumption after ICH, it remains unknown when to resume in the absence of randomized data. The median time of VKA resumption in observational studies varied considerably ranging from 3 days to 30 weeks depending on the indication for anticoagulation, as recently shown for patients with high thromboembolic risk (mechanical heart valves) even resuming anticoagulation after 2 weeks balanced haemorrhagic risk.[46,52] Only a nationwide Swedish retrospective observational study focused specifically on timing of OAC resumption in patients with a history of ICH and concomitant AF.[53] The study included 2619 patients (232 OAC starters) with a follow up of 5759 patient-years. The lowest estimated cumulative incidence of vascular death or nonfatal stroke was reported when OAC was resumed after a 7- to 8-week interval. For high risk women, the total risk of vascular death or stroke recurrence within 3 years was 17.0% when OAC was resumed 8 weeks after ICH, as compared with 28.6% without any antithrombotic treatment (95% CI for difference, 1.4%–21.8%). The corresponding risk for high risk men was 14.3% versus 23.6% (95% CI for difference, 0.4%–18.2%). Nevertheless, results should be interpreted with caution because of the observational nature of the study. Several ongoing randomized controlled trials will provide more strong evidence about the optimal treatment strategy in ICH survivors with AF, most of them testing NOAC vs. other treatment strategies, including left atrial appendage occlusion (LAAO).

Recommendations:

Enrolment in randomized controlled trials investigating the optimal antithrombotic management after ICH is strongly recommended.

In selected ICH patients, (re)initiation of OAC compared to no OAC may improve outcomes without increasing the rate of ICH recurrence **(Grade C).**

NOAC over VKA may offer a safer choice for ICH survivors with NVAF **(Grade C).**

Re-initiation of OAC in NVAF between the first 4-8 weeks from index ICH seems to be safe **(Grade C).**

Individual decision making on OAC after ICH should consider **(Grade C):**

- Quality of blood pressure control
- Age
- ICH location
- Burden of small vessel disease (cerebral microbleeds, leukoaraiosis, cortical superficial siderosis, cerebral amyloid angiopathy)
- Additional antiplatelet therapy

Session 9 – Talk 3) Antithrombotic management in patients with atrial fibrillation and microbleeds

Speaker: *Andreas Charidimou*

Q4: In patients after a CAA-related lobar ICH with concomitant indication for oral anticoagulation due to AF, how is optimal antithrombotic management achieved to improve outcomes (mortality, functional outcome, and rates of thromboembolic/haemorrhagic complications)?

Background:

Cerebral amyloid angiopathy (CAA) is a common small vessel disease characterised by amyloid deposition in small cortical and leptomeningeal arteries.[54] CAA commonly accompanies stroke due to spontaneous lobar intracerebral haemorrhage (ICH) in elderly people, often associated with high recurrence risk, around 7% (95%CI: 3-12%) per year in well-phenotyped patients using MRI.[55] For this reason, when there is suspicion of CAA-related ICH, clinicians are often hesitant in prescribing oral anticoagulation in patients in whom it is otherwise indicated, including non-valvular atrial fibrillation (AF).[56] The presence of a strictly lobar cerebral microbleeds (CMBs) pattern on blood-sensitive MRI sequences (SWI or T2*-GRE), in patients with spontaneous lobar ICH, sets the diagnosis of possible or probable CAA according to the validated Boston criteria.[44] Given the high recurrence rates after CAA-related ICH (compared to non-CAA-related ICH cohorts), a common approach has been to avoid anticoagulation when possible, in an effort to mitigate ICH recurrence risk.[57,58] However, there is a paucity of real-world data on the effect of CAA on the risk of anticoagulation-related ICH.[59] Despite CAA-related ICH being associated with a high risk of recurrence, it is becoming better appreciated that this risk is not homogenous.[56] Particularly, it seems that cortical superficial siderosis (cSS)[60] – a recently discovered haemorrhagic MRI signature of CAA – is the most potent independent marker of individuals at highest risk for lobar CAA-related ICH.[60–62] Recently, inadequate blood pressure control in ICH patients from a large single centre observational study was associated with hazard ratios of

3.53 (95% CI, 1.65-7.54) for recurrent lobar ICH (and of 4.23 (95% CI, 1.02-17.52) for non-lobar ICH) when compared to those with adequately controlled blood pressure.[63] A subgroup analysis of the PROGRESS trial [64] demonstrated that lowering blood pressure using the antihypertensive drug perindopril (with or without indapamide) reduced the risk of probable CAA-related ICH recurrence rate by 77% (95% CI, 19%–93%) over a follow-up period of 3.9 years.

Data directly relevant for oral anticoagulation resumption – predominantly with warfarin – after CAA-related lobar ICH come from a recent patient-level meta-analysis among three centres.[44] This study demonstrated in propensity-score adjusted analyses, that restarting oral anticoagulation in patients with lobar ICH (n=379) is associated with decreased mortality (HR=0.29, 95%CI: 0.17–0.45, p<0.0001), favourable functional outcome (mRS=0-3, HR: 4.08, 95%CI: 2.48–6.72, p<0.0001), and decreased subsequent ischaemic strokes (HR: 0.48, 95%CI: 0.25–0.75, p=0.003), without an increase in recurrent ICH risk (HR: 1.26; 95%CI: 0.88–1.71, p=0.221) at 1 year of follow-up.[44] These benefits persisted beyond 1 year of follow-up from the index event in a single centre subset of lobar ICH patients (n=102): decreased mortality (HR= 0.33, 95% CI: 0.12–0.87, p=0.026), favourable functional outcome (mRS=0-3, HR: 3.89, 95%CI: 1.26–11.98, p= 0.019), and decreased subsequent ischaemic strokes (HR: 0.48, 95%CI: 0.25–0.94, p=0.032), again without an increase in recurrent ICH risk (HR: 1.21, 95%CI: 0.86–1.70, p=0.27).[44] A subset of 190/379 (50%) lobar ICH survivors had available MRI data to formulate a diagnosis of possible (n=136) or probable (n=54) CAA based on the Boston criteria.[35] Oral anticoagulation resumption in both possible and probable CAA was associated with decreased mortality (HR: 0.27, 95%CI: 0.08–0.86, p=0.028 and HR: 0.30, 95%CI: 0.10–0.92, p=0.037, respectively) and favourable outcome (HR: 3.40, 95%CI: 1.22–9.46, p=0.020, and HR: 3.11, 95%CI: 1.08–8.97, p=0.038, respectively).[44] Presence of multiple (2 or more) strictly lobar cerebral microbleeds or cSS did not seem to modify the associations between oral anticoagulation resumption and mortality/favourable outcome after lobar ICH (all interaction p values > 0.20).[44] Due to the limited number of strokes occurring in this subset of lobar ICH patients (11 recurrent ICH cases and 12 ischaemic strokes), the authors did not perform analyses investigating the association of oral anticoagulation resumption and future ICH risk.[44] However, the CAA-related lobar ICH recurrence in this patient subgroup with MRI was not significantly increased with oral anticoagulation (personal communication).

NOACs might be an attractive option in CAA-related ICH survivors, in view of their 50% lower risk of ICH relative to warfarin, with absolute rates of ICH that are similar to aspirin monotherapy.[65] For example apixaban has a similar intracranial bleeding risk profile as aspirin, but is more effective at reducing ischaemic stroke risk.[66] Although patients with history of symptomatic ICH were excluded from all randomized trials investigating NOACs for stroke prevention in AF,[67] several Phase II randomized controlled trials in ICH survivors with atrial fibrillation, including patients with CAA-related ICH, are underway.[68]

The evidence base for the optimal antithrombotic management in patients after a CAA-related lobar ICH with concomitant indication for oral anticoagulation due to AF, remains limited. In this setting, an accurate assessment of haemorrhage risk based on the predominant type/severity of the underlying haemorrhage-prone microangiopathy using MRI blood sensitive sequences biomarkers (multiple strictly lobar CMBs and cSS presence and severity) is important for stratification. Even after a CAA-related lobar ICH, the presence of AF might confer enough risk for ischaemic stroke, poor outcomes and mortality to offset the presumed risk of ICH recurrence in selected patient groups - especially in the absence of cSS. Oral anticoagulation can be considered after CAA-related lobar ICH in the presence of AF on a case-by-case basis with individual risk vs. benefit risk stratification. Initiation of oral anticoagulation is probably indicated in CAA-related lobar ICH patients (a) without disseminated

cSS on MRI and (b) blood pressure sufficiently controlled (long-term blood pressure target consistently lower than 130/80 mmHg, with frequent follow-up until target attained). When oral anticoagulation is considered in this patient population, a NOAC over warfarin should be considered.

Recommendation:

In patients with CAA-related lobar ICH in need of OAC:

- The presence of AF might confer enough risk for ischaemic stroke, poor outcomes and mortality to offset the presumed risk of ICH recurrence in selected patients **(Grade C).**

The following parameters can be considered for an individual risk versus benefit stratification, in order of significance based on observational data **(Grade C):**

- uncontrolled hypertension
- disseminated cSS
- multiple strictly lobar CMB patterns
- Severe white matter hyperintensities of presumed vascular origin

NOACs should preferentially be used over VKA in NVAF **(Grade C).**

In NVAF patients with high bleeding risk LAAO may be an alternative **(Grade C).**

Q5: In patients after <u>acute ischaemic stroke with cerebral microbleeds (CMBs)</u> on MRI and the concomitant indication for oral anticoagulation due to non-valvular atrial fibrillation (AF), how is optimal antithrombotic management achieved to improve outcomes (mortality, functional outcome, and rates of thromboembolic/haemorrhagic complications)?

Background:

The risk of atrial fibrillation-associated ischaemic stroke can be significantly mitigated by oral anticoagulation, with either vitamin K antagonists (VKAs) or direct oral anticoagulants (NOACs) resulting in most individuals in a proven 67% relative risk reduction in future ischaemic stroke compared with no antithrombotic use.[69] However, the concern about symptomatic intracerebral haemorrhage (ICH), the most devastating of all bleeding complications in terms of mortality and morbidity,[70] remains a key clinical concern in anticoagulation decision-making. This concern is further amplified in patients with cerebral microbleeds (CMBs). CMBs are small, hypointense, round or ovoid areas identified detected on T2*-weighted gradient-recalled echo (T2*-GRE) and susceptibility-weighted imaging (SWI) MRI.[71,72] In most cases, CMBs correspond pathologically to small clusters of haemosiderin-laden macrophages presumably resulting from minute self-limiting haemorrhages.[73] Thus, they are considered a promising neuroimaging marker of haemorrhagic-prone small vessel disease in the brain, that is thought to underlie most spontaneous intracerebral haemorrhages.[72] CMBs are common in populations that might require anticoagulation therapy, being found in at least a quarter of patients with ischaemic stroke,[74,75] and they might be a specific and clinically relevant predictor of anticoagulant-related intracerebral haemorrhage.

A meta-analysis examining the risk of CMBs for future ischaemic and haemorrhagic strokes following an ischaemic stroke or transient ischaemic attack (not limited to patients taking oral anticoagulation), pooled data of 5068 patients across 15 observational studies and reported that CMB presence was associated with greater relative risk of both ischaemic and haemorrhagic strokes over a median follow-up of 18 months.[71] However, the relative and absolute risks of haemorrhagic stroke increased more steeply with greater CMB counts compared to the risks of ischaemic stroke, magnifying once questions surrounding optimal antithrombotic therapy in ischaemic stroke/TIA patients with CMBs, particularly in patients with greater CMB counts (≥ 5 CMBs), multiple strictly lobar CMBs indicative of cerebral amyloid angiopathy or mixed CMB pattern presumably marking more advanced small vessel disease.[73] An aggregate meta-analysis pooled data from eight centres, including 1552 patients with recent ischaemic stroke on oral anticoagulation and AF, suggested that cerebral microbleeds are associated with increased intracerebral haemorrhage risk.[76] These were mainly small retrospective and prospective cohorts, with variable completeness and follow-up duration and could not adjust for confounding factors. Baseline CMB presence was associated with intracerebral haemorrhage during follow-up (OR: 2.68; 95%CI: 1.19-6.01; p=0.017).[76] Presence of ≥5 CMB was related with higher future ICH risk (OR: 5.50; 95%CI: 2.07-14.66; p=0.001).[76] The pooled annual ICH incidence increased from 0.30% (95%CI: 0.04%-0.55%) among CMBs-negative patients, to 0.81% (95%CI: 0.17-1.45) in CMBs-positive (p=0.01) and 2.48% (95%CI: 1.2%-6.2%) in ≥5 CMBs patients (p=0.001).[76] There was no association between CMBs and recurrent ischaemic stroke.[76]

Recently, the CROMIS-2 (Clinical Relevance Of Microbleeds in Stroke) results were published.[77] CROMIS-2 was an observational, predominantly UK-based, multicentre, prospective inception cohort study (n=1490, 24 month follow-up, 3366 patient-years of follow-up) designed to determine whether CMBs are independently associated with a higher risk of intracranial haemorrhage in patients with recent acute ischaemic stroke or transient ischaemic attack associated with atrial fibrillation and started for the first time on oral anticoagulation (mostly warfarin).[77] In this cohort, the symptomatic intracranial haemorrhage rate in patients with CMBs was 9.8 per 1000 patient-years (95% CI 4.0–20.3) compared with 2.6 per 1000 patient-years (95% CI 1.1–5.4) in those without cerebral microbleeds (adjusted hazard ratio 3.67, 95% CI: 1.27–10.60). The risk of intracranial haemorrhage increases as CMBs burden increases, but the absolute event rate for ischaemic stroke remained higher than that of intracranial haemorrhage, even in patients with multiple CMBs.[77] The study also developed a risk prediction score for intracranial haemorrhage, showing that the inclusion of CMBs presence as a neuroimaging biomarker improved the predictive value of the HAS-BLED score.[77] NOACs might be an attractive option in the presence of CMBs for this patient population. Anticoagulation with NOACs appears at least equally effective as anticoagulation with warfarin for ischaemic stroke prevention (RR versus warfarin, 0.92; 95% CI, 0.83–1.02).[50] In contrast, intracranial haemorrhage is relatively less frequent in patients taking NOACs compared with warfarin. A meta-analysis of the NOAC trials showed reduced haemorrhagic stroke (RR, 0.49; 95% CI, 0.38–0.64) or intracranial haemorrhage (RR, 0.48; 95% CI, 0.39–0.59) relative to warfarin.[50]

Further reassurances are provided from a MRI sub-study embedded within AVERROES trial, which reported similar CMB accrual during follow-up in AF patients treated with apixaban vs. aspirin.[78] Hence, the magnitude of benefit vs. harm with NOACs in this disease population is likely greater. However, in the absence of randomised controlled trials of anticoagulation in the setting of CMBs, circumferential evidence and decision-analysis models provide a framework for understanding the decision “tipping point,” that is, the threshold at which the risks of anticoagulation outweigh its benefits.[79] A recent model, demonstrated that the current net clinical benefit estimates from the

available literature suggests that the benefits of anticoagulant therapy in AF, and in particular those of NOACs, persist in ischaemic stroke/TIA patients with CMBs, including patients with the most concerning CMB burden and distribution on MRI.[79]

In the absence of randomised controlled studies of anticoagulation in the setting of CMBs, the threshold at which the risks of anticoagulation outweigh its benefits is challenging to define. Prospective observational studies and meta-analyses suggest that while CMBs do independently increase the relative risk of symptomatic intracerebral haemorrhage, the absolute event rate for ischaemic stroke remains higher than that of intracranial haemorrhage. Given that previous studies have demonstrated an estimated 2-fold increased rate of haemorrhagic stroke with warfarin over no antithrombotic therapy, and the reported halving of haemorrhagic stroke rates with NOACs relative to warfarin in recent trials, the latter might be an attractive option in the presence of CMBs, but no head-to-head comparisons in this this population are available. Further pooled meta-analyses of individual participant data from large prospective cohorts are needed to increase the precision of risk estimates and to determine whether high CMBs counts can identify a patients subgroup who will experience net harm from oral anticoagulation. Ultimately, well-designed, adequately-powered randomized clinical trials are warranted to definitely address this clinical dilemma.

Recommendations:

In patients with ischaemic stroke and need of OAC:

- OAC in patients with evidence of CMBs should not be withheld **(Grade C).**
- NOACs should preferentially be used over VKA in NVAF **(Grade C).**

References

1. Flibotte JJ, Hagan N, O'Donnell J, et al. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. *Neurology* 2004; 63: 1059–1064.

2. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA* 2015; 313: 824–836.

3. Purrucker JC, Haas K, Rizos T, et al. Early Clinical and Radiological Course, Management, and Outcome of Intracerebral Hemorrhage Related to New Oral Anticoagulants. *JAMA Neurol* 2016; 73: 169–177.

4. Gerner ST, Kuramatsu JB, Sembill JA, et al. Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. *Ann Neurol* 2018; 83: 186–196.

5. Wilson D, Seiffge DJ, Traenka C, et al. Outcome of intracerebral hemorrhage associated with different oral anticoagulants. *Neurology* 2017; 88: 1693–1700.

6. Tsivgoulis G, Wilson D, Katsanos AH, et al. Neuroimaging and clinical outcomes of oral anticoagulant-associated intracerebral hemorrhage. *Ann Neurol*. Epub ahead of print 26 September 2018. DOI: 10.1002/ana.25342.

7. Steiner T, Poli S, Griebe M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *Lancet Neurol* 2016; 15: 566–573.

8. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011; 124: 1573–1579.

9. Barco S, Whitney Cheung Y, Coppens M, et al. In vivo reversal of the anticoagulant effect of rivaroxaban with four-factor prothrombin complex concentrate. *Br J Haematol* 2016; 172: 255–261.

10. Brown KS, Wickremasingha P, Parasrampuria DA, et al. The impact of a three-factor prothrombin complex concentrate on the anticoagulatory effects of the factor Xa inhibitor edoxaban. *Thromb Res* 2015; 136: 825–831.

11. Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. *Circulation* 2015; 131: 82–90.

12. Cheung YW, Barco S, Hutten BA, et al. In vivo increase in thrombin generation by four-factor prothrombin complex concentrate in apixaban-treated healthy volunteers. *J Thromb Haemost JTH* 2015; 13: 1799–1805.

13. Levi M, Moore KT, Castillejos CF, et al. Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. *J Thromb Haemost JTH* 2014; 12: 1428–1436.

14. Schmidt K, Krüger K, Langer E, et al. Reversal of apixaban induced alterations in haemostasis by different coagulation factor concentrates in patients after hip or knee replacement surgery. *Blood Transfus Trasfus Sangue* 2018; 1–6.

15. Körber MK, Langer E, Ziemer S, et al. Measurement and reversal of prophylactic and therapeutic peak levels of rivaroxaban: an in vitro study. *Clin Appl Thromb Off J Int Acad Clin Appl Thromb* 2014; 20: 735–740.

16. Perzborn E, Heitmeier S, Laux V, et al. Reversal of rivaroxaban-induced anticoagulation with prothrombin complex concentrate, activated prothrombin complex concentrate and recombinant activated factor VII in vitro. *Thromb Res* 2014; 133: 671–681.

17. Levi M, Levy JH, Andersen HF, et al. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med* 2010; 363: 1791–1800.

18. Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. *N Engl J Med* 2017; 377: 431–441.

19. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *N Engl J Med* 2015; 373: 2413–2424.

20. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med* 2016; 375: 1131–1141.

21. Xian Y, Liang L, Smith EE, et al. Risks of intracranial hemorrhage among patients with acute ischemic stroke receiving warfarin and treated with intravenous tissue plasminogen activator. *JAMA* 2012; 307: 2600–2608.

22. Xian Y, Federspiel JJ, Hernandez AF, et al. Use of Intravenous Recombinant Tissue Plasminogen Activator in Patients With Acute Ischemic Stroke Who Take Non-Vitamin K Antagonist Oral Anticoagulants Before Stroke. *Circulation* 2017; 135: 1024–1035.

23. Jin C, Huang RJ, Peterson ED, et al. Intravenous tPA (Tissue-Type Plasminogen Activator) in Patients With Acute Ischemic Stroke Taking Non-Vitamin K Antagonist Oral Anticoagulants Preceding Stroke. *Stroke* 2018; 49: 2237–2240.

24. Giannandrea D, Caponi C, Mengoni A, et al. Intravenous thrombolysis in stroke after dabigatran reversal with idarucizumab: case series and systematic review. *J Neurol Neurosurg Psychiatry*. Epub ahead of print 21 July 2018. DOI: 10.1136/jnnp-2018-318658.

25. Chausson N, Soumah D, Aghasaryan M, et al. Reversal of Vitamin K Antagonist Therapy Before Thrombolysis for Acute Ischemic Stroke. *Stroke* 2018; 49: 2526–2528.

26. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015; 372: 1009–1018.

27. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015; 372: 2285–2295.

28. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; 372: 11–20.

29. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015; 372: 2296–2306.

30. Rozeman AD, Wermer MJH, Lycklama à Nijeholt GJ, et al. Safety of intra-arterial treatment in acute ischaemic stroke patients on oral anticoagulants. A cohort study and systematic review. *Eur J Neurol* 2016; 23: 290–296.

31. Mundiyanapurath S, Tillmann A, Möhlenbruch MA, et al. Endovascular stroke therapy may be safe in patients with elevated international normalized ratio. *J Neurointerventional Surg* 2017; 9: 1187–1190.

32. Rebello LC, Haussen DC, Belagaje S, et al. Endovascular Treatment for Acute Ischemic Stroke in the Setting of Anticoagulation. *Stroke* 2015; 46: 3536–3539.

33. Purrucker JC, Wolf M, Haas K, et al. Safety of Endovascular Thrombectomy in Patients Receiving Non-Vitamin K Antagonist Oral Anticoagulants. *Stroke* 2016; 47: 1127–1130.

34. Drouet L, Bal Dit Sollier C, Steiner T, et al. Measuring non-vitamin K antagonist oral anticoagulant levels: When is it appropriate and which methods should be used? *Int J Stroke Off J Int Stroke Soc* 2016; 11: 748–758.

35. Pernod G, Albaladejo P, Godier A, et al. Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors: proposals of the working group on perioperative haemostasis (GIHP) - March 2013. *Arch Cardiovasc Dis* 2013; 106: 382–393.

36. Albaladejo P, Pernod G, Godier A, et al. Management of bleeding and emergency invasive procedures in patients on dabigatran: Updated guidelines from the French Working Group on Perioperative Haemostasis (GIHP) - September 2016. *Anaesth Crit Care Pain Med* 2018; 37: 391–399.

37. Ebner M, Birschmann I, Peter A, et al. Limitations of Specific Coagulation Tests for Direct Oral Anticoagulants: A Critical Analysis. *J Am Heart Assoc* 2018; 7: e009807.

38. Ebner M, Birschmann I, Peter A, et al. Point-of-care testing for emergency assessment of coagulation in patients treated with direct oral anticoagulants. *Crit Care Lond Engl* 2017; 21: 32.

39. Härtig F.J., Birschmann I., Peter A., et al. Point-of-care testing of coagulation in patients treated with the non-vitamin k antagonist oral anticoagulant edoxaban. *Stroke*; 49, http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L621005582 (2018).

40. Nielsen PB, Larsen TB, Skjøth F, et al. Restarting Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding: A Nationwide Cohort Study. *Circulation* 2015; 132: 517–525.

41. Murthy SB, Gupta A, Merkler AE, et al. Restarting Anticoagulant Therapy After Intracranial Hemorrhage: A Systematic Review and Meta-Analysis. *Stroke* 2017; 48: 1594–1600.

42. Zhou Z, Yu J, Carcel C, et al. Resuming anticoagulants after anticoagulation-associated intracranial haemorrhage: systematic review and meta-analysis. *BMJ Open* 2018; 8: e019672.

43. Korompoki E, Filippidis FT, Nielsen PB, et al. Long-term antithrombotic treatment in intracranial hemorrhage survivors with atrial fibrillation. *Neurology* 2017; 89: 687–696.

44. Biffi A, Kuramatsu JB, Leasure A, et al. Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage. *Ann Neurol* 2017; 82: 755–765.

45. Murphy MP, Kuramatsu JB, Leasure A, et al. Cardioembolic Stroke Risk and Recovery After Anticoagulation-Related Intracerebral Hemorrhage. *Stroke* 2018; 49: 2652–2658.

46. Hawkes MA, Rabinstein AA. Anticoagulation for atrial fibrillation after intracranial hemorrhage: A systematic review. *Neurol Clin Pract* 2018; 8: 48–57.

47. Li Y-G, Lip GYH. Anticoagulation Resumption After Intracerebral Hemorrhage. *Curr Atheroscler Rep* 2018; 20: 32.

48. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; 37: 2893–2962.

49. Chatterjee S, Sardar P, Biondi-Zoccai G, et al. New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. *JAMA Neurol* 2013; 70: 1486–1490.

50. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet Lond Engl* 2014; 383: 955–962.

51. Inohara T, Xian Y, Liang L, et al. Association of Intracerebral Hemorrhage Among Patients Taking Non-Vitamin K Antagonist vs Vitamin K Antagonist Oral Anticoagulants With In-Hospital Mortality. *JAMA* 2018; 319: 463–473.

52. Kuramatsu JB, Sembill JA, Gerner ST, et al. Management of therapeutic anticoagulation in patients with intracerebral haemorrhage and mechanical heart valves. *Eur Heart J* 2018; 39: 1709–1723.

53. Pennlert J, Overholser R, Asplund K, et al. Optimal Timing of Anticoagulant Treatment After Intracerebral Hemorrhage in Patients With Atrial Fibrillation. *Stroke* 2017; 48: 314–320.

54. Charidimou A, Boulouis G, Gurol ME, et al. Emerging concepts in sporadic cerebral amyloid angiopathy. *Brain J Neurol* 2017; 140: 1829–1850.

55. Charidimou A, Imaizumi T, Moulin S, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis. *Neurology* 2017; 89: 820–829.

56. Charidimou A, Shoamanesh A, Al-Shahi Salman R, et al. Cerebral amyloid angiopathy, cerebral microbleeds and implications for anticoagulation decisions: The need for a balanced approach. *Int J Stroke Off J Int Stroke Soc* 2018; 13: 117–120.

57. Eckman MH, Rosand J, Knudsen KA, et al. Can patients be anticoagulated after intracerebral hemorrhage? A decision analysis. *Stroke* 2003; 34: 1710–1716.

58. Hofmeijer J, Kappelle LJ, Klijn CJM. Antithrombotic treatment and intracerebral haemorrhage: between Scylla and Charybdis. *Pract Neurol* 2015; 15: 250–256.

59. Steiner T. Resumption of oral anticoagulation after warfarin-associated intracerebral hemorrhage: yes. *Stroke* 2011; 42: 3661–3662.

60. Charidimou A, Peeters AP, Jäger R, et al. Cortical superficial siderosis and intracerebral hemorrhage risk in cerebral amyloid angiopathy. *Neurology* 2013; 81: 1666–1673.

61. Charidimou A, Boulouis G, Roongpiboonsopit D, et al. Cortical superficial siderosis multifocality in cerebral amyloid angiopathy: A prospective study. *Neurology* 2017; 89: 2128–2135.

62. Charidimou A, Linn J, Vernooij MW, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. *Brain J Neurol* 2015; 138: 2126–2139.

63. Biffi A, Anderson CD, Battey TWK, et al. Association Between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage. *JAMA* 2015; 314: 904–912.

64. Arima H, Tzourio C, Anderson C, et al. Effects of perindopril-based lowering of blood pressure on intracerebral hemorrhage related to amyloid angiopathy: the PROGRESS trial. *Stroke* 2010; 41: 394–396.

65. Ntaios G, Papavasileiou V, Diener H-C, et al. Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: An updated systematic review and meta-analysis of randomized controlled trials. *Int J Stroke Off J Int Stroke Soc* 2017; 12: 589–596.

66. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; 364: 806–817.

67. Wilson D, Al-Shahi Salman R, Klijn CJM, et al. Intracerebral haemorrhage, atrial fibrillation, and anticoagulation. *Lancet Lond Engl* 2015; 386: 1736–1737.

68. Perry LA, Berge E, Bowditch J, et al. Antithrombotic treatment after stroke due to intracerebral haemorrhage. *Cochrane Database Syst Rev* 2017; 5: CD012144.

69. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; 146: 857–867.

70. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med* 2007; 120: 700–705.

71. Wilson D, Charidimou A, Ambler G, et al. Recurrent stroke risk and cerebral microbleed burden in ischemic stroke and TIA: A meta-analysis. *Neurology* 2016; 87: 1501–1510.

72. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013; 12: 822–838.

73. Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: histopathological correlation of neuroimaging. *Cerebrovasc Dis Basel Switz* 2011; 32: 528–534.

74. Wang Z, Soo YOY, Mok VCT. Cerebral microbleeds: is antithrombotic therapy safe to administer? *Stroke* 2014; 45: 2811–2817.

75. Horstmann S, Möhlenbruch M, Wegele C, et al. Prevalence of atrial fibrillation and association of previous antithrombotic treatment in patients with cerebral microbleeds. *Eur J Neurol* 2015; 22: 1355–1362.

76. Charidimou A, Karayiannis C, Song T-J, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: Meta-analysis in stroke patients with AF. *Neurology* 2017; 89: 2317–2326.

77. Wilson D, Ambler G, Shakeshaft C, et al. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. *Lancet Neurol* 2018; 17: 539–547.

78. O'Donnell MJ, Eikelboom JW, Yusuf S, et al. Effect of apixaban on brain infarction and microbleeds: AVERROES-MRI assessment study. *Am Heart J* 2016; 178: 145–150.

79. Shoamanesh A, Charidimou A, Sharma M, et al. Should Patients With Ischemic Stroke or Transient Ischemic Attack With Atrial Fibrillation and Microbleeds Be Anticoagulated? *Stroke* 2017; 48: 3408–3412.

Session 10: IVT in acute ischemic stroke

Chair: Götz Thomalla (Hamburg) and Robert Mikulik (Brno). Secretary: Michael Mazya (Stockholm).

The following Consensus Statement was (if approved) adopted by the 12th ESO Karolinska Stroke Update meeting on November 12th/13th, 2018.

The Consensus Statement was prepared by a writing committee (Eivind Berge, Michael Mazya, Robert Mikulik, Pooja Khatri, Götz Thomalla, William Whiteley) and proposed by the chair of the session, Prof. Robert Mikulik (Brno), Prof. Götz Thomalla (Hamburg), and the session secretary, Dr. Michael Mazya (Stocklholm), together with the speakers of the session, Prof. Eivind Berge (Oslo), Prof. Pooja Khatri (Cincinnati), Dr. William Whiteley (Edinburgh).

The speakers in this session discuss the following questions/issues:

1. Should patients with minor stroke be treated with intravenous thrombolysis?

2. Should patients in an extended time-window beyond 4.5 hours be treated with intravenous thrombolysis?

3. Should patients with unknown onset stroke be treated with intravenous thrombolysis?

4. Should tenecteplase be used for intravenous thrombolysis instead of alteplase?

Session 10 – Talks 1 & 2) Thrombolysis in minor stroke: no need for IVT on minor stroke or there is still good evidence to continue treating minor stroke with IVT?

Speakers: *Pooja Khatri & William Whiteley*

Background:

Minor strokes – frequently operationalized as those with a low NIHSS of 0 to 5 – are a common problem [1]. Few trials of alteplase in acute ischaemic stroke recruited large numbers of participants with NIHSS between 0 and 5. Two trials recruited over 100 participants with minor stroke: (1) the Third International Stroke Trial (IST-3) which included participants for whom the randomising clinician was substantially uncertain about the balance of risks and benefits of alteplase (the 'uncertainty principle') [2, 3], and (2) the Study of the Efficacy and Safety of Alteplase in Participants With Mild Stroke (PRISMS) that studied patients with minor stroke defined as a NIHSS scores of 0-5 with deficits deemed to be not "clearly disabling" by the enrolling physician in consultation with the patient [3].

Two patients with a similar low NIHSS score may be differently affected by the stroke: a similar stroke impairment can limit participation in everyday life for one person and not another. The PRISMS trial defined "clearly disabling" deficits as those that would reduce the performance of basic activities of daily living or return to employment (if they were working).

In the Stroke Thrombolysis Trialists Collaboration (STTC), published before PRISMS was completed, 10% of patients included had an NIHSS score of 0-4 [4]. This analysis showed that the proportional benefits of alteplase, as compared with control, were similar in mild, moderate and severe stroke, after adjusting for time to randomisation and age. Alteplase, as compared with control, had a benefit in low NIHSS patients [odds ratio (OR) for modified Rankin Scale (mRS) at 90 days 0-1, 1.48 (95% confidence interval (CI) 1.07-2.06)] [4]. Details about the level of disability or the specific deficits at randomisation were not reported for the trials included in this analysis, although all trials apart from IST-3 aimed to exclude patients with low NIHSS or nondisabling deficits.

In 2018, PRISMS provided additional data on alteplase in patients with minor stroke without a clearly-disabling deficit. Eligible patients were randomly allocated to alteplase or immediate aspirin alone. The trial stopped early because of delayed recruitment targets after enrolling 313 of the 948 planned patients. The median baseline NIHSS score was 2. There was no significant difference in the proportion of patients with a favourable outcome defined as mRS 0-1 at 90 days after stroke (122 patients (78.2%) in the alteplase group vs 128 (81.5%); adjusted risk difference −1.1%; 95% CI −9.4%

to 7.3%) and a 3.2% increase in symptomatic intracranial haemorrhage (risk difference 3.3%; 95% CI, 0.8%-7.4%) [3].

To summarize, pooled analysis of trials predating PRISMS support treatment of patients with low NIHSS values with a deficit considered disabling. PRISMS, which included patients with low NIHSS and deficits considered non-disabling, did not show evidence of treatment effect of alteplase over aspirin, but showed the expected sICH risk. The apparent contradictory findings may be explained by the inclusion of patients with disabling versus nondisabling deficits in the respective trials or analyses. Other explanations could be the use of active comparator of very early aspirin in PRISMS or chance alone. One trial of tenecteplase in patients with minor stroke, defined as NIHSS 0-5 with nondisabling deficits (per the local investigator's judgment), and who also had visualized intracranial occlusion on CT angiogram, is ongoing, and we encourage recruitment (TEMPO-2, NCT02398656).

Recommendations:

1. For patients with minor stroke considered disabling at assessment, treatment with intravenous alteplase can be considered **(Grade A).**
2. For patients with minor stroke considered non-disabling at assessment, routine treatment with intravenous alteplase is not recommended **(Grade B).** In cases considered to be at high risk of neurological deterioration, treatment with intravenous thrombolysis can be considered **(Grade C).**

Q2. Should patients with known symptom onset beyond 4.5 hours be treated with intravenous thrombolysis?

Background:

Previous trials assessing participants with plain CT at baseline did not demonstrate efficacy of intravenous alteplase in patients between 4.5 and 6 hours of stroke. Six trials in the STTC included at least one patient recruited beyond 4.5 hours (ATLANTIS A and B, ECASS I, II, III, IST-3), and in the pooled analysis of data from these trials there was significant interaction between the effect of alteplase on good clinical outcome with time to randomisation (p=0.016), and the subgroup of patients randomized >4.5 hours did not show a significant treatment benefit (OR 1.15, 95% CI 0.95-1.40) [2].

More recent trials using MRI with penumbral imaging to select patients for intravenous thrombolysis with alteplase also failed to demonstrate an effect within 3-6 hours [5], as did trials of desmoteplase 4.5-9 hours of symptom onset [6-10].

In October 2018, results of the EXTEND trial were presented at the World Stroke Congress in Montreal. At the time of finalization of the Karolinska Stroke Update consensus recommendations, the trial results are not yet available in peer-reviewed publication; thus, only a preliminary evaluation of the limited information from the congress presentation can be judged. However, as the results will be relevant for clinical practice, we decided to include them, in a preliminary fashion, in these recommendations. In EXTEND, penumbral imaging by either CT with CT perfusion or MRI with diffusion weighted imaging (DWI) and perfusion imaging was used to randomize patients within 3 or 4.5 and 9 hours of known symptom onset or with unknown time of symptom onset to treatment with intravenous alteplase as licensed in the corresponding country or placebo in the presence of a

"penumbral mismatch" [11]. "Penumbral mismatch" was defined as an 'penumbra to core' lesion volume ratio >1.2 and an absolute 'penumbra to core' difference >10 ml (with penumbra defined as MR or CT Tmax >6s delay perfusion lesion, and core defined as MR-DWI or CT-CBF <30%) assessed by the RAPID software, and an infarct core lesion volume ≤70 ml. According to the congress presentation, treatment with alteplase was associated with better functional outcome, i.e., favourable outcome defined by an MRS 0-1 at 90 days (unpublished data).

The concept of DWI-FLAIR-mismatch, i.e., the mismatch between the visibility of an acute ischemic lesion on DWI in the absence of a visible marked parenchymal hyperintensity on FLAIR in the corresponding area, as established in the WAKE-UP trial, has not been evaluated and is not suitable for the selection of patients with known symptom onset >4.5 hours for treatment with intravenous alteplase.

Recommendations:

1. For patients with acute ischemic stroke 4.5-9 hours from symptom onset with a "penumbral mismatch" identified by MRI or CT perfusion, intravenous alteplase may be considered **(Grade C).** *Randomized trial results are expected shortly and may result in a strengthened recommendation at a higher grade of evidence.*
2. For patients with acute ischemic stroke beyond 4.5 hours from symptom onset, but with no evidence of penumbral mismatch (e.g., patients selected by non-contrast CT only), intravenous alteplase is not recommended **(Grade A).**

Session 10 – Talk 3) Criteria for identification of possible candidates for late IVT (wake up or unknown time of onset)

Speaker: *Götz Thomalla.*

Q3. Should patients with unknown onset stroke be treated with intravenous thrombolysis?

Background:

In WAKE-UP, patients with an unknown stroke onset time who presented with a mismatch between an acute ischemic lesion visible on DWI but no clearly visible parenchymal hyperintensity in the corresponding region in FLAIR (a pattern labelled DWI-FLAIR-mismatch), were randomly allocated to treatment with intravenous alteplase or placebo [12]. The trial was stopped after randomization of 503 of 800 planned patients due to cessation of funding. Intravenous alteplase resulted in a significantly better functional outcome with 53.3% favourable outcome in the alteplase group and 41.8% in the placebo group (adjusted OR 1.61, 95% CI 1.09 to 2.36). A clear treatment benefit was also observed for the ordinal analysis of the mRS, the so-called "shift analysis" (adjusted OR 1.62, 95% CI 1.17 to 2.23) and other secondary clinical endpoints. Numerically more deaths due to intracranial hemorrhages were observed in the alteplase group. Only 107 of 503 patients (21.3%) randomized in WAKE-UP had a large vessel occlusion (intracranial carotid artery or middle cerebral artery main stem), and median NIHSS at baseline was 6.

As detailed above, the main results of the unpublished EXTEND trial were presented at WSC 2018. EXTEND also randomized patients with unknown time of symptom onset within a maximum of 9 hours from the midpoint between last known to be normal and time of symptom recognition if

patients showed a “penumbral mismatch” on MRI or CT perfusion. According to the congress presentation, treatment with alteplase was associated with better functional outcome, i.e., favourable outcome defined by an MRS 0-1 at 90 days (unpublished data).

WAKE-UP and EXTEND used different imaging criteria to select patients with unknown stroke onset (i.e., the DWI-FLAIR-mismatch in WAKE-UP and penumbral mismatch in EXTEND), and both trials demonstrated efficacy of intravenous alteplase for patients treated based on the applied imaging criteria. At the same time, the results of WAKE-UP and EXTEND are not generalisable to patients not meeting the trial criteria. Therefore, for patients evaluated with acute MRI for whom information on both DWI-FLAIR-mismatch and penumbral mismatch”is available, there is evidence of efficacy of intravenous alteplase if either one of the two imaging criteria is met (i.e., presence DWI-FLAIR-mismatch or “penumbral mismatch”), no matter if the other criterion is not met.

One CT-based trial of tenecteplase in patients with wake-up stroke, which does not select patients based on the finding of penumbral mismatch or other findings from advanced imaging, is ongoing (TWIST, NCT03181360).

Recommendations:

1. Intravenous alteplase is recommended in patients with acute ischemic stroke with an unknown onset time in the presence of a DWI-FLAIR-mismatch on acute MRI (i.e., the mismatch between the visibility of an acute ischemic lesion on DWI in the absence of a visible marked parenchymal hyperintensity on FLAIR in the corresponding area) **(Grade B).**
2. For patients with acute ischemic stroke with an unknown onset time with presence of a “penumbral mismatch” on MRI or CT perfusion, intravenous alteplase may be considered **(Grade C).** *Randomized trial results are expected shortly and may result in a strengthened recommendation at a higher grade of evidence.*
3. For patients without access to advanced imaging (MRI or CT perfusion), or those without DWI-FLAIR-mismatch and without penumbral mismatch, alteplase is not recommended **(Grade C)** and enrolment into randomised controlled trials is encouraged.

Session 10 – Talk 4) Should tenecteplase replace alteplase in routine care?

Speaker: *Eivind Berge.*

Q4. Should tenecteplase be used for intravenous thrombolysis instead of alteplase?

Background:

Trials to date comparing tenecteplase with alteplase for acute ischemic stroke are inconclusive. In the TAAIS trial, which randomized 75 patients, tenecteplase 0.1 mg per kilogram or 0.25 mg per kilogram resulted in better clinical outcome and higher rates of reperfusion than alteplase in patients selected by CT perfusion [13]. In ATTEST, 104 patients were randomized to 0.25 mg/kg tenecteplase or

alteplase, and neurological and radiological outcomes (salvaged penumbra area at 24 h) did not differ between groups, although the trial was small and therefore underpowered.[14]

In NOR-TEST, 1,100 stroke patients were randomly allocated to 0.4 mg/kg tenecteplase or alteplase; treatment with tenecteplase was not superior to alteplase with a similar safety profile [15]. Rates of excellent outcome were similar in both groups (64% vs. 63%; OR 1.08, 95% CI 0.84-1.38), as were rates of symptomatic intracranial hemorrhage (3% vs. 2%; OR 1.16, 95% CI 0.51-2.68). The study has some methodological limitations, including the open-label design, the large proportion of stroke mimics randomized (17%), and inclusion of mostly mild strokes (median NIHSS 4).

The optimal dose of tenecteplase remains unclear. An earlier trial with an adaptive sequential design, the 0.4 mg/kg dose was discarded early in the course of the trial as inferior compared to 0.1 or 0.25 mg/kg, based on assessment of major neurological improvement balanced against occurrence of symptomatic intracranial hemorrhage [16]. The cohort in that trial was more severe, with a median NIHSS in the 0.4 mg/kg cohort (n=19) of 9 (IQR 5-17). An individual patient data meta-analysis of the available stroke trials (prior to NOR-TEST) comparing tenecteplase with alteplase revealed no significant differences between treatment with tenecteplase and alteplase, while point estimates suggested potentially greater efficacy of 0.25 and 0.1 mg/kg doses with no difference in symptomatic intracerebral hemorrhage, and potentially higher symptomatic intracerebral hemorrhage risk with 0.4 mg/kg dose[17].

No trial has formally shown non-inferiority or superiority of tenecteplase vs. alteplase in stroke patients eligible for intravenous thrombolytic treatment without selection based on advanced imaging. There are ongoing trials of tenecteplase for acute ischemic stroke (ATTEST-2 (NCT02814409) and TASTE (ACTRN12613000243718), and enrolment is encouraged.

The question whether tenecteplase should be used for intravenous thrombolysis instead of alteplase in patients eligible for thrombectomy is considered separately in the paragraph on mechanical thrombectomy.

Recommmendation:

1. Tenecteplase instead of alteplase is not recommended for treatment of patients with acute ischemic stroke in routine practice **(Grade C).**

References

1. Reeves M, Khoury J, Alwell K, Moomaw C, Flaherty M, Woo D, et al. Distribution of National Institutes of Health Stroke Scale in the Cincinnati/Northern Kentucky Sroke Study. *Stroke*. 2013;44:3211-3213
2. I.S.T. collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): A randomised controlled trial. *Lancet*. 2012;379:2352-2363
3. Khatri P, Kleindorfer DO, Devlin T, Sawyer RN, Jr., Starr M, Mejilla J, et al. Effect of alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits: The PRISMS randomized clinical trial. *JAMA*. 2018;320:156-166

4. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929-1935
5. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, et al. Effects of alteplase beyond 3 h after stroke in the echoplanar imaging thrombolytic evaluation trial (EPITHET): A placebo-controlled randomised trial. *Lancet Neurol*. 2008;7:299-309
6. Albers GW, von Kummer R, Truelsen T, Jensen JK, Ravn GM, Gronning BA, et al. Safety and efficacy of desmoteplase given 3-9 h after ischaemic stroke in patients with occlusion or high-grade stenosis in major cerebral arteries (DIAS-3): A double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Neurol*. 2015;14:575-584
7. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, et al. Dose escalation of desmoteplase for acute ischemic stroke (DEDAS): Evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke*. 2006;37:1227-1231
8. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, et al. The desmoteplase in acute ischemic stroke trial (dias): A phase ii MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke*. 2005;36:66-73
9. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRIperfusion-diffusion weighted imaging or perfusion ct (DIAS2): A prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol*. 2009;8:141-150
10. von Kummer R, Mori E, Truelsen T, Jensen JS, Gronning BA, Fiebach JB, et al. Desmoteplase 3 to 9 hours after major artery occlusion stroke: The DIAS-4 trial (efficacy and safety study of desmoteplase to treat acute ischemic stroke). *Stroke*. 2016;47:2880-2887
11. Ma H, Parsons MW, Christensen S, Campbell BC, Churilov L, Connelly A, et al. A multicentre, randomized, double-blinded, placebo-controlled phase iii study to investigate extending the time for thrombolysis in emergency neurological deficits (EXTEND). *Int J Stroke*. 2012;7:74-80
12. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, et al. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 2018;379:611-622
13. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med*. 2012;366:1099-1107
14. Huang X, Cheripelli BK, Lloyd SM, Kalladka D, Moreton FC, Siddiqui A, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): A phase 2, randomised, open-label, blinded endpoint study. *Lancet Neurol*. 2015;14:368-376
15. Logallo N, Novotny V, Assmus J, Kvistad CE, Alteheld L, Ronning OM, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): A phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol*. 2017;16:781-788
16. Haley EC, Jr., Thompson JL, Grotta JC, Lyden PD, Hemmen TG, Brown DL, et al. Phase iib/iii trial of tenecteplase in acute ischemic stroke: Results of a prematurely terminated randomized clinical trial. *Stroke*. 2010;41:707-711
17. Huang X, MacIsaac R, Thompson JL, Levin B, Buchsbaum R, Haley EC, Jr., et al. Tenecteplase versus alteplase in stroke thrombolysis: An individual patient data meta-analysis of randomized controlled trials. *Int J Stroke*. 2016;11:534-543

Session 11: Mechanical Thrombectomy

Chair: Gary A. Ford (Oxford) and Joan Martí-Fábregas (Barcelona). Secretary: Åsa Kuntze Söderqvist (Stockholm).

The following Consensus Statement was (if approved) adopted by the 12th ESO Karolinska Stroke Update meeting on November 12th/13th, 2018.

The Consensus Statement was prepared by a writing committee D.W.J. Dippel, G.A. Ford, J. Martí-Fàbregas, S. Mustanoja, M. Rasmussen, Å.K. Söderqvist and proposed by the chair (s) of the session, Professor G.A. Ford (Oxford) and Dr J. Marti-Fabregas (Barcelona), and the session secretary, Dr Å.K. Söderqvist (Stockholm) together with the speakers of the session, *title, full name (city)*

The speakers in this session discussed the following questions:

1. In patients with acute ischaemic stroke with presenting with large vessel occlusion and possible to administer iv thrombolytics within 4.5 hours where thrombectomy is planned, should iv thrombolytics be administered?

2. Which patients presenting beyond 6 hours or with unwitnessed stroke does thrombectomy improve the likelihood of a good outcome?

3. What imaging is recommended to select patients presenting beyond 6 hours or with unwitnessed stroke for thrombectomy?

4. In patients undergoing endovascular procedures should conscious sedation or general anaesthesia be used?

Session 11 – Talk 1) Intravenous thrombolysis before endovascular treatment: beneficial or just dangerous?

Speaker: *Diederik W.J. Dipplel.*

Q1. In patients with acute ischaemic stroke with presenting with large vessel occlusion and possible to administer iv thrombolytics within 4.5 hours where thrombectomy is planned, should iv thrombolytics be administered?

Background:

Treatment with IV alteplase for acute ischemic stroke is effective. Observational studies suggest that in patients with ischemic stroke caused by proximal intracranial thrombo-embolic occlusions of carotid artery, and proximal middle cerebral artery, the treatment is less effective than in patients with occlusion of smaller intracranial arterial branches.[1] The treatment is associated with a risk of intracranial haemorrhage, which reduces its overall effectiveness. Tenecteplase is a promising alternative to alteplase, because of its ease of administration, but until now, convincing evidence of superiority or non-inferiority is not yet available.[2-6]

Mechanical thrombectomy is an effective treatment for patients with acute ischemic stroke caused by proximal intracranial occlusions, and the associated risk of haemorrhage is small. All nine recent randomised trials of mechanical thrombectomy, eight of which used stent retrievers as a first line of defence, in patients with imaging confirmed acute intracranial thrombo-embolic occlusions causing

ischemic stroke included patients who had been treated with intravenous alteplase.[7-15] Some of these trials restricted inclusion to patients receiving alteplase, but several did not. These trials included patients who were not considered eligible for treatment with IV alteplase, because they presented outside 4.5 hour time window, or because they had contra-indications for this treatment, such as anticoagulant use or a history intracranial haemorrhage, or recent ischemic stroke. In subgroup analyses, there was no difference in treatment effect between patients who were and were not treated with IV alteplase. The risk of intracranial haemorrhage in these two groups did not differ.

The size of the effect of both mechanical thrombectomy and treatment with IV thrombolytics diminishes rapidly with time.

In patients presenting in a primary stroke centre without facilities for endovascular treatment, treatment with IV thrombolytics is the only option. Subsequent transfer to an intervention centre in case intracranial occlusion has been established (ship and drip) is the next step. For patients with a proximal occlusion presenting primarily in an intervention centre, one might consider direct mechanical thrombectomy, to avoid delays and to avoid the potential risk of haemorrhage. Several randomized trials addressing this dilemma are ongoing, no results have been reported so far.

Observational patient series and registries of thrombectomy with or without preceding intravenous thrombolysis report varying and contradictory results. The comparison of thrombolytics or not in both the subgroup analyses of thrombectomy RCTs and observational studies is biased, because only patients able to undergo thrombectomy were included and those not randomised because either they recovered quickly, or experience complications are not included in these analyses

Consensus Statement:

Patients with acute ischemic stroke should be treated with IV alteplase without delay if there are no contra-indications. Subsequent transportation to an intervention centre if a proximal intracranial arterial occlusion is considered present should follow urgently (drip and ship). As long as there is no direct evidence of superiority, or at least non-inferiority of thrombectomy without preceding IV alteplase in patients who are eligible for both treatments, we advise that patients who present directly at an intervention centre should be treated with IV alteplase as indicated and thrombectomy should follow as soon as possible.

Recommendation:

Patients with acute ischemic stroke should be treated with IV alteplase without delay if there are no contra-indications. In case of a proximal intracranial thromboembolic occlusion causing the ischemic stroke, thrombectomy should follow as soon as possible after starting thrombolysis **(Grade C).**

The effect of immediate thrombectomy, bypassing treatment with IV thrombolysis needs to be addressed in specifically designed randomised trials ***(not graded).***

References

1. del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol. 1992;32:78-86
2. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med. 2018;378:1573-1582
3. Haley EC, Jr., Thompson JL, Grotta JC, Lyden PD, Hemmen TG, Brown DL, et al. Phase IIb/III trial of tenecteplase in acute ischemic stroke: Results of a prematurely terminated randomized clinical trial. Stroke. 2010;41:707-711

4. Huang X, Cheripelli BK, Lloyd SM, Kalladka D, Moreton FC, Siddiqui A, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (attest): A phase 2, randomised, open-label, blinded endpoint study. Lancet Neurology. 2015;14:368-376
5. Logallo N, Novotny V, Assmus J, Kvistad CE, Alteheld L, Ronning OM, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (nor-test): A phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol. 2017;16:781-788
6. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med. 2012;366:1099-1107
7. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11-20
8. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019-1030
9. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009-1018
10. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296-2306
11. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-pa vs. T-pa alone in stroke. N Engl J Med. 2015;372:2285-2295
12. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (thrace): A randomised controlled trial. Lancet Neurol. 2016;15:1138-1147
13. Muir KW, Ford GA, Messow CM, Ford I, Murray A, Clifton A, et al. Endovascular therapy for acute ischaemic stroke: The pragmatic ischaemic stroke thrombectomy evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2017;88:38-44
14. Mocco J, Zaidat OO, von Kummer R, Yoo AJ, Gupta R, Lopes D, et al. Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. Stroke. 2016;47:2331-2338
15. Khoury NN, Darsaut TE, Ghostine J, Deschaintre Y, Daneault N, Durocher A, et al. Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: A randomized care trial. J Neuroradiol. 2017;44:198-202

Session 11 – Talk 2) Thrombectomy beyond the conventional therapeutic window and in unwitnessed stroke.

Speaker: *Satu Mustanoja*

Q2. Which patients presenting beyond 6 hours or with unwitnessed stroke does thrombectomy improve the likelihood of a good outcome?

Q3. What imaging is recommended to select patients presenting beyond 6 hours or with unwitnessed stroke for thrombectomy?

Background:

Endovascular thrombectomy (EVT) has been proven to be effective in large-vessel occlusion (LVO) in the anterior cerebral circulation within the first 6 h after onset of stroke, in various randomized clinical trials, (1) and is the only approved treatment for acute ischaemic stroke in addition to intravenous thrombolysis. Non-randomized trials suggested that patients with a penumbra

(mismatch between the volume of brain tissue that may be salvaged and already infarcted brain) could benefit from EVT beyond 6 h after the patient was last known to be well. (2, 3)

Two prospective trials showed to have high efficacy up to 24 h after suspected symptom onset with careful patient selection: DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and DEFUSE-3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke). (4,5) The study results confirmed the use of advanced neuroimaging techniques to define an acute ischaemic stroke population that may benefit from EVT in an extended time window. Both trials were terminated early for efficacy (after 206 and 182 patients had undergone randomization), with half of the patients reaching a good outcome mRS ≤2 at 3 months.

The DAWN trial investigated the safety and efficacy of EVT performed 6–24 h after the onset of ischemic stroke, including wakeup strokes, and the mismatch was defined according to the clinical deficit, age and infarct volume, with a rather complex patient selection. In DEFUSE-3 the patients, last known to be well between 6 and 16 h, were included using automated software to detect the initial infarct volume. These trial results led to a Level I-A recommendation in the American Heart Association and American Stroke Association acute ischaemic stroke guidelines that selected patients within 6 to 24 h of last known well benefit from thrombectomy, when the imaging and other eligibility criteria from DAWN and DEFUSE 3 are strictly applied. (6). MR DWI/FLAIR imaging has been shown to be an effective imaging strategy to select patients for iv thrombolysis in wake up stroke patients but has not been used to select patients presenting after 6 hours for EVT.

The ESCAPE trial used collateral imaging and ASPECTS scoring to select patients for EVT including 32 patients were included in the 6-9 hour window, and 17 patients in the 9-12 hour window. The treatment effect in these groups was similar to the main effect in the trial.

Consensus statement

According to the study results from DAWN and DEFUSE-3 trials, the efficacy of thrombectomy in carefully selected patients with LVO in the anterior circulation up to 24 h after suspected stroke symptom onset can be considered to be safe and efficient. The use of collateral imaging to select patients presenting beyond 6 hours for EVT appears promising but further data are needed before this can be recommended for routine use in selecting patients for EVT in the later time window. Detection of LVO in the new treatment window demands (sufficient organization of services to ensure) rapid transfer of more (eligible) patients to centers providing EVT, with immediate access to multi-modal advanced imaging and its interpretation, and a well-trained multi-disciplinary workforce to deliver specialist pre-, peri-, and post-thrombectomy care.

Recommendation:

For patients presenting 6-24 hours after onset with ICA or M1 occlusion with a disabling deficit NIHSS >6 and no significant pre-stroke disability, selection for thrombectomy can be guided by utilizing perfusion imaging to identify patients with an imaging profile treated in the DAWN/DEFUSE trials **(Grade A).**

References

1. Goyal M, Menon BK, van Zwam WH, Dippel DW, et al (2016) Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 387(10029):1723–1731.

2. Jovin TG, Liebeskind DS, Gupta R, Rymer M (2011) Imaging-based endovascular therapy for acute ischemic stroke due to proximal intracranial anterior circulation occlusion treated beyond 8 hours from time last seen well: retrospective multicenter analysis of 237 consecutive patients. Stroke 42(8):2206–2211 10.
3. Jovin TG, Chamorro A, Cobo E, de Miquel MA, et al (2015) Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 372(24):2296–2306.
4. Albers GW, Marks MP, Kemp S, Christensen S, et al (2018) Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 378(8):708–718.
5. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A (2018) Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl Jmed 378(1):11–21.
6. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, et al, on behalf of the American Heart Association Stroke Council (2018) 2018 guidelines for the early management of patients with acute ischemic stroke *Stroke* 49:e46–e110.

Session 11 – Talk 3) Conscious sedation or general anaesthesia in patients undergoing endovascular procedures?

Speaker: *Mads Rasmussen.*

Q5. In patients undergoing endovascular procedures should conscious sedation or general anaesthesia be used?

Background:

Retrospective observational studies have suggested that general anesthesia (GA) compared to conscious sedation (CS) is associated with worse outcomes after EVT for acute ischemic stroke (1-3). However, most of the retrospective studies and meta-analyses are biased due to confounding by indication, as patients with more severe stroke and poorer presentation are more likely to receive GA. In contrast, 3 recent randomized trials were all in agreement in showing no difference in outcomes in patients receiving either GA or CS during EVT (4-6). The primary outcome parameters from the recent randomized trials are shown in the table.

Trial	N	Primary outcome	GA	CS	Diff	P-value
SIESTA	150	Change in 24-hour NIHSS, mean (95% CI)	-3.2 (-5.6 to -0.8)	-3.6 (-5.5 to -1.7)	-0.4	0.82
AnStroke	90	mRS at 90 days, median (interquartile range)	3 (1-4)	3 (1-5.5)	0	0.5
GOLIATH	128	Infarct growth on MRI, median (interquartile range), ml	8.2 (2.2-38.6)	19.4 (2.4-79)	11.2	0.1

Consensus statement:

Until further data are available, GA and CS can equally be considered for EVT procedural sedation. It is suggested that the specific choice of anesthetic technique during EVT for LVO is individualized and based on clinical neurological presentation (especially involuntary movements), co-morbidity and current medical condition (airway, vomiting). Management of anesthesia for EVT is preferably performed by a dedicated anesthesia team in order to rigorously maintain blood pressure (systolic blood pressure > 140 mmHg) (7) and minimize time delay.

Recommendations:

- We recommend an anaesthetist is present during EVT **(Grade C).**

- No preference for general anesthesia and conscious sedation/local anesthesia can be recommended when there is no indication for general anesthesia **(Grade C).**

References

1. Berkhemer OA, van den Berg LA, Fransen PSS, Beumer D, Yoo AJ, Lingsma HF, et al. The effect of anesthetic management during intra-Arterial therapy for acute stroke in MR CLEAN. Neurology. 2016;87:656–64.
2. Bekelis K, Missios S, MacKenzie TA, Tjoumakaris S, Jabbour P. Anesthesia Technique and Outcomes of Mechanical Thrombectomy in Patients With Acute Ischemic Stroke.Stroke.2017;48:361-663. Brinjikji W, Pasternak J, Murad MH, Cloft HJ, Welch TL, Kallmes DF, et al. Anesthesia-Related Outcomes for Endovascular Stroke Revascularization. Stroke. 2017;48:2784-2791.
3. Campbell BC V, van Zwam WH, Goyal M, Menon BK, Dippel DWJ, Demchuk AM, et al. Effect of general anaesthesia on functional outcome in patients with anterior circulation ischaemic stroke having endovascular thrombectomy versus standard care: a meta-analysis of individual patient data. Lancet Neurol. 2018;17:47-53.
4. Schönenberger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S, Purrucker JC, et al. Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy A Randomized Clinical Trial. 2016;316(19):1986-1996
5. Löwhagen Hendén P, Rentzos A, Karlsson J-E, Rosengren L, Leiram B, Sundeman H, et al. General Anesthesia Versus Conscious Sedation for Endovascular Treatment of Acute Ischemic Stroke. Stroke. 2017;48(6):1601-1607
6. Simonsen CZ, Yoo AJ, Sørensen LH, Juul N, Johnsen SP, Andersen G, et al.Effect of General Anesthesia and Conscious Sedation During Endovascular Therapy on Infarct Growth and Clinical Outcomes in Acute Ischemic Stroke. JAMA Neurol. 2018;10.1001/jamaneurol.**2017**.4474.
7. Rasmussen M, Espelund US, Juul N, Yoo AJ, Sørensen LH, Sørensen KE, et al. The influence of blood pressure management on neurological outcome in endovascular therapy for acute ischaemic stroke. Br J Anaesth 2018; doi:10.1016/j.bja.2018.01.039.

Acknowledgements

Marius Matusevicius and Boris Kesselman for their assistance with collection and formatting the document, SITS International Coordination members for their active logistic support and Congrex Switzerland Ltd assist in organising the conference. We thank all the participants of the meeting.

Declaration of conflicting interests

N Ahmed is chair of SITS International, which receives a grant from Boehringer Ingelheim for the SITS-ISTR. T Steiner received research funding from Octapharma, speakers honoraria from Boehringer Ingelheim, BMS Pifzer, Bayer, Daiichy Sanky, consultancy fees from Boehringer Ingelheim, BMS Pifzer, Bayer, Daiichy Sanky. G€otz Thomalla: Dr. Thomalla reports receiving consulting fees from Acandis, grant support and lecture fees from Bayer, lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo, consulting fees and lecture fees from Stryker, funding from the European Union's 7th Framework Programme for Research under grant agreement no. 278276 (WAKE-UP), funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 754640 (TENSION). Robert Mikulik: Dr. Mikulik has received speakers fee from Boehringer Ingelheim. Gary A Ford: Dr. Ford has received speaker honoraria from Amgen, Bayer, Medtronic, and Styker; advisory board fees from Amgen, AstraZeneca, Medtronic, and Stryker; consultancy fees from Pfizer; and unrestricted educational grants from Medtronic. Joan Martí-Fabregas: Dr. Martí-Fabregas reports receiving speaker honoraria/Consultancy from Boehringer Ingelheim, BMS Pfizer, Bayer. H. Bart van der Worp: Dr. Van der Worp reports speaker's fees from and consultancy for Boehringer Ingelheim. Robert Hart: Dr. Robert Hart reports receiving research support and stipend from Bayer AG. Pooja Khatri: Pooja Khatri's department has received funding from Genentech (PRISMS trial PI), Lumosa (DSMB, consulting), Cerenovus (ENDOLOW TRIAL IIS), and Nervive (NIH SBIR coinvestigator). Thorsten Steiner: Dr. Thorsten Steiner reports fees for consultation and speaker fees by Bayer, BMS Pfizer, Boehringer, Daiichy Sankyo. ESO receives unconditional grants from several companies: please see https://eso-stroke.org.

Ethics approval

Not applicable.

Funding

ESO–Karolinska Stroke Update Conference was sponsored by Abbot, Amgen, Boehringer Ingelheim, Brainomix, GE Healthcare, Medtronic, SITS International. No funding sources had part in the recommendations and consensus statements, or preparation, review or approval of the recommendations and consensus statements; or the decision to submit the recommendations and consensus statements for publication.

Informed consent

Not applicable.

Guarantor

NA and TS as conference chairs.

Contributorship

Each session's recommendations were prepared by a writing committee consisting of session chair(s), scientific secretary and speakers. IEM and NA drafted the final manuscript. All authors critically revised and edited the manuscript and approved the final version.