Guideline

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Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 11–13 November 2018

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 B 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 Stibrant 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 (N Ahmed, 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

Abstract

The purpose of the European Stroke Organisation–Karolinska Stroke Update Conference is to provide updates on recent stroke therapy research and to give an opportunity for the participants to discuss how these results may be implemented into clinical routine. The meeting started 22 years ago as Karolinska Stroke Update, but since 2014 it is a joint conference with European Stroke Organisation. Importantly, it provides a platform for discussion on the European Stroke Organisation guidelines process and on recommendations to the European Stroke Organisation guidelines committee on specific topics. By this, it adds a direct influence from stroke professionals otherwise not involved in committees and work groups on the guideline procedure. The discussions at the conference may also inspire new guidelines when motivated. The topics raised at the meeting are selected by the scientific programme committee mainly based on recent important scientific publications. This year's European Stroke Organisation–Karolinska Stroke Update Meeting was held in Stockholm on 11–13 November 2018. There were 11 scientific sessions discussed in the meeting including two short sessions. Each session except the short sessions produced a consensus statement (*Full version with background, issues, conclusions and references are published as web-material and at* www.eso-karolinska.org *and* http://eso-stroke.org) and recommendations which were prepared by a writing committee consisting of session chair(s), scientific secretary and speakers. These statements were presented to the 250 participants of the meeting. In the open meeting, general participants commented on the consensus statement and recommendations and the final document were adjusted based on the discussion from the general participants Recommendations (grade of evidence) were graded according to the 1998 Karolinska Stroke Update meeting with regard to the strength of evidence. Grade A Evidence: Strong support from randomised controlled trials and statistical reviews (at least one randomised controlled trial plus one statistical review). Grade B Evidence: Support from randomised controlled trials and statistical reviews (one randomised controlled trial or one statistical review). Grade C Evidence: No reasonable support from randomised controlled trials, recommendations based on small randomised and/or non-randomised controlled trials evidence.

Keywords

Stroke, thrombolysis, thrombectomy, oral anticoagulation, patent foramen ovale, prehospital, intracerebral haemorrhage, ischaemic stroke

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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).

Session 1: Prehospital management, patient selection

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

[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

Speakers: Heinrich Audebert (Berlin), Urs Fischer (Bern), Guillaume Turc (Paris).

What is proven (glyceryl trinitrate, oxygen, preconditioning, mobile stroke units)?

Q1: For acute ischaemic stroke (AIS) patients: Does prehospital glyceryl trinitrate application improve outcome?

Recommendation: There is currently not sufficient evidence to recommend the application of GTN in the prehospital field (Grade C).

Q2: Does prehospital oxygen supply improve outcome in ischaemic stroke patients? Recommendation: There is no evidence available from prehospital 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 prehospital stroke management (Grade C).

Q3: Does preconditioning lead to better outcomes in ischaemic or haemorrhagic stroke?

Recommendation: There is currently not sufficient evidence to recommend remote ischaemic preconditioning in prehospital stroke care (Grade C).

Q4: For AIS patients: Do mobile stroke units (MSU) reduce time to treatment?

Q5: For AIS patients: Do mobile stroke units improve outcome?

Recommendation: 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 AIS 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).

Prehospital identification of candidates for mechanical thrombectomy

Q1: Can clinical scores reliably predict a large artery occlusion (LAO) in unselected patients with a suspected AIS in the prehospital setting?

Q2: Different clinical scores have been designed to predict LAO in AIS patients: are all scores equally predictive or are several scores superior to others?

Q3: Should cut-off levels be recommended to triage patients?

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

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).

Recommended cut-off level of any triage score depends on the geographic situation and hospital infrastructure. In the proximity of Mechanical thrombectomy (MT) capable stroke centres, 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 centre, a high specificity to detect LAO is reasonable (Grade C).

Drip-and-ship versus mothership for thrombectomy

Q1: What referral system works best for endovascular treatment?

Recommendation: 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).

For patients without identified contraindication to Intravenous thrombolysis (IVT), if estimated transportation time to a comprehensive stroke centre is considerably longer than transportation to the nearest primary stroke centre (approximately more than 30–45 min), the drip-and-ship model should be considered (Grade C).

Conversely, if the difference in travel time between the nearest primary stroke centre and the nearest comprehensive stroke centre is below 30–45 min, or if contraindications to IVT are suspected in the field (i.e. recent surgery, oral anticoagulation…), direct transportation to the comprehensive stroke centre should be considered if LAO is deemed clinically plausible (Grade C).

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 centre, evaluation and treatment for patients with suspected ischaemic 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 centre. In case of intravenous thrombolysis, the door-to-needle time should be kept as low as possible, ideally below 30 min (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 min and 60 min respectively (Grade C).

Session 2: Acute management of subarachnoid haemorrhage (SAH)/ intracerebral haemorrhage (ICH)

Chair: Charlotte Cordonnier (Lille), Hanne Christensen (Copenhagen). Secretary: Erik Lundström (Stockholm). Speakers: Gabriel J. E. Rinkel (Utrech), Charlotte Cordonnier (Lille), Hanne Christensen (Copenhagen).

Q1: SAH – Which diagnostic test and when?

Recommendation:

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 h after the onset of headache and is read negative by a radiologist experienced in reading brain CT, Cerebrospinal fluid (CSF) examination is not indicated. If CT is performed more than 6 h after onset and negative, lumbar puncture should be performed more than 12 h after headache onset, and CSF examined for bilirubin (Grade B).

3. In patients with SAH, computed tomography angiography (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 three 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 Digital subtraction angiography (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 three months (Grade C).

Q2: Intracerebral haemorrhage (ICH) – Which diagnostic test and when?

Recommendation:

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/Computed tomography venography (CTV) or Magnetic resonance angiography (MRA)/Magnetic resonance venography (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 cerebral amyloid angiopathy (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 two and six months after ICH (Grade C).

Q3: TICH-2 (Tranexamic acid for hyperacute primary intracerebral haemorrhage trial): what lessons have we learned?

Recommendation:

1. Inclusion window in acute ICH trials aiming at preventing haematoma expansion should be as short as possible and no longer than 4.5 h from ictus (Grade C).

2. As part of future trial protocols, BP should be controlled ($\leq$140 mmHg systolic) (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).

Session 3: Blood pressure (BP) and glucose control after stroke

Chair: Simona Sacco (L'Alquila), Else Charlotte Sandset (Oslo). Secretary: Marius Matusevicius (Stockholm). Speakers: Georgios Tsivgoulis (Athens), Thorsten Steiner (Heidelberg), Else Charlotte Sandset (Oslo).

Q1: Does blood glucose influence outcome in acute ischaemic or haemorrhagic stroke, and how should it be managed?

Recommendation: Hypo- and hyperglycaemia in the acute phase of both ischaemic and haemorrhagic stroke is associated with adverse outcomes (Grade C).

Tight glycaemic control with intravenous insulin does not improve stroke outcomes and is associated with increased risk of hypoglycaemia (Grade A).

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

Hyperglycaemia 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).

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

Q2: Should BP be lowered in the chain of treatment in patients with AIS and high BP?

Recommendation: In patients with AIS who do not receive recanalization therapy, BP should not be lowered unless, very high (>220/120 mmHg). Treatment should be individualized and tailored according to previous hypertension and other comorbidities (Grade B).

In AIS patients treated with IVT, we suggest to keep the BP thresholds of the clinical trials: ≤185/110 mmHg before treatment, and of ≤180/105 mmHg for the first 24 h after treatment (Grade C).

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

Q3: Should hypertension be induced in patients with ischaemic stroke?

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

Q4: What is the optimal BP in acute ICH?

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

In patient with acute ICH, we recommend to lower BP *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 h (Grade C).

Still, after this period, BP should be kept <140 mmHg, because haematoma expansion does occur even after this time (Grade C).

Q5: BP lowering in acute ICH: What is the influence of time, haematoma volume, choice of agent and previous hypertension?

Recommendation: In patients with acute ICH and previous hypertension recommend to lower BP *as soon and fast as possible* (Grade C).

The optimal OTT to impact on clinical outcome may be 2.5 h, but BP should be kept <140 mmHg, because the risk of haematoma 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).

In patients with acute ICH and small bleeding volumes we recommend to lower BP as soon and fast as possible to an 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).

Session 4: Title: Update on work-up and secondary prevention issues I

Chair: Andreas Charidimou (Boston), George Ntaios (Larissa). Secretary: Tiago Moreira (Stockholm). Speakers: George Ntaios (Larissa), Haralampos Milionis (Ioannina), Marta Rubiera (Barcelona), Robert G. Hart (Hamilton).

Q1: What is good clinical practice in work up for suspected cardio-embolic cases? Echo and monitoring in all patients?

Recommendation:

1. A good medical history, physical examination, laboratory testing, a 24-h 12-lead electrocardiogram (ECG) and transthoracic echocardiogram (TTE) are the mainstays of cardioembolic source detection (Grade A).
2. Screening of patent foramen ovale (PFO) with bubble test-transcranial Doppler or transoesophageal echocardiogram (TEE) is recommended in patients with embolic stroke of undetermined aetiology despite recommended diagnostic work up, who would be eligible for PFO closure (Grade A).
3. Screening of aortic arch atheroma (AAA) with CTA or TTE is recommended in embolic strokes of undetermined source (ESUS); however, TEE is still the gold standard for AAA evaluation (Grade C).
4. Detection of some minor structural abnormalities on TEE has uncertain therapeutic implications (Grade C).
5. Continuous monitoring of heart rhythm up to 30 days is reasonable in patients with embolic stroke of undetermined aetiology despite recommended diagnostic work up to increase covert atrial fibrillation (AF) 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).
6. 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).

Q2: How to choose secondary prevention in ESUS?
Recommendation:

1. The best current secondary prevention in ESUS patients is antiplatelet treatment (Grade A) ***(pending publication of the RE-SPECT ESUS trial)*.**
2. 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).
3. Subgroups of ESUS patients who may benefit from anticoagulation have not yet been validated by clinical trials (Grade C).

Q3: What secondary prevention in multiple stroke aetiologies?
Recommendation:

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

Q4: Lipids and stroke: Statins, PCSK9 inhibitors, and Low-density lipoprotein cholesterol (LDL-C) levels; and whom not to treat?
Recommendation:

1. We recommend that statins be used as a part of standard secondary prophylactic treatment after an ischaemic stroke or a transient ischaemic 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).
2. 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 ischaemic stroke in patients with stabilized cardiovascular disease and the addition of alirocumab reduced the risk of ischaemic stroke in patients with acute coronary syndrome (Grade A). Evolocumab has been reported to reduce atherosclerotic vascular disease (AVD) risk in patients with a previous history of stroke (Grade B)**.**
3. The use of statins in secondary prevention of ischaemic stroke caused by less frequent non-atherosclerotic aetiologies such as arterial dissection and PFO requires further investigations**.**
4. Lipid lowering treatment with statins in combination with lifestyle changes is recommended is the mainstay for primary prevention of ischaemic 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)**.**
5. 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 CAA-related lobar ICH, statin use should probably be reserved for compelling indications (Grade C)**.**
6. There is no evidence from Randomized controlled trials (RCTs) to support the routine use of statins in the acute phase of stroke (first two 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 three 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).

Session 5: Update on secondary prevention issues 2

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

Speakers: Christina Sjöstrand (Stockholm), Christian Pristipino (Rome), Grethe Andersen (Aarhus) and Peter Schellinger (Minden).

Q1: Does percutaneous closure of PFO versus antiplatelet therapy reduce the risk of stroke recurrence?

Recommendation: In patients aged 18–60 years old with cryptogenic stroke/TIA and with high risk PFO features (moderate or severe shunt, atrial septal aneurysm (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).

Q2: Does percutaneous closure of PFO versus oral anticoagulants reduce the risk of stroke recurrence?

Recommendation: Based on the few available data, percutaneous closure and Oral anticoagulation (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.

Q3: Does oral anticoagulant therapy versus antiplatelet therapy reduce the risk of stroke recurrence?

Recommendation: 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 (VKAs) 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 to perform adequately dimensioned head-to-head randomised clinical trials addressing the comparison between single antiplatelet drugs versus OAC (vitamin-K antagonists or Direct oral anticoagulants (DOAC)) in patients in which percutaneous closure has been excluded.

Q4: In patients with non-valvular AF and previous ischaemic stroke or TIA, does left atrial appendage closure reduce risk of recurrent stroke or thromboembolism compared to oral anticoagulant treatment?

Q5: In patients with non-valvular AF and previous ischaemic stroke or TIA, does left atrial appendage closure lead to lower risk of serious adverse events compared to oral anticoagulant treatment?

Q6: In patients with non-valvular AF and previous ischaemic 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?

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 ischaemic stroke or TIA, as an alternative to oral anticoagulant therapy.

Recommendation: Patients with non-valvular AF and previous ischaemic 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 six months or lifelong may be used (Grade C).

Session 6: Clinical stroke trials

Chair: Hanne Christensen (Copenhagen) and Martin Köhrmann (Essen). Secretary: Konstantinos Kostulas (Stockholm). Speakers: Martin Köhrmann (Essen), Georgios Tsivgoulis (Athens).

Q1: How do we increase the generalisability of future stroke trials especially as to women and the old?

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:

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

Q2: Clinical end-point trials for prolonged cardiac monitoring in stroke.

Consensus statement: More evidence from adequately powered randomized clinical trials with sufficient follow-up time is needed to further investigate the impact of Prolonged cardiac monitoring (PCM) on secondary stroke prevention and other clinical endpoints.

Recommendation:

1. PCM can identify a significant proportion of Ischemic stroke (IS) patients with occult PAF, not detected by conventional cardiac monitoring (Grade A).
2. 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).
3. 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).

Session 8: Post-stroke early mobilisation

Chair: Niaz Ahmed (Stockholm). Speaker: Katharina Sunnerhagen (Göteborg)

Q1: Should we avoid early mobilization after AVERT (A very early rehabilitation trial)?

Recommendations:

The evidence point to that early mobilization is safe in 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 is fine (Grade A).

Patient 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).

Session 9: Oral anticoagulation and reversal agents after stroke

Chair: Joji Kuramatsu (Erlangen) and Thorsten Steiner (Frankfurt/Main). Secretary: Boris Keselman (Stockholm). Speakers: Andreas Charidimou (Boston), Eleni Korompoki (Athens/London) and Jan Purrucker (Heidelberg).

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

Recommendation:

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 four-factor Prothrombine complex concentrate (PCC) (30 IU/kg):

- If INR $\geq$ 2.0 (Grade B).
- If INR $\geq$ 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 2 × 2.5 g intravenously) (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 AIS, how is optimal reversal under VKA or NOAC achieved to minimize bleeding complications with revascularization therapies?

Recommendations: Patients with AIS under VKA or NOAC treatment with proven large vessel occlusion should be offered IVT (if feasible) and endovascular treatment (thrombectomy) (Grade C).

In AIS under VKA treatment and otherwise eligible for thrombolysis:

- In INR $\leq$ 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 AIS 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 2 × 2.5 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.

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)?

Recommendation: Enrolment in randomised 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 four to eight weeks from index ICH seems to be safe (Grade C).

Individual decision making on OAC after ICH should consider (Grade C): quality of BP control, age, ICH location, burden of small vessel disease (cerebral microbleeds (CMBs), leukoaraiosis, cortical superficial siderosis, CAA), additional antiplatelet therapy.

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

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: uncontrolled hypertension, disseminated Cortical superficial siderosis (cSS), multiple strictly lobar CMB patterns, severe white matter hyperintensities of presumed vascular origin (Grade C).
- 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 AIS with 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)?

Recommendation: 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).

Session 10: IVT in AIS

Chair: Götz Thomalla (Hamburg) and Robert Mikulik (Brno). Secretary: Michael Mazya (Stockholm). Speakers: Pooja Khatri (Cincinnati), William Whiteley (Edinburg), Götz Thomalla (Hamburg), Eivind Berge (Oslo).

Q1: Should patients with minor stroke be treated with intravenous thrombolysis?

Consensus statement:

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 h be treated with intravenous thrombolysis?

Consensus statement: 1. For patients with AIS 4.5–9 h 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 AIS beyond 4.5 h 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).

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

Consensus statement:

1. Intravenous alteplase is recommended in patients with AIS with an unknown onset time in the presence of a DWI (Diffusion weighted imaging)–FLAIR (Fluid-attenuated inversion recovery) mismatch on acute MRI (i.e. the mismatch between the visibility of an acute ischaemic lesion on DWI in the absence of a visible marked parenchymal hyperintensity on FLAIR in the corresponding area) (Grade B).

2. For patients with AIS 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.

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

Consensus statement: Tenecteplase instead of alteplase is not recommended for treatment of patients with AIS in routine practice (Grade C).

Session 11: Mechanical thrombectomy

Chair: Gary A. Ford (Oxford) and Joan Marti-Fabregas (Barcelona). Secretary: Åsa Kuntze Söderqvist (Stockholm). Speakers: Diederik W.J. Dippel (Roterdam), Gary A. Ford (Oxford), Satu Mustanoja (Helsinki), Mads Rasmussen (Aarhus).

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

Consensus statement: Patients with AIS 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 AIS should be treated with IV alteplase without delay if there are no contra-indications. In case of a proximal intracranial thromboembolic occlusion causing the ischaemic 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).

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 h or with unwitnessed stroke for thrombectomy?

Consensus statement: According to the study results from DAWN and DEFUSE-3 trials, the efficacy of thrombectomy in carefully selected patients with Large vessel occlusion (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 h for Endovascular thrombectomy (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 centres providing EVT, with immediate access to multi-modal advanced imaging and its interpretation, and a well-trained multidisciplinary workforce to deliver specialist pre-, peri-, and post-thrombectomy care.

Recommendation: For patients presenting 6–24 h after onset with ICA or M1 occlusion with a disabling deficit National Institutes of Health Stroke Scale (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).

Q4: In patients undergoing endovascular procedures should conscious sedation or general anaesthesia be used?

Consensus statement: Until further data are available, General anaesthesia (GA) and Conscious sedation (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), comorbidity and current medical condition (airway, vomiting). Management of anaesthesia for EVT is preferably performed by a dedicated anaesthesia team in order to rigorously maintain BP (systolic BP >140 mmHg) (7) and minimize time delay.

Recommendation: We recommend an anaesthetist is present during EVT (Grade C).

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

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ORCID iD

Niaz Ahmed https://orcid.org/0000-0001-7970-0146
Joan Martí-Fàbregas https://orcid.org/0000-0001-9229-8649
Michael Mazya https://orcid.org/0000-0002-0377-3506
Irene Escudero-Martínez https://orcid.org/0000-0003-1838-0235