ESO-Karolinska Stroke Update Conference, Stockholm 13-15 November 2016, Consensus Statements for all sessions

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Session No 1

Management of cervical artery dissection

The Consensus Statement is formed as a recommendation to the European Stroke Organisation (ESO) on revision of ESO Guidelines. Please note that the final text of the Guidelines, is decided by ESO and that the recommendation in this document may not be the final guidelines version. As soon as the guidelines are confirmed, they will appear on this website as well as on the ESO website www.eso-stroke.org
Karolinska Stroke Update Consensus Statement and Recommendations to the ESO Guidelines Committee.

The following Consensus Statement was adopted by the 11th Karolinska Stroke Update Conference on November 14th/15th 2016.

The Consensus Statement was prepared by a writing committee (in alphabetic order: Marcel Arnold, Stephanie Debette, Stefan Engelter, Erik Lundström, Hugh Markus and Turgut Tatlisumak) and proposed by the chairman of the session, Professor Tatlisumak, Gothenburg, and the session secretary, Dr Lundström, Stockholm, together with the speakers of the session, Professor Debette, Bordeaux, and Professor Markus, Cambridge.
The statement was then finally approved by the participants of the meeting, after listening to the different presentations.

Abbreviation: CAD = Cervicocerebral Artery Dissection, IAD = Intra Arterial Dissection

The speakers in this session were controversy to discuss at the 2016 consensus session:

- What is the best method to diagnose CAD?
- Acute stroke in the setting of CAD: is thrombolysis safe?
- Should we use anticoagulants or antiplatelet drugs to prevent CAD?
- Is there a role for angioplasty and stenting?
- What is the optimal duration of medical treatment?

Background

Cervicocerebral artery dissection (CAD) is an important cause of stroke in young adults. Dissections are characterized by separation of the arterial wall layers by a haematoma, which may be secondary to an intimal tear or result from rupture of the vasa vasorum. Blood usually dissects between the layers of the intima and media, typically causing stenosis of the lumen. More rarely, blood dissects between the media and the adventitia leading to the formation of a dissecting aneurysm.
CAD can occur in the setting of trauma to the head or neck, most often trivial trauma, which should be more accurately considered as mechanical trigger events (1) , or appear spontaneously. (2) Cerebral ischaemic events result mostly from thromboembolism or – less often – by hypoperfusion due to a hemodynamic significant stenosis. (3) CAD is classified as extracranial or intracranial, and according to the site

of the artery affected. Extracranial segments of the carotid and vertebral arteries seem more likely to undergo dissection than their intracranial segments in European populations, while intracranial artery dissection appears to be more common than CAD dissection in East Asian studies. (4)
In the setting of intracranial artery dissection, the absence of an external elastic lumina, thin adventitial layer, and paucity of elastic fibres in the media may lead to rupture of the vessel with subarachnoid haemorrhage in 50-60% of the patients according to published series. (4)

Consensus Statement and Recommendation

Diagnosis: for CAD, vascular imaging is essential to establish the diagnosis. The presence of at least one of the following criteria: Visualization of a mural hematoma, aneurysmal dilatation, long tapering stenosis, intimal flap, double lumen or occlusion >2 cm above the carotid bifurcation revealing an aneurismal dilatation or a long tapering stenosis after recanalization in the internal carotid or vertebral artery is required. (1,5) These imaging features are most accurately visualized by Magnetic Resonance Imaging (MRI), with identification of mural hematoma by fat suppressed T1 sequences. (5), However an acute intramural haematoma may not be well visualized on fat-saturated T1-weighted MR until the blood is metabolized to methaemoglobin, which may take a few days. Visualization of the characteristic angiographic features of CAD is possible by Contrast Computed Tomography Angiography. Compared to MR-Imaging or CTA, neurosonography has a lower sensitivity in the diagnosis of CAD, and may miss carotid distal dissections. is metabolized to methaemoglobin.

For intracranial dissections digital subtraction angiography may be required. However, although it remains the gold standard, given its invasive nature it is mainly performed when CT or MR imaging is inconclusive, when patients present with SAH, or when surgical or endovascular treatment is being considered. Mural haematoma is difficult to detect intracranially, but the detection can be facilitated by high resolution 3 Tesla MRI including 3D fat-suppressed T1-weighted images with black blood effect. (4)

Recommendation

Contrast enhanced MRA and MRI with T1-fat suppression sequences is the recommended imaging modality to diagnose extra- and intracranial CAD. When not available CT and CTA is an alternative.

Intravenous thrombolysis in CAD

Based on the pathophysiology of CAD, there might be the risk of an increasing mural hematoma of the dissected vessel if treated with intravenous thrombolysis in the acute setting. This might potentially lead to a hemodynamic worsening and to infarct growth. Although established as safe and efficacious in patients with ischemic stroke from different etiologies (6,7) the evidence for the use of IVT in CAD patients is scarce and based on observational, non-randomized data only. There is currently no available evidence from randomised controlled trials regarding the efficacy or safety of thrombolytic therapy in acute ischaemic stroke associated with CAD. However observational studies suggest that the complication rate of intravenous thrombolysis

with tissue plasminogen activator (tPA) and intra-arterial thrombolysis in acute stroke is not different from other causes of stroke. (4,8)
Current guidelines of acute stroke treatment do not specifically recommend against IVT in CAD patients. (9)

However, regarding the existing evidence on IVT in CAD, this seems to be a theoretical concern and there is currently no convincing reason to withhold IVT or EVT in CAD patients. As IVT and EVT are likely to increase the odds of recanalization of an occluded artery in CAD patients, too, it is reasonable to recommend their use in extracranial CAD. Further research is encouraged.

Most intravenous thrombolysis-treated patients had extracranial internal carotid artery dissections rather than vertebral artery dissections.

IVT in non-CAD ischemic stroke patients and in CAD patients was compared in observational, registry-based studies. (8,10) In one of these studies, CAD patients showed a slightly (but statistically significant after adjustment for age, gender and stroke severity) lower recovery rate than patients with a stroke attributable to another cause. In this study, only 36% CAD patients vs 44% non-CAD patients ($OR_{adjusted}$ 0.50 [95% CI, 0.27-0.95], P = .03) reached an excellent outcome at 3 months (i.e. excellent outcome defined as a modified Rankin Scale score of 0 or 1). (8) There was a high rate (67.7%) of CAD patients with a large artery occlusion in this study. Known as a negative prognostic factor in IVT treated stroke patients, this higher rate of large artery occlusion might - at least in part - explain the lower recovery rate of CAD patients. Yet, another study compared meta-analysed data from observational studies and case reports of IVT-treated CAD patients with data from age- and stroke-severity matched patient data from the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). (10) In this study, 3-month mortality, the rate of symptomatic ICH and the number of patients reaching excellent 3-month outcome did not differ between IVT treated CAD and non-CAD patients.

Data on comparisons of CAD patients receiving IVT versus those who did not are scarce. Analyses on the data from the CAD and Ischemic Stroke Patients (CADISP) consortium showed identical rates of favourable recovery after CAD related ischemic stroke in both IVT treated and non-IVT treated patients ($OR_{adjusted}$ 0.95 [95% CI, 0.45-2.00]). A meta-analysis across observational studies (n=10) identified 174 CAD patients receiving IVT (or some other form of thrombolytic treatment, n=26=) who were compared to 672 CAD patients who did not receive thrombolysis. Most importantly, the odds for achieving a favourable 3-month outcome were similar in thrombolyzed and non-thrombolyzed CAD patients (OR 0.782 [95% CI, 0.49-1.33], p=0.441). Although there was a higher rate of intracranial haemorrhage in thrombolyzed patients (OR 2.65 [95% CI, 0.49-1.33], p=0.042), a symptomatic haemorrhage occurred in one non-thrombolyzed patient only. (11)

There are only a few case reports of patients with ischemic stroke due to pure intracranial dissections who underwent thrombolysis. (4)

Endovascular therapy in CAD

Endovascular thrombectomy with or without IVT is of benefit for patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location (Goyal Lancet 2016) as shown in several randomized controlled trials, recently metaanalysed. (12) No analysis by the presence or absence of CAD was performed. The endovascular approach seems feasible in CAD although there might be the risk, that the false lumen of the dissected artery is cannulated instead of the true lumen.

The current evidence on EVT in CAD is based on case series and small non-randomized studies and should therefore be interpreted very cautiously. In a series of 24 CAD patients receiving EVT (with or without IVT) adjusted (National Institute of Health Stroke Scale (NIHSS) and age) favourable 3-month outcome (mRS 0-2) was equally frequent compared to CAD patients who did not receive EVT (OR 0.62 (0.12-3.14), p=0.56) (13). A meta-analysis across five non-randomized observational case series (14) comparing IVT-treated to EVT-treated CAD patients found similar likelihood of a favourable outcome (modified Rankin Scale 0-2) in both groups (OR 1.41 [95% CI, 0.45-3.45], p = 0.46). Endovascular treatment might be particularly important in patients presenting with tandem occlusion (i.e. occlusion of the dissected artery and a distally located intracranial artery). If compared to CAD patients receiving IVT only (n=11) the odds of a favourable 3-month outcome in EVT-treated CAD patients were similar (OR 1.32 (0.16-10.72), p=0.79). Likewise, there was no difference in the odds of a favourable 3-month outcome if EVT-treated CAD-patients (n=24) were compared to EVT – treated non-CAD patients (n=421) (OR 0.58 (0.19-1.78), p=0.34). (13) In a retrospective study of 258 EVT-treated patients (15), 20 patients with tandem occlusion due to internal carotid artery dissection (ICAD) were compared to non-CAD patients with isolated intracranial artery occlusion. Recanalization rates were similar in both groups (p=0.23). Likewise, favourable outcome was achieved equally frequent in both groups (CAD-patients 70% vs non-CAD patients 50%, p=0.093). However, comparisons in this study were not adjusted for confounding variables or differences in baseline characteristics (e.g. stroke severity).

Recommendation

Acute ischaemic stroke patients who may have extracranial CAD should not be excluded from intravenous or intra-arterial thrombolysis or mechanical thrombectomy (grade C).

Recurrent ischemic events and prophylactic antithrombotic treatment in CAD
Some observational data suggest a high rate of early recurrent stroke after CAD, of the order of 10-15% (16,17), although other data suggest a much lower rate of 1%. (18,19) This has led to the routine use of antithrombotic treatment, either antiplatelet agents or anticoagulants, although there is no trial data demonstrating their efficacy over placebo. Most data comparing the efficacy of antiplatelet agents versus anticoagulants is observational although there has been one recent randomized controlled trial. (18)

Yet, there is consensus on the need for any antithrombotic treatment as primary or secondary prophylaxis of (recurrent) cerebral ischemic events in acute or subacute CAD. Unfortunately, at the current stage, there is still equipoise on the choice of the

antithrombotic therapy (anticoagulation or antiplatelets). Participation in ongoing trials is recommended

Observational data

There have been meta-analyses, based on observational data, comparing antiplatelets to anticoagulants in CAD-patients. (14,20–23) These used different statistical approaches and showed conflicting results. No difference with regard to occurrence of stroke or death was reported by Kennedy et al. in 2008. (21) A non-significant trend in favour of anticoagulants was reported in a later Cochrane Review with regard to the endpoint of death or disability (OR 1.77 [95% CI, 0.98-3.22], p=0.06). (20) However, in this analysis major bleeds (symptomatic intracranial haemorrhage (5/627; 0.8%) and major extracranial haemorrhage (7/425; 1.6%) occurred solely in the anticoagulation group. In turn, Sarikaya et al. (22) found a beneficial effect of antiplatelets with regard to a composite outcome of ischemic stroke, intracranial haemorrhage or death (RR 0.32 [95% CI, 0.12-0.64].

Randomised controlled trial data

In 2015 the first randomized-controlled study comparing antiplatelet treatment to anticoagulants in CAD patients was published. The CAD in Stroke Study (CADISS) was designed as a prospective feasibility study randomly assigning CAD patients to either antiplatelet therapy (aspirin, dipyridamole or clopidogrel alone or in combination) or to anticoagulation therapy (heparin followed by warfarin with a target INR of 2-3). (24) 250 CAD patients mainly presenting with stroke or transient ischemic attack (n=224). With regard to the primary outcome (ipsilateral stroke or death) there was no statistically significant difference between both groups (Intention-to-treat population: OR 0.335 [95% CI, 0.006-4.233], p=0.63). There was one major bleeding which occurred in the anticoagulation group. Central reading of the patient baseline imaging confirmed CAD diagnosis in 197 of the 250 study participants. However, the main results of the study did not differ in the per-protocol population. A striking finding was the low rate of recurrent stroke of approximately 2%. (4 of 196 in the per-protocol population). Based on the very low event rates of the purely clinical primary outcome in this study, the authors calculated that 4876 patients per group would be needed to show significant differences between groups. (24)

Ongoing trial

The use of a surrogate outcome might help to overcome the feasibility issue in a therapy trial in CAD patients. Indeed, there is another prospective, randomized multicentre trial investigating aspirin versus anticoagulation (phenprocoumon) in acute CAD. The “Biomarkers and Antithrombotic Treatment in CAD - TREAT-CAD (25) trial uses a composite primary outcome including both clinical and - also imaging surrogate outcome measures. New ischaemic lesions on diffusion weighted imaging (DWI) in CAD-patients were observed in up to 25% of patients undergoing repeated brain MRI. (26) and therefore their inclusion in the composite primary outcome will reduce the necessary sample size. The TREAT-CAD study started recruitment in 2013. Currently (November 8th), 103 out of the planed 169 patients have participated. Study completion is expected in 2018.

Treatment duration

The ideal duration of antithrombotic a treatment has not yet been studied in clinical trials and is therefore unclear.
Most recurrent ischemic events occur within the first two weeks. There are no reliable data on the optimum duration of antithrombotic treatment in CAD. A minimum of 3 months was used in the CADISS trial (18), and if anticoagulation is given most clinicians continue it for 3 to 6 months.

Stroke prevention – intracranial dissection

The use of anticoagulant therapy during the acute stage of intracranial dissection is controversial since it might promote subarachnoid bleeding. However, a single centre retrospective observational study involving 81 patients suggests that intracranial dissection in the absence of aneurysm or SAH (based on clinical and brain CT/MRI findings) can be safely treated with anticoagulants. (27) However, the risk of SAH is higher in intracranial artery dissection than in CAD, and several studies have reported patients with intracranial artery dissection with initial ischaemic manifestations who subsequently or concurrently developed SAH, prompting caution. (28) There are no evidence based data that anticoagulation is superior to aspirin (grade C).

In patients with non-SAH intracranial artery dissection and no signs of cerebral ischaemia, prescribing no antithrombotic treatment, with close monitoring, has been proposed. (29) (grade C).

Recommendation

For extracranial CAD:

1. Antithrombotic treatment is strongly recommended. (Grade C)
2. There is no evidence of any difference between antiplatelets and anticoagulants (heparin followed by warfarin). (Grade B)

For intracranial dissection in the absence of SAH antiplatelet drugs are recommended. (expert opinion)

Angioplasty and stenting

For CAD, angioplasty and stenting can be considered in recurrent ischaemic symptoms despite antithrombotic treatment, or significantly compromised cerebral blood flow. However, there are no data from randomised controlled trials to demonstrate safety and efficacy of these interventions. It is important to remember that most dissection stenoses spontaneously resolve as the hematoma settles.
For intracranial artery dissection, there are also no randomised trials and only observational studies with relatively small sample sizes. While intracranial artery dissection patients with SAH are usually treated by surgery or endovascular procedures, because up to 40% of the patients experience rebleeding within the first days after the dissection, for non-SAH intracranial artery dissection, endovascular treatment is usually reserved to cases of recurrent ischaemic symptoms despite optimal medical treatment, or, sometimes, when the dissecting aneurysm has

increased in size to prevent rupture, or more rarely to reduce signs of brainstem compression. (4)

Recommendation

Angioplasty and stenting may be considered in CAD patients with recurrent ischaemic symptoms despite antithrombotic treatment. (Grade C)

Follow-up

Specialized follow-up in is recommended in patients with CAD, generally at 3 to 6 months.

The rate of recurrence of CAD is estimated to be low (between 0 and 8%). Data on the rate of long-term recurrences is lacking. (2) Little information is available on the risk of recurrent intracranial artery dissection. One study reported a 9% recurrence rate during a mean follow-up of 3.4 years. (3)

Although functional outcome is good in most patients with CAD (three quarters of patients who suffered a stroke) (2,4), the impact in terms of fatigue and residual anxiety is considerable, with quality of life being impaired in about half of long-term survivors after CAD, even in patients with local or transient symptoms only or without functional disability. (30) While lifestyle recommendations should be given, especially to avoid cervical trauma, patients should also be encouraged to resume a normal lifestyle. Important questions in terms of quality of life also include the risk related to pregnancy after a dissection, for which evidence-based data is lacking. Although this question should be addressed on a case by case basis, based on current empirical evidence future pregnancies should probably not be contraindicated - neurological follow-up during the pregnancy and post-partum period is recommended (31) (grade C).

Recommendation

Antithrombotic treatment is recommended for at least 6-12 months. In patients in whom full recanalisation of the dissected artery has occurred and there have been no recurrent symptoms stopping antithrombotic treatment may be considered. In case of a residual dissecting aneurysm or stenosis, long-term antiplatelet treatment is recommended. (Grade C)

Genetic testing

According to current estimates on the largest published series, the rate of familial CADs is less than 2% in the literature, and in less than 1% of patients CAD is a complication of an underlying inherited connective tissue disease. (32) If such a condition is suspected patients should be referred to a specialized centre for detailed diagnostic work-up.
In the vast majority of patients with sporadic CADs, without any family history or clinical features of inherited connective tissue disease, genetic investigations are generally not recommended. Although common genetic polymorphisms were recently found to be associated with risk of CAD, (33) the effect size is low and there is currently no

indication for genotyping of these polymorphisms in a clinical setting. Genetic determinants of intracranial artery dissection are unknown.

Recommendation

Routine genetic testing in patients with CAD and IAD is not recommended, unless there is a family history or clinical suspicion of underlying inherited connective tissue disease. (Expert opinion)

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Session No 2

Update on secondary prevention issues

The Consensus Statements include two parts, the Consensus Statement itself, and the Recommendation to the European Stroke Organisation (ESO) on revision of ESO Guidelines.
Please note that the final text of the Guidelines, is decided by ESO and that the recommendation in this document may not be the final guidelines version. As soon as the guidelines are confirmed, they will appear on this website as well as on the ESO website www.eso-stroke.org

Recommendations (grade of evidence)

At the 1998 Karolinska Stroke Update meeting, the following definitions were made with regard to the strength of evidence supporting recommendations:
Instruction

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.

I. ESO Karolinska Stroke Update Consensus Statement

Theme 1: Anticoagulation and its timing – lessons from the RAF study

The following Consensus Statement was adopted by the 11th Karolinska Stroke Update Conference on November 14th/15th 2016.

The Consensus Statement was proposed by the chairmen of the session, Professor Natan Bornstein, Tel-Aviv, Israel, and Associate Professor Niaz Ahmed, Stockholm, Sweden, and the session secretary Dr Charith Cooray, Stockholm, Sweden, together with the speakers of the session, M. Paciaroni (Perugia, Italy), R. Bulbulia (Oxford, England), H. Mattle (Bern, Switzerland), N. Bornstein (Jerusalem, Israel). The statement was then finally approved by the participants of the meeting, after listening to the different presentations. The speaker on this topic was Doctor Maurizio Paciaroni, Perugia, Italy.

Issues for the 2016 consensus session:

- Is the best time for initiating anticoagulation treatment as secondary prevention of stroke 4 to 14 days from the acute event?
- Should low molecular weight heparin (LMWH) not be used alone or prior to start of oral anticoagulation treatment in patients with AF and ischemic stroke?
- The RAF study results apply only to Vitamin K antagonists (VKA). Is a future randomized study assessing the efficacy of direct oral anticoagulants in the acute phase of stroke in patients with AF warranted?

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Patients with AF have a fivefold increased risk of ischaemic stroke. Guidelines recommend that patients with AF suffering an ischaemic stroke or transient ischaemic attack (TIA) should receive long-term anticoagulation therapy unless contraindicated. Until 2009, vitamin K antagonists, e.g. warfarin, were the only available oral anticoagulants (OACs). Several new oral agents, directly inhibiting thrombin or activated factor X, have recently been developed[1-3] . These direct OACs have been shown at least as safe and effective as warfarin for prevention of stroke and systemic embolism in patients with non-valvular AF[4]. However, trials evaluating direct OACs excluded patients with stroke within the previous 10-14 days, and severe disabling stroke within 3-6 months. Therefore, the timing of treatment initiation for secondary stroke prevention remains an open question. If untreated, the risk of early recurrence of ischaemic stroke in patients with AF can reach up to 7.5% within the first 2 weeks[5].

Despite the fact that warfarin has been the standard OAC therapy for decades, the timing of its initiation for secondary stroke prevention in AF is based on weak evidence, mainly consisting of expert opinion. The European Society of Cardiology (ESC) recommends initiating OACs within12 days after acute stroke, after an assessment of stroke severity using NIHSS has been performed: at 3 days from stroke onset for mild stroke (NIHSS<8), at 6 days for moderate stroke (NIHSS 8-16) and at 12 days in patients with severe stroke (NIHSS<16)[6]. European Stroke Organization guidelines are silent on this issue. The 2014 joint guidelines from the American Heart Association/American Stroke Organization (AHA/ASA) refer to the American College of Chest Physicians (ACCP) guidelines from 2012, recommending initiating anticoagulation within 2 weeks of stroke, except for patients with large infarcts or other risk factors for haemorrhage[7].

The risk of initiating direct OACs or warfarin within the first 14 days following ischaemic stroke of different severity has not been systematically investigated. The RAF study was a prospective observational study conducted between 2012 and 2014[8]. In this study 1029 ischemic stroke patients with atrial fibrillation, treated with either anticoagulants (alone or in combination with antiplatelets) only antiplatetets or no treatment, were prospectively followed. The main outcome studied was a composite endpoint composed of recurrent ischemic cerebrovascular events (stroke or TIA) and symptomatic systemic embolisms;
symptomatic cerebral bleedings and major extracerebral bleeding at 90 days. In this study the optimum timing for initiating anticoagulant treatment was between 4 and 14 days. Patients treated with oral anticoagulants alone had better outcomes compared

with patients treated with low molecular weight heparins alone or before oral anticoagulants.

Conclusions

- Regarding the best time for initiating anticoagulation treatment in patients with acute ischemic stroke, current limited evidence argues in favour of the 4-14day window post-acute event. However, index infarct size and severity of stroke need to be taken into account before making any decision. That is, in patients with mild stroke and small infarct anticoagulation treatment may be started at day 4 from index stroke. For moderate infarct, anticoagulation treatment may be started at day 7 from index stroke. For large infarct, anticoagulation treatment may be started at day 14 from index stroke. More data from randomized controlled trials and registries are needed to verify these time-points.
- In patients with acute ischemic stroke and atrial fibrillation, secondary prevention using bridging therapy with low molecular weighted heparin, before starting oral anticoagulants was associated with a higher risk of haemorrhagic transformation of the ischemic lesion when compared to oral anticoagulation alone. Therefore, the risks associated with bridging therapy need to be carefully considered.
- The RAF study results principally apply to the use of Vitamin K antagonists (VKA). A future randomized study assessing the efficacy of direct oral anticoagulants in the acute phase of stroke in patients with AF seems warranted.

II. Summary of updated recommendations to ESO Guidelines Committee:

Patients with atrial fibrillation and acute ischemic stroke- timing of anticoagulation (Secondary prevention)

- In patients with acute ischaemic stroke and atrial fibrillation, we recommend that oral anticoagulation treatment may be started at day 4 in mild stroke and small infarct, at day 7 in moderate stroke with medium infarcts, and at day 14 in severe stroke with large infarcts from index stroke. More data from randomized controlled trials and prospective registries are needed to verify these time-points, in particular for direct oral anticoagulants (Grade C)
- Based on observational study results, bridging therapy with low molecular weight heparin, prior to oral anticoagulation therapy may not be used in patients with atrial fibrillation and ischemic stroke. (Grade C)

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Theme 2: Prevention of stroke in patients with patent foramen ovale, an update

I. ESO Karolinska Stroke Update Consensus Statement

The following Consensus Statement was adopted by the 11th Karolinska Stroke Update meeting on November 14th/15th 2016.

The Consensus Statement was proposed by the chairmen of the session, Professor Natan Bornstein, Tel-Aviv, Israel, and Associate Professor Niaz Ahmed, Stockholm, Sweden, and the session secretary Dr Charith Cooray, Stockholm, Sweden, together with the speakers of the session, M. Paciaroni (Perugia, Italy), R. Bulbulia (Oxford, England), H. Mattle (Bern, Switzerland), N. Bornstein (Tel Aviv, Israel). The statement was then finally approved by the participants of the meeting, after listening to the different presentations. The speaker on this topic was Professor Heinrich Mattle, Bern, Switzerland.

Issues for the 2016 consensus session:

- The current guidance on PFO closure (American Academy of Neurology, AAN) vs. the pooled analysis of completed RCTs- why is the conclusion and the interpretation of the results of these same trials different in these 2 publications?
- Considering the best medical treatment-Antiplatelets vs. Anticoagulation. Long term follow-up with no crossover and loss of follow-up in the studies is a

serious concern. Are further studies feasible?
- Are there sufficient data from the available RCTs to recommend device closure of a symptomatic (Stroke/TIA) PFO? To whom?
- Is the RoPE score good enough to differentiate between "incidental" and "causal" PFO?

Background

The prevalence of patent foramen ovale (PFO) is up to 25% and the prevalence of an atrial septal aneurysm up to 5% in the general population. To date, epidemiologic studies have not shown thromboembolic events to occur more frequently in subjects with PFO, and therefore no special primary intervention is needed [1,2]. In patients with stroke of unknown cause (cryptogenic stroke), however, the prevalence of PFO is substantially higher and approximates 50%[3]. Case reports and case controls studies of cryptogenic strokes compared to strokes with known aetiology or non-stroke controls confirmed an association of PFO and stroke. Therefore, the presence of a PFO after stroke or emboli to other organs raises important questions on the management of such patients. Prospective cohort studies and randomized controlled trials have shown that the overall risk of recurrent stroke or TIA is low. Aspirin or anticoagulation with a vitamin K antagonist such as warfarin reduce the risk of recurrent stroke in the average patient with PFO to similar levels[4]. Therefore aspirin should be considered the treatment of choice. The ROPE score addresses the question, whether a PFO in a given patient is pathogenic or only an innocent bystander[5]. A high ROPE score characterizes younger patients with few or without vascular risk factors. A high ROPE score indicates a high probability that a discovered PFO is likely stroke-related and raises the question whether such a PFO should be closed. Retrospective cohort and long-term propensity score-matched comparisons on percutaneous device closure demonstrate a long-term benefit of this procedure[6,7]. However, 3 randomized controlled trials, all of them underpowered, did not meet their primary aim to reduce recurrent stroke or TIA or death[8]. Only the recently presented long-term data of the RESPECT trial indicated effectiveness of PFO closure for secondary stroke prevention (presented at the TCT meeting 2016). The practice advisory of the American Academy of Neurology states that percutaneous PFO closure should not routinely be offered to patients with cryptogenic ischemic stroke except in the rare circumstances when cryptogenic strokes recur despite adequate medical therapy[9]. Nevertheless, in the pooled analysis of the completed randomized trials closure reduced recurrent stroke[10]. More data from ongoing trials pending it is currently reasonable to use percutaneous device closure for PFOs with a high ROPE score, but general use is not recommended.

Conclusions

- The practice advisory of the American Academy of Neurology is based on the intention to treat analysis of the 3 completed randomized trials that showed a nonsignificant trend favouring percutaneous PFO closure over best medical treatment. The practice advisory states that closure should not routinely be offered to patients with cryptogenic ischemic stroke except in the rare circumstance when a cryptogenic stroke recurs despite adequate medical therapy. Nevertheless, in the pooled analysis of individual patient data as treated and also in the long-term follow-up of RESPECT, closure reduced recurrent stroke significantly. Therefore, when a PFO is likely pathogenic and

not an innocent bystander it is reasonable to offer percutaneous PFO closure to patients with cryptogenic stroke and PFO.

- The TACTICS-PFO study, an individual participant data meta-analysis from 12 databases of medically treated patients with cryptogenic stroke and PFO did not find any difference comparing oral anticoagulation and antiplatelet therapy for secondary prevention.[i] Therefore, randomized trials comparing different antithrombotic approaches in these patients are justified, especially trials that include the non-vitamin K antagonist oral anticoagulants.
- All randomized controlled trials of percutaneous PFO closure for secondary prevention after cryptogenic stroke assumed higher event rates in the planning phase than the rates that occurred in the trials. Therefore, all trials were underpowered to provide a statistically firm answer. The meta-analysis of the pooled individual patient data provides currently the best evidence of the efficacy of PFO closure. Data from additional ongoing trials are desirable. As individual trials they are underpowered as well, but will add data to the data pool for a meta-analysis.
- The RoPE score uses clinical characteristics identified in cryptogenic stroke patients. Except in the very rare situation where a thrombus passing the PFO is identified the RoPE score represents currently the best tool to estimate the probability that a discovered PFO is likely stroke-related or incidental. It is desirable that the ROPE score be validated in a prospective large cohort.

II. Summary of updated recommendations to ESO Guidelines Committee: Prevention of stroke in patients with patent foramen ovale, an update

- 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).
- 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 oral anticoagulants (Grade B).
- Currently, the 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).

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Theme 3: Update on Carotid Surgery and Stenting

I. ESO Karolinska Stroke Update Consensus Statement

The following Consensus Statement was adopted by the 11th Karolinska Stroke Update Conference on November 14th/15th 2016.

The Consensus Statement was proposed by the chairmen of the session, Professor Natan Bornstein, Tel-Aviv, Israel, and Associate Professor Niaz Ahmed, Stockholm, Sweden, and the session secretary Dr Charith Cooray, Stockholm, Sweden, together with the speakers of the session, M. Paciaroni (Perugia, Italy), R. Bulbulia (Oxford, England), H. Mattle (Bern, Switzerland), N. Bornstein (Tel Aviv, Israel). The statement was then finally approved by the participants of the meeting, after listening to the different presentations. The speaker on this topic was Dr R. Bulbulia (Oxford, England)

Issues for the 2016 consensus session:

- Given the recent improvements in medical therapy, should we continue to base our treatment decisions on data from “old” symptomatic carotid trials?
- Is it ever appropriate to intervene on a <50% symptomatic stenosis?
- Does gender matter – Do women really derive less benefit from carotid intervention than men?
- With more experience, better case selection and technological advances, can CAS compete with CEA?

Background

Given the recent improvements in medical therapy, should we continue to base our treatment decisions on data from “old” symptomatic carotid trials?

Patients with overt vascular disease should receive “triple medical therapy” (ie, anti-platelet therapy, anti-hypertensives and statins), which significantly reduce the risk of heart attacks and strokes (1-3). In the North American and European symptomatic CEA trials which largely recruited in the 1980s, lipid-lowering therapy was infrequent, blood pressure control was rarely optimal and whilst anti-thrombotic therapy was widely used, it may be considered sub-optimal by current standards. To derive benefit from carotid intervention, a patient’s procedural risk needs to be offset by long-term reductions in stroke. Given the significant improvements in contemporary medical therapy there is renewed uncertainty as to whether intervention plus medical therapy, or medical therapy alone, is best in patients with lower risk symptomatic carotid stenosis.

Symptomatic Carotid Stenosis: Time to change intervention thresholds?

Pooled analysis of individual patient data from NASCET, ECST, and VA309 (combined sample = 6092 participants) demonstrated that CEA was beneficial in patients with stenosis >70% (absolute risk reduction 16.0%, $p<0.001$) and 50-69% (absolute risk reduction 4.6%, $p=0.04$). Intervention was not effective in those with 30-49% stenosis, and harmful in individuals with stenosis <30% ($p=0.05$) (4). In addition, the greatest gains were seen if surgery was performed early, hence the recommendation that CEA should ideally be performed within 2 weeks of the onset of neurological symptoms (5). Collectively, these trials and accompanying meta-analyses provide high level evidence to justify widespread and expeditious use of CEA in patients with symptomatic carotid stenosis.

Is it ever appropriate to intervene on a <50% symptomatic stenosis?

In an IPD of symptomatic patients with carotid stenosis <50% randomised to carotid endarterectomy versus medical therapy, allocation to surgery was either ineffective or harmful (4). Accordingly, there is widespread agreement that such patients are managed conservatively, which now involves dual anti-platelet therapy during the acute presentation, tight blood pressure control and intensive lipid-lowering therapy. However, the further management of a patient with a <50% stenosis who has ongoing ipsilateral symptoms despite intensive medical therapy is controversial. Such plaques may be very unstable, with overlying thrombus and at particularly high risk of distal embolization (6).

Does gender matter – Do women really derive less benefit from carotid intervention than men?

A belief that women derive less benefit than men following carotid intervention first arose following publication of the large North American and European symptomatic carotid trials. Subgroup analysis of these trials (which included 1723 [28%] women) showed a higher procedural risk amongst women together with a lower 5-year risk of stroke, resulting in a smaller absolute risk reduction in women than in men. Despite the fact that such extreme results in sub-group analyses can more plausibly be ascribed to the play of chance, the belief that women benefited less than men took hold and was reinforced by a misinterpretation of ACST-1 5-year results; whilst the results among the 2000 men, based on 95 strokes, were very definite, those in the 1000 women randomised, based on just 40 strokes, were less so, but nevertheless entirely consistent with the overall result. Publication of the 10-year results of ACST-1, which clearly demonstrated similar long-term benefits in both men and women following successful surgery has helped clarify matters. (7) Nevertheless, several guidelines still discriminate against women.

Some of the reluctance to operate on women arises from concerns that they are at increased risk of procedural complications. Whilst randomised trials are necessary to determine the long-term protective effects of intervention when compared to medical therapy, they rarely provide reliable evidence about early procedural risks (which tend to occur infrequently in trials). Large registries, with tens or preferably hundreds of thousands of procedures and hence hundreds of peri-operative events are a much more appropriate source of information when considering operative risks. For example, analysis of the Nationwide Inpatient Sample Database (>220,000 CEAs) showed no significant difference in peri-operative stroke rates amongst men and women. (8)

With more experience, better case selection, technological advances and emerging data on long-term durability, can CAS compete with CEA?

Unlike coronary artery disease and peripheral artery disease, where endovascular treatments now predominate, the development of effective endovascular treatments for carotid stenosis has been more protracted. Early small and/or single centre trials evaluating percutaneous carotid interventions in symptomatic patients reported high peri-procedural stroke rates and their results are largely uninformative. But 4 subsequent larger trials (EVA-3S, SPACE, ICSS and CREST) contribute around 80% of the totality of evidence for the comparison of CAS v CEA in symptomatic patients (9-12). In a pre-planned meta-analysis of pooled individual patient data from EVA3S, SPACE and ICSS, patients treated with CAS rather than with CEA had a statistically significant 53% relative increase in the risk of any stroke or death within 120 days after randomization (pooled risk: 8.9% in patients treated with CAS versus 5.8% in patients treated with CEA, risk ratio [RR] 1.53, 95% confidence interval [CI] 1.20-1.95).(13) An analysis of the subset of 1321 symptomatic patients included in CREST yielded results consistent with these findings: 6% 30-day stroke and death rate in patients treated with CAS versus 3.2% in those treated with CEA (HR = 1.89, 95%CI: 1.11-3.21) (12). In all four trials the excess stroke risk associated with CAS occurred during the peri-procedural period, but thereafter stroke rates were similar in both groups, suggesting that CAS is as effective as CEA for the long-term prevention of recurrent stroke (9,14). Consequently, there is now a strong focus on reducing peri-procedural risks of CAS,

with an emphasis on experience (both individual and institutional), better case selection and technological advances.

Volume-outcome relationship for CAS

Carotid artery stenting is technically challenging, with arch angiography and selective catheterisation of the internal carotid artery exposing the patient to a substantial risk of embolic stroke. It has been suggested that following 2 years' concentrated experience, an operator may achieve a stroke rate of <5% in symptomatic patients, and that a total operator experience of 72 CAS procedures is required to achieve a procedural stroke rate of <3% (15).

Case selection: Identifying low-risk CAS patients

I) Symptom status

Unlike symptomatic lesions, for which the risks of CAS are substantial and hence CEA is generally preferred (13), asymptomatic lesions (ie, no prior stroke or none within 6 months) tend to be more stable, so the peri-procedural hazards of stenting are less. Some results have now emerged for the comparison of CEA and CAS in asymptomatic patients. The North American Asymptomatic Carotid Trial-1 (ACT-1) recruited and randomised 1453 asymptomatic patients to CEA and CAS in a 1:3 ratio (16). In addition, subgroup analyses have been reported for the CREST trial (1181 asymptomatic patients) (14). Neither ACT-1 nor the asymptomatic subgroup of CREST demonstrated a difference in composite peri-procedural events between CEA and CAS (20,22). In ACT-1, the rates of stroke, myocardial infarction, or death were 2.6% in the CEA group and 3.3% in the CAS group (p=0.60), with a non-significantly higher rate of minor peri-procedural strokes in the CAS group (2.4% CAS vs 1.1% CEA, p=0.20). In CREST, the peri-procedural hazards were 3.6% in the CEA group and 3.5% in the CAS group. Consideration of all CREST participants (symptomatic & asymptomatic) also suggested that patients allocated CAS had a higher peri-procedural stroke rate, but a lower peri-procedural myocardial infarction rate compared to those allocated CEA. Whether these two events can be considered comparable has been a topic of ongoing discussion.

CREST-1 has recently reported medium and long-term follow-up and found that the long-term stroke rates were similar amongst those allocated CEA and CAS. CREST-1 demonstrated 10-year stroke rates of 7.9% in asymptomatic patients randomised to CEA compared to 8.6% in those randomised to CAS (p=0.41). Similarly, ACT-1 demonstrated 5-year stroke rates of 5.3% in the CEA group and 6.9% in the CAS group. However, these results are based on a relatively small number of non-procedural strokes and both trials were
under-powered to detect moderate but clinically meaningful differences between CEA and CAS.

II) Age

In a recent IPD meta-analysis of 4 randomised trials comparing CEA vs CAS in symptomatic patients, whilst increasing age had no effect on procedural risk amongst those allocated to surgery, there was a monotonous increase in peri-procedural risk amongst those allocated to stenting from 65 years of age upwards. Consequently, CEA

was found to be clearly superior to CAS in those aged 70-74 and older, and this excess risk was almost wholly attributable to peri-procedural complications. (17)

III) Timing of intervention

CAS within 2 weeks of an index event appears to be associated with a two-fold excess risk of stroke compared to delayed intervention (CAPTURE), but this non-randomised comparison could be highly confounded. (18)

IV) Technological Advances

Since the hazards of CAS appear concentrated during the peri-procedural period, recent technological advances have sought to reduce embolization during and shortly after CAS.

a) Cerebral Protection Devices

There is no robust randomised evidence that CPD reduces the risk of clinically significant stroke, but observational studies do suggest higher rates of stroke and new ischaemic lesions on DWI amongst patients undergoing unprotected CAS and their use is increasing (19,20). First generation CPD involved placing a filter distal to the carotid stenosis, and hence necessitated crossing the lesion with a wire before filter deployment with a consequent risk of CPD related stroke. Second generation CPD include flow-reversal devices which can be deployed before the lesion is crossed, and are gaining in popularity. Finally, a recently developed trans-carotid neuroprotection system creates a circuit between the common carotid artery and the femoral vein, allowing extra-corporeal flow reversal during carotid stent placement, with atheromatous debris captured in a filter.

b) Direct Cervical Access

Since arch angiography contributes significantly to the procedural risk of CAS, a system has been developed to allow direct cannulation of the common carotid artery via an incision just above the clavicle, following which a stent can be placed across the carotid stenosis (TCAR). This approach, when combined with an extra-corporeal neuroprotection flow-reversal circuit has been evaluated in a single arm prospective trial with rates of DWI detected cerebral embol*i comparable to those seen with surgery. (21)*

c) Stent designs

It has been suggested that closed cell stents are associated with a reduced rate of embolization, since atheromatous material is less likely to extrude through the smaller interstices as the stent dilates. However, closed cell stents are less flexible than open cell stents and perform poorly in tortuous anatomy. Several “hybrid” stents have been developed, with both an “open cell” outer stent which can adapt to challenging anatomy and an ultra-fine “closed-cell” inner stent which reduces the risk of plaque extrusion.

Conclusions

- Whilst dual anti-platelet therapy, intensive statins and tight blood pressure control will lower stroke risk in acutely symptomatic patients, the absolute gains in patients at high risk of recurrent stroke (eg, >70% stenosis, event < 2 weeks previously) are so large that it is highly probable that such patients will continue to derive significant additional benefit from timely intervention.
- It is possible that, in some lower-risk symptomatic patients (eg, 50-69% stenosis, retinal symptoms only, event > 2 weeks previously, diabetes(?)), carotid intervention may be ineffective (or harmful). Such patients could be randomised to trials comparing carotid intervention plus medical therapy vs medical therapy alone (eg, ECST-2).
- When faced with recurrent ischaemic symptoms and an ipsilateral stenosis of <50%: First, exclude alternative pathologies (eg, cardio-embolic source, more proximal or distal tandem lesions stroke mimics) and secondly, assure good adherence to medical therapy. In such circumstances, and following discussion at a multi-disciplinary team meeting (including surgeons / interventionists, radiologists and neurologists/stroke physicians), carotid intervention on <50% stenosis may be considered. Research to help identify the *vulnerable plaque* and hence higher risk patient is ongoing.
- Women are consistently under-represented in randomised trials, and apparent differential treatment effects can be misleading. Large-scale contemporary registry data show similar procedural risks in both men and women. The decision whether or not to intervene should not be based on gender.
- Careful case selection of patients at lower risk for CAS (ie, not recently symptomatic patients, those <70 years of age, no prior ischemic brain damage), improved experience and technological advances in cerebral protection, access and stent design may help close the gap in peri-procedural complication rates between CEA and CAS.

II. Summary of updated recommendations to ESO Guidelines Committee: Update on Carotid Surgery and Stenting.

- Patients with symptomatic carotid stenosis and a high risk of recurrent stroke (eg, >70% carotid stenosis, ischemic event <2 weeks previously) should be offered timely intervention with carotid intervention (Grade A).
- Patients with symptomatic carotid stenosis and lower-risk of recurrent stroke (eg, moderate carotid stenosis, retinal symptoms only, event > 2 weeks previously,) may be randomised to trials comparing carotid intervention plus medical therapy vs medical therapy alone (ECST-2 / CREST-2) if clinician and patient substantially uncertain about the benefits of intervention(Grade B).
- Almost all patients with <50% symptomatic carotid stenosis should not be treated with intervention. However, intervention in certain patients may be considered if the stenosis causes recurrent symptoms despite optimal medical therapy (Grade C?).
- Decisions on whether or not to intervene on patients with carotid stenosis should not be based on gender (Grade A?).
- CAS is an effective alternative intervention in selected cases (eg, not recently symptomatic, age <70 years, no prior ischemic brain damage) when done by experienced interventionists. Technological advances in cerebral protection, access and stent design should be considered in patients treated with CAS (Grade A).

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Session No 3
Lipid lowering for primary and secondary stroke prevention

The following Consensus Statement was adopted by the ESO-Karolinska Stroke Update Conference on November 14th/15th 2016.

The Consensus Statement was proposed by the chairperson in the session, Professor Eivind Berge (Oslo, Norway), the session secretary Tiago Prazeres Moreira (Stockholm, Sweden), together with the speakers in 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 Georgios Ntaios (Larissa, Greece) and Dr Andreas Charidimou (London, UK).

Questions for the 2016 consensus session:

- Should aggressive lipid lowering therapy be given for secondary prevention of stroke?
- Should lipid lowering therapy be given in the acute phase of stroke?
- Should statins be used after intracerebral haemorrhage?
- Is there a place for PCSK9 inhibitors for patients with dyslipidaemia and previous stroke or transient ischaemic attack?
- Should lipid lowering therapy be given for primary prevention?

Effects of lipid lowering therapy for primary and secondary prevention of stroke

In patients with high risk of cardiovascular events, there is reliable evidence that statin treatment results in a modest but important reduction in the risk of stroke (relative risk reduction 21%) [1].

In the Heart Protection Study (HPS) more than 20,000 patients at high risk of vascular events and with total plasma cholesterol of ≥3.5 mmol/L were treated with simvastatin 40 mg or placebo daily [2]. 3280 patients (16% of all patients) had a previous stroke or TIA, out of whom 1820 had no known coronary artery disease (CAD). For all patients there was a 20% relative reduction (and a 5.1% absolute reduction) of the risk for a major vascular event during the 5 year follow-up period. For patients with previous stroke/TIA there was a 23% relative risk reduction (absolute risk reduction 4.9%). Statin treatment was initiated on average more than 4 years after stroke onset. At 11 years follow-up there was no significant difference in the rate of stroke between the statin-treated and placebo-treated groups, with no increased risk of haemorrhagic stroke (38 [0·4%] vs 51 [0·6%]; p=0·13), indicating that long-term statin was safe in this patient group. (Heart Protection Study Collaborative Group, Lancet 2011; 378: 2013–20) [3].

In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, 638 of 5804 patients (11%) aged 70-82 years had a previous stroke. Overall, there was a 15% relative risk reduction of vascular events during 3.2 years

(absolute risk reduction 2.1%), but no risk reduction for stroke (although this study was underpowered for this estimate) [4].

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial 4,731 patients with recent (<6 months) non-cardioembolic stroke or TIA and with no known CAD were randomised to atorvastatin 80 mg per day or placebo [5]. After 4.9 years of follow-up, there was a statistically significant 16% relative reduction in the risk of stroke (primary end-point) in the atorvastatin group compared to the placebo group (absolute risk reduction 2.2 %), despite a small increase in the risk of haemorrhagic stroke. There was also a statistically significant 35% reduction in major coronary events, 42% reduction in all coronary events, and a 45% reduction in revascularisation procedures.

A meta-analysis of data from 170 000 participants in 26 randomised-controlled trials of more versus less intensive statin regimens (5 trials; 39 612 participants; median follow-up 5·1 years) and of statin versus control (21 trials; 129 526 participants; median follow-up 4·8 years) showed a 16% risk reduction of ischaemic stroke (95% CI 11–21; p<0.0001) per 1 mmol/L LDL cholesterol reduction, with a highly significant reduction in ischaemic stroke (1427 vs 1751; rate ratio 0.79, 95% CI 0.74–0.85; p<0.0001) and a nonsignificant increase in haemorrhagic stroke (257 vs 220; rate ratio 1.12, 95% CI 0.93–1.35; p=0.2). Stroke did not significantly contribute to increased case fatality (rate ratio 0·96, 95% CI0·84–1·09; p=0·5) [6].

When considering patients at low (<10%) 5-year risk of cardiovascular events, a meta-analysis of individual participant data from 22 trials of statin versus control (n=134 537; mean LDL cholesterol difference 1.08 mmol/L; median follow-up 4·8 years) and 5 trials of more versus less statin (n=39 612; difference 0.51 mmol/L; 5·1 years) showed similar rates of ischemic stroke risk reduction compared to high-risk patients (rate ratio 0.76, 99% CI: 0.61–0.95; p=0 · 0012). There was no evidence that the rate ratios for haemorrhagic stroke varied by degree of cardiovascular risk at baseline (1.15, 95% CI 0.97–1.38) [7].

Regarding stroke caused by large artery atherosclerosis, a 3-year, prospective, observational study of statin treatment in 7 tertiary stroke centers found greater neurologic improvement during hospitalisation and higher rates of 30-day favourable functional outcome in patients with large artery atherosclerosis pretreated with statins (n=192) than patients with large artery atherosclerosis but not treated with statins (n=324 OR 2.44; 95% CI: 1.07–5.53) [8].

A clinical concern exists regarding statin use in patients with intracerebral haemorrhage (ICH). In the SPARCL trial 93/4731 patients (~2 %) had an ICH as the qualifying baseline event, equally randomised between high dose atorvastatin and placebo. In the atorvastatin group 55 ICHs were observed during follow-up vs. 33 in the placebo group (HR: 1.66; 95%CI: 1.08–2.55, p=0.02). In a post hoc Cox-regression analysis of patients with ICH, the benefit in ischemic stroke prevention was found to be hampered by an increase in incident ICH independent from LDL levels [9]. A meta-analysis of 7 RCTs where high-dose statin treatment in 31099 patients was compared to placebo in 31105 patients. High dose statin treatment as defined as atorvastatin 80 mg,

simvastatin 80 mg, pravastatin 40 mg, rosuvastatin 20 mg once daily. Results from this study pointed to a higher risk for ICH with high-dose statin regimens (risk ratio = 1.53; 95% CI: 1.16–2.01; p=0.002) [10].

A likely important step in decision making for statin use or avoidance in ICH patients is an accurate assessment of haemorrhage recurrence risk based on the presumed cause of ICH and the predominant type/severity of the underlying haemorrhage-prone small vessel disease. A key difference between the two broad aetiologies of ICH is the much higher annual recurrence rate in cerebral amyloid angiopathy-related lobar ICH compared to hypertensive arteriopathy-related ICH (~10%/year vs 2-3%/year, respectively) [11]. A Markov decision analysis suggested that if statin use does increase the risk of ICH, avoidance of statins should be considered particularly in patients lobar ICH due to cerebral amyloid angiopathy [12]. Due to the paucity of data from further randomised-controlled trials and well-designed prospective observational studies it remains uncertain whether statin use and low blood cholesterol levels increase risk of recurrent ICH.

A retrospective study analysing 8535 patients from the Virtual International Stroke Trials Archive (VISTA) using propensity score matching showed that prior statin use (n=1309) was not associated with an increased risk of symptomatic ICH or any ICH (adjusted OR 1.33 [0.83-2.14] and 1.35 [0.92-1.98, respectively]. No evidence of a negative interaction with thrombolysis was observed, and initiation of statin treatment within three days of acute ischaemic stroke (n=626) was not associated with an increased rate of ICH when compared to patients not started on statins (adjusted HR 1.60; 0.70–3.65) [13].

Similarly, analysis of 1660 patients from the SITS-EAST Register did not show a significant increase in symptomatic ICH in patients pretreated with statins (OR as per NINDS definition 1.41 [0.83–2.39]; OR as per ECASS II definition 1.13 [0.60–2.14]; OR as per SITS definition, 1.89 [0.75–4.77]). Death and favourable functional outcomes were equally not affected by statin pretreatment (OR 0.92 [0.57–1.49] and OR 0.81 [0.52–1.27], respectively). Statin pretreatment was independently associated to a higher likelihood of early clinical recovery (OR 1.91 [1.25–1.92]) [14].

Recently, two proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab) were approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of hypercholesterolemia. These molecules are fully human monoclonal antibodies which selectively block PCSK9, and hence permit the low-density lipoprotein (LDL) receptor to effectively recycle to the surface of liver cells. Recent studies in different patient populations have shown that the administration of PCSK9 inhibitors is associated with an LDL-cholesterol lowering of 50-60% when given as an add-on treatment to aggressive lipid-lowering treatment [15,16]. Recently, the development of bococizumab was discontinued.

Ongoing randomised- and placebo-controlled studies aim to investigate whether the administration of PCSK9 inhibitors is associated with a significant

reduction of cardiovascular events. In the meantime, there have been some primary results about hard clinical outcomes: the OSLER study enrolled 4465 patients who had completed 1 of 12 phase 2 or 3 studies of evolocumab. Eligible patients were randomly assigned in a 2:1 ratio to receive either evolocumab plus standard therapy or standard therapy alone and were followed for a median of 11.1 months. As compared with standard therapy alone, evolocumab reduced LDL-cholesterol by 61% from a median of 120 mg/dl (3.1 mmol/L) to 48 mg/dl (1.2 mmol/L) (P<0.001). The 1-year rate of cardiovascular events was 2.18% in the standard-therapy group and 0.95% in the evolocumab group (hazard ratio 0.47; 95% CI 0.28-0.78) [15]. Similarly, the ODYSSEY long-term study enrolled 2341 patients at high risk for cardiovascular events with LDL-cholesterol ≥70mg/dl (1.8 mmol/L) who were on maximum tolerated dose of statin to receive alirocumab (150 mg) or placebo as a 1 ml subcutaneous injection every 2 weeks for 78 weeks. At 24 weeks the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL-cholesterol level was 62%. The rate of major adverse cardiovascular events was 1.7% in the alirocumab group and 3.3% in the placebo group (hazard ratio 0.52, 95 CI 0.31-0.90) [16].

In a recent review, lowering LDL cholesterol by 2 mmol/L (77 mg/dL) with e.g. atorvastatin 40 mg daily over 5 years was proposed to have a 10% absolute benefit in preventing major cardiovascular events in patients with pre-existing vascular disease (secondary prevention) and a 5% absolute benefit in patients who are at increased risk but have not yet had a vascular event (primary prevention). Typically, rates of myopathy are 0,05%, of rhabdomyolysis 0.01%, of diabetes mellitus 0.5 to 1% and of haemorrhagic stroke 0,05 to 0,1% over the same period of time [17]. Concerning diabetes, the randomised, double-blind JUPITER primary prevention trial of rosuvastatin 20 mg versus placebo enrolled 17603 participants without previous cardiovascular or diabetes, showed that in patients with at least one major risk factor for diabetes there were 134 vascular events or deaths that were avoided for every 54 new cases of diabetes diagnosed, i.e. there was a 39% reduction in the primary endpoint (hazard ratio [HR] 0·61, 95% CI 0·47–0·79, p=0·0001), a 36% reduction in venous thromboembolism (0·64, 0·39–1·06, p=0·08), a 17% reduction in total mortality (0·83, 0·64–1·07, p=0·15), and a 28% increase in diabetes (1·28, 1·07–1·54, p=0·01). Thus, statin benefit against cardiovascular disease and death considerably exceeds the risk of developing diabetes [18].

As for guidelines for stroke primary prevention, the American Heart Association (AHA)/American Heart Association (ASA) in 2014 recommend statin treatment, in addition to lifestyle changes, for the primary prevention of ischemic stroke in patients estimated to have a high 10-year risk for cardiovascular events (Class I; Level of Evidence A) [19]. The strongest level of recommendations for primary prevention with statins include adults with LDL-C > 190 mg/dL (4.9 mmol/L) (Class I, Level of Evidence B), adults > 40 years-old with diabetes mellitus and LDL-C from 70 to 189 mg/dL (i.e. 1.8 to 4.9 mmol/L) (Class I, Level of Evidence A) and adults > 40 years-old with LDL-C from 70 to 189 mg/dL without clinical cardiovascular disease or diabetes but have an estimated 10 year atherosclerotic cardiovascular risk of at least 7.5 % or higher (Class I, Level of Evidence A), as proposed in the 2013 ACC/AHA Guidelines for the treatment

of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [20].

Conclusions

- We recommend that statins are used as a part of standard secondary prophylactic treatment after an ischaemic stroke or a transient ischemic attack (TIA). Benefits were observed both with atorvastatin 80 mg and with simvastatin 40 mg *(Grade A, Level 1a, KSU Grade A)*. – *upgraded level of evidence.* The use of statins in secondary prevention of ischemic stroke caused by less frequent non-atherosclerotic etiologies such as arterial dissection and patent foramen ovale requires further investigations.
- There is no evidence from randomised clinical trials 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 intracranial haemorrhage 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 acute ischemic stroke or at least during follow-up *(Grade B, Level 2b, KSU Grade C)*. – *new*.
- Statins should be used with caution in patients with previous spontaneous intracerebral haemorrhage *(Grade B, Level 3c, KSU Grade C)*. – *changed.* Avoiding high-dose statin regimens in patients with intracerebral haemorrhage should be considered (*Grade A, Level 1a, KSU Grade A*) – *new*. In a subgroup of patients with cerebral amyloid angiopathy-related lobar intracerebral haemorrhage, statin use should probably be reserved for compelling indications *(Grade C, Level 2c, KSU Grade C)*. – *new.*
- PCSK9 inhibitors could be considered for patients with previous ischaemic stroke or TIA who a) have elevated LDL-cholesterol despite aggressive lipid-lowering treatment (defined as atorvastatin 40/80 mg (or rosuvastatin 20/40 mg) plus ezetimibe 10 mg), or b) have specific statin-related complications (e.g. myopathy, rhabdomyolysis, other idiosyncratic side-effects) *(Grade A, Level 1b, KSU Grade B)*. - *new*
- Lipid lowering treatment in combination with lifestyle changes is recommended for primary prevention in patients who have high 10-year risk for cardiovascular events *(Grade A, Level 1a, KSU Grade A)*. The drug-class and the intensity of the lipid-lowering treatment as well as the treatment goals are thus depend on patient characteristics *(Grade B, Level 1a, KSU Grade A)*. – *new*.

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Appendix A:

Strength of evidence supporting recommendations as defined by the Karolinska Stroke Update consensus meeting (1998):
KSU GRADE A evidence: Strong support from randomized controlled trials and statistical reviews (at least one randomized controlled trial plus one statistical review)
KSU GRADE B evidence: Support from randomized controlled trials and statistical reviews (one randomized controlled trial or one statistical review)
KSU GRADE C evidence: No reasonable support from randomized controlled trials, recommendations based on small randomized and/or non-randomized controlled trials evidence.

Appendix B:

Levels and grades of evidence for therapy/prevention as defined by the Oxford centre for evidence-based medicine (2009), resumed:
Grade A: consistent Level 1 studies
Grade B: consistent level 2 or 3 studies or extrapolations from level 1 studies
Grade C: level 4 studies or extrapolations from level 2 or 3 studies
Level 1a: systematic review (homogeneity) of RCTs
Level 1b: individual RCT (with narrow confidence interval)
Level 2a: systematic review (homogeneity) of cohort studies
Level 2b: individual cohort study/low quality RCT e.g. with less than 80% follow-up
Level 3a: systematic review (homogeneity) of case-control studies
Level 3b: individual case-control study
Level 4: case-series
Level 5: expert opinion

Session No 4

Guideline for prophylaxis for venous thromboembolism in immobile patients with acute ischemic stroke

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The Consensus Statement includes two parts, the Consensus Statement itself, and a Recommendation to the European Stroke Organisation (ESO) to endorse the proposed guidelines or suggest amendments. Please note that the final text of the Guidelines, is decided by ESO and that the recommendation in this document may not be included in the final guidelines.

I. ESO Karolinska Stroke Update Consensus Statement

The following Consensus Statement was (if approved) adopted by the 11th ESO Karolinska Stroke Update meeting on November 14th/15th 2016.

The Consensus Statement was proposed by the chairman of the session, Professor Gary Ford, Oxford, England, and the session secretary Dr Maria Lantz, Stockholm, 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 Valeria Caso, Perugia, Italy, and Dr Christina Sjöstrand, Stockholm, Sweden.

Issues for the 2016 consensus session:

- Proposed guideline on prophylaxis for venous thromboembolism in immobile patients with acute ischemic stroke.
- Independent comment

Theme 1: Summary of the proposed guideline

Introduction

Venous thromboembolism (VTE), a term encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with stroke. Estimates of its frequency in cohorts and trials vary from 5-20% and depend on the characteristics of patients, and the timing and method of screening. Severe strokes and those associated with immobility, dehydration, infection, co-morbidities (cancer, heart failure), obesity and prior history of thrombosis have been associated with higher rates of VTE (1-3). The risk of VTE appears to be highest during the early post stroke phase and then falls over the next few weeks and months (2-3). Although clinically overt DVTs occur in about 5% of hospitalised patients, if DVTs are screened for with different forms of imaging they can be detected in many more. Estimates of frequency of proximal or distal DVT in acute stroke in-patients vary: 20% with compression duplex ultrasound; 73% with radiolabelled fibrinogen scanning (4-5) and 43% with magnetic resonance direct thrombus imaging (6). Similarly, PEs are only diagnosed in clinical practice in 1–2% of hospitalized stroke patients, but in those rare studies where PE has been screened for, the frequency is much higher, 10% in one study (6). Also, in

earlier studies from an era where hospital autopsies were much more common, PE could be identified in about half of the patients dying after stroke (7). Despite the uncertainties about the frequency of the problem, it is generally accepted that VTE is an important cause of morbidity and death in hospitalised stroke patients. Since VTE is regarded as an important, and potentially preventable cause of death, clinicians caring for stroke patients are expected to assess their patients' risk of VTE and to provide the most effective and safe prophylaxis. Patients are considered immobile if they are unable to walk to the toilet without the help of another person. These patients are likely to be at high enough risk to justify prophylaxis. These are the following options that have been evaluated.

Graduated compression stockings

A meta-analysis included one large (n=2.518) (8) and one small trial (n=97) (9) and indicated that graduated compression stockings had no significant effect on death (during treatment period and follow up), death or dependency at six months, DVT (symptomatic or asymptomatic) or pulmonary embolism during treatment. The CLOTS trial evaluated a single type of thigh-length graduated compression stockings, whereas the small trial evaluated two types of thigh-length stocking. The quality of this evidence was judged to be moderate because of a lack of power to demonstrate an effect on the most important outcomes, e.g. survival, functional status, symptomatic PE. The only statistically significant effect of graduated compression stockings was an increase of the risk of skin breaks in the patients allocated graduated compression stockings.

Anticoagulants

A meta-analysis included one very large trial (n=14,578) (10) and four small trials of unfractionated heparin (UFH) (4, 5, 11, 12), eight small trials of low molecular weight heparin (LMWHs) or heparinoids (13-20) and one of a heparinoid (21). Prophylactic anticoagulants were not associated with any significant effect on death during the treatment period or follow up, or functional status by final follow up. However, it was associated with a statistically significant reduction in symptomatic pulmonary emboli (OR=0.69) (95% CI 0.49-0.98). The quality of this evidence was judged to be moderate, because of a lack of blinding and imprecision with respect to this outcome. Anticoagulation was associated with a reduction in DVT (OR=0.21) (95%CI 0.15-0.29) but the quality of the evidence was judged to be low because there was significant heterogeneity between trials, almost all DVTs were asymptomatic and the more positive trials based their diagnosis on isotope scanning only, which is of dubious reliability and limited clinical relevance. There were also statistically significant increases in symptomatic intracranial haemorrhage (OR=1.68 95%CI 1.11-2.55) and symptomatic extracranial haemorrhages (OR=1.65 95%CI 1.0-2.75).

LMWHs of heparinoids or UFH

A meta-analysis included one large trial (n=1762) (22) and two smaller trials comparing LMWHs with UFH (23-24) and four small trials comparing heparinoids with UFH (25-28). There were no significant effects on death during follow up, death or disability. We judged the quality of this evidence to be moderate due to imprecision with respect to these outcomes. There were non-significant trends towards reduction in pulmonary emboli and symptomatic intracranial haemorrhage with LMWH, but there was a

statistically significant increase in major extracranial haemorrhage (OR =3.79) (95%CI 1.30-11.03) with LMWH. The use of LMWH was associated with a statistically significant reduction in DVTs (OR=0.55) (95%CI 0.44-0.70) which were mostly asymptomatic.

Intermittent pneumatic compression (ICP)

The meta-analysis included one large (n=2876) (29, 30) and two small trials. (31, 32) This showed that IPC had no significant effect on death and dependency at final follow-up, despite a strong trend on deaths during treatment period (OR=0.82; 95%CI 0.66 to 1.02) and improved survival to six months (hazard ratio=0.86) (95% CI 0.74 to 0.99). There was no statistically significant effect on functional status or pulmonary embolism or symptomatic DVT (OR=0.73; 95%CI 0.53-1.01). IPC significantly reduced the risk of any DVT (including asymptomatic DVT) (OR=0.73; 95%CI 0.61-0.88). IPC also increased the risk of skin breaks (OR=2.15; 95%CI 1.31-3.59).

Suggested guidelines

A multidisciplinary group identified related questions and developed its recommendations based on evidence from randomized controlled trials using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Population: Hospitalised acute ischaemic stroke patients with reduced mobility.

Intervention: Graduated compression stockings, IPC, UFH, LMWH

Comparison: Because treatment with antiplatelet medication is now standard for patients with acute ischaemic stroke, trials which directly compared anticoagulants with antiplatelet medication were not included. Trials which evaluated combinations of compatible prophylactic interventions, comparing the combination against either intervention alone (e.g. external compression plus anticoagulants vs. either alone) were included as well as trials comparing two similar interventions (e.g. LMWH and UFH).

Outcomes: The following outcomes have been included: DVT, PE, survival and functional outcome, skin breaks and haemorrhages, defined as intracranial haemorrhage (symptomatic/asymptomatic), haemorrhagic transformation, or bleeding into other intracranial compartments and other major extracranial haemorrhages, such as gastrointestinal or soft tissue bleeds.

Conclusions

Graduated compression stockings:

- We recommend that graduated compression stockings should not be used in patients with ischaemic stroke.
- Quality of evidence: Moderate. Strength of recommendation: Strong against this intervention.

Anti-coagulant:

- Prophylactic anticoagulation with UFH (5000Ux2, or 3 daily) or LMWH or heparinoid should be considered in immobile patients with ischaemic stroke in whom the benefits of reducing the risk of venous thromboembolism is high enough to offset the increased risks of intracranial and extracranial bleeding associated with their use. See definition of bleeding.
- Quality of evidence: Moderate. Strength of recommendation: Weak for this intervention.

LMWHs of heparinoids or UFH

- Where a judgement has been made that prophylactic anticoagulation is indicated LMWH or heparinoid should be considered instead of UFH because of its greater reduction in risk of DVT, the greater convenience, reduced staff costs and patient comfort associated single daily dose vs. multiple daily injections but these advantages should be weighed against the higher risk of extracranial bleeding, higher drug costs and risks in elderly patients with poor renal function.
- Quality of evidence: Moderate. Strength of recommendation: Weak for this intervention

Intermittent Pneumatic Compression

- We recommend that IPC (thigh-length, sequential) should be used for immobile patients with ischaemic stroke. It should not be used in patients with open wounds on the legs and should be used with caution in those with existing DVT, heart failure, severe peripheral vascular disease or confusion where attempts to mobilize when unsupervised could lead to falls and injury.
- Quality of evidence: Moderate. Strength of recommendation: Strong for this intervention

Theme 2: Independent comment

Venous thromboembolism (VTE) consists of deep venous thrombosis in the leg and pulmonary embolism. Almost all pulmonary emboli have their origin in the veins of the legs or in the deep veins in the pelvic area. Deep venous thromboses from the upper part of the leg, above the popliteal vein, more often result in pulmonary embolism than more distal thromboses in the leg. There are no clear gender differences over age, but VTE is more common in younger women related to the use of contraceptives including estrogens and increased risk during the postpartum period, whereas men are somewhat more likely to suffer from VTE later in life. Clinical probability score for venous thromboembolism (VTE) can be graded by the so called Wells score, both regarding deep venous thrombosis in the leg and pulmonary embolism (33). Reducing the risk for deep venous thrombosis in the leg subsequently reduces the risk for pulmonary embolism. A Wells score >2 indicates a high probability for VTE. Risk grading of probability for VTE in the leg includes several factors that might be related to ischemic stroke; bedridden recently ≥3 days, paralysis, paresis, or recent plaster immobilization of the lower extremity. I.e. this generates a risk score of 2 for most immobile patients with ischemic stroke. Furthermore, when stroke patients have a

history of VTE, are dehydrated, suffer from infections or co-morbidities like cancer the risk increases.

Graduated compression stockings have been widely used in clinical practice at stroke units, but there is no evidence that the use of these stockings is associated with a better outcome. It should not be routinely used for VTE prophylaxis; however it may help reduce dependant oedema in stroke patients with reduced mobility. Having been used for many years as a routine it is probably still used in many patients. We will need to educate staff at the stroke units about the lack of evidence for this preventive treatment.

Anticoagulants have shown to prevent VTE. The use of anticoagulants for prevention of VTE is recommended in several international guidelines, hence it is widely used. LMWH should be preferred before unfractionated heparin since it has been shown to be more effective in preventing DVT in these patients. It is also convenient for the patient with a single-dose injection subcutaneously. Since the risk for VTE is increased being bedridden for more than 3 days preventive treatment should probably be administered already during the very early phase after stroke onset. It is always of greatest concern to weigh the advantages of preventive treatment in relation to the risk of bleeding. The risk for bleeding should be assessed before VTE prophylaxis is administered. The current guideline does not suggest any prediction tool for assessing the risk-benefit balance. Lately the IMPROVE Bleeding Risk Score has been suggested to help assess the bleeding risk in medical in-patients in need of VTE prophylaxis. However it has not been studied in patients with ischemic stroke, and it remains to be seen if this risk score can be validated also in patients with ischemic stroke (34, 35).

Intermittent pneumatic compression sleeves can be used for VTE prophylaxis following acute ischemic stroke. These sleeves can be used in the ICU where patients are bedridden, maybe in a ventilator and/or sedated, and thus being more immobilized than most patients in the ordinary stroke unit. Early mobilization of stroke patients should be encouraged and the mobilization can be inhibited by this quite bulky device.

We should always focus on effective treatments to prevent VTE in our stroke patients, with an individual approach, with concerns regarding risk/benefit. Further research need to be done regarding timing of VTE prophylaxis and assessment for bleeding risk in stroke patients.

II. Summary of updated recommendations to ESO Guidelines Committee:

Recommendations

A. To endorse the proposed guideline on prophylaxis for venous thromboembolism in immobile patients with acute ischemic stroke as follows:

- We recommend that graduated compression stockings should not be used in patients with ischaemic stroke. (Level I, Class A)
- We recommend that IPC (thigh-length, sequential) should be used for immobile patients with ischaemic stroke. It should not be used in patients with open wounds on the legs and should be used with caution in those with

existing DVT, heart failure, severe peripheral vascular disease or confusion. (Level I, Class A)

- To consider prophylactic anticoagulation with UFH, LMWH or heparinoid in immobile patients with ischaemic stroke in whom the benefits of reducing the risk of venous thromboembolism is high enough to offset the increased risks of intracranial and extracranial bleeding associated with their use. (Level I, Class A)
- Where prophylactic anticoagulation is indicated LMWH or heparinoid should be considered instead of UFH because of its greater reduction in risk of DVT, the greater convenience, reduced staff costs and patient comfort. These advantages should be weighed against the higher risk of extracranial bleeding, higher drug costs and risks in elderly patients with poor renal function. (Level I, Class A)

B. To ask the ESO to consider the following remarks in relation to the new guidelines

- IPC should be used for 30 days or until the patient is mobilizing independently.
- IPC should not be commenced if more than 72hr post stroke, unless pre-existing DVT has been ruled out.
- Prophylactic anticoagulation should be used if IPC is not tolerated. Treatment should be used for 30 days or until mobilized. Prophylactic anticoagulation may be used in combination with IPC in patients with high risk of venous thromboembolism (e.g. active cancer, coagulation disorder or previous dvt).
- If prophylactic anticoagulation with LMWH is used, standard prophylaxis doses should be applied. For Enoxaprin subcutaneous injection of 40 mg once daily (20 mg if creatinine clearance < 30 ml/minute) and for Dalteparin subcutaneous injection of 5000 IE once daily (2500 IE if creatinine clearance < 30 ml/minute)
- The risk for bleeding should be assessed before VTE prophylaxis is administered. Research is needed to validate a risk assessment tool to evaluate bleeding risk in patients with ischemic stroke.
- In patients with poor renal function (creatinine clearance < 30 ml/minute), or a higher risk for extracranial bleedings (e.g. recent GI bleeding, known gastric ulceration), UFH can be considered before LMWH.
- In other clinical settings, NOACs have been shown effective for prophylactic treatment of venous thromboembolism. Further research is warranted to investigate if NOAC may be an option for prophylaxis of venous thromboembolism in patients with ischemic stroke.

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Session No 5
Stroke, seizures and epilepsy

The following Consensus Statement was adopted by the 11th ESO Karolinska Stroke Update meeting on November 14th/15th 2016.

The Consensus Statement was proposed by Hanne Krarup Christensen, Torbjörn Tomson, Martin Holtkamp and Anna Steinberg who were working based on the draft from the ESO guidelines for the management of post-stroke seizures and epilepsy. The speakers in the session were Hanne Krarup Christensen, Torbjörn Tomson, Martin Holtkamp and Anna Steinberg.

Issues for the 2016 consensus session:

- Should primary prophylaxis of acute symptomatic or unprovoked seizures be recommended after stroke?
- Should secondary prophylaxis of seizures be recommended after one or more acute symptomatic or unprovoked seizure in patients after stroke?

Theme 1: Primary prevention of seizures

Prevention of acute symptomatic seizures

Resume of evidence: The risk of acute symptomatic seizures is reported generally low in stroke, however higher in intracerebral haemorrhage involving cortex[1]. Only one underpowered RCT exists exploring possible benefits of antiepileptic drugs (AEDs) for primary prevention of acute symptomatic seizures. This RCT failed to demonstrate a difference in risk of acute symptomatic seizures after intracerebral haemorrhage between treatment with valproic acid and placebo[2]. No other evidence in terms of RCTs exists to guide treatment decisions.

Prevention of unprovoked seizures

Resume of evidence: The risk of unprovoked seizures, i.e. occurring later than a week following a stroke has been estimated to be 8-12%, increasing with the duration of follow-up[3]. Higher rates are seen among patients with space-occupying MCA infarctions resulting in decompressive surgery, patients with SAH with large ICH and ICH with cortical involvement[4-6]. The possible benefit of primary prevention with AEDs on risk of developing unprovoked seizures after stroke has not been evaluated in RCTs. There is very little – and ambiguous - data on the effects of AEDs on functional outcome or mortality after stroke[2,7-9] . However short-term (3 days) treatment with diazepam was associated with increased risk of pneumonia in patients with ICH in an RCT[7].

Conclusions

There is insufficient RCT data to support the use of AEDs for primary prevention of seizures (acute symptomatic or unprovoked) after stroke. In most presentations of stroke the risk of seizures is low, although e.g. sinus venous thromboembolism and cortical ICH carry a substantial risk. Given the lack of conclusive data, primary prevention of post stroke seizures with AEDs cannot be suggested.

Theme 2: Secondary prevention of seizures

Prevention of acute symptomatic seizures

Resume of evidence: Patients who have suffered one acute symptomatic seizure after stroke are at increased risk of further acute symptomatic seizures, in the order of 10-20%[10-11]. However, no RCTs have compared the effect of AEDs vs. no treatment in the prevention of recurrence of acute symptomatic seizures among patients who have suffered one such seizure after stroke.

Prevention of unprovoked seizures

Resume of evidence: In patients with a first unprovoked seizure after stroke, the 10-year risk of recurrence has been reported at more than 70%[12] thus meeting the new operational criteria for epilepsy[13]. There are no RCTs investigating the benefit of AEDs in this specific population. However, there are open RCTs in non-stroke populations of first unprovoked seizure patients demonstrating a reduced recurrence rate among those randomized to treatment with AEDs[14-15].

Conclusions

There is insufficient RCT data to support the use of AEDs for secondary prevention of recurrence of acute symptomatic seizures after stroke. Should nevertheless AED treatment be initiated after a single acute symptomatic seizure, withdrawal is recommended after the acute phase.

Unprovoked seizures after stroke carry a high risk of recurrence. There are no RCTs of AED in this specific population. However, open RCTs in non-stroke populations have demonstrated a significant reduction in recurrence risk. Initiation of long-term AED treatment after one unprovoked seizure following stroke should be considered. Withdrawal of AED treatment after years of seizure freedom should be based on individual considerations.

Summary of updated recommendations to ESO Guidelines Committee:

A: Primary prevention of seizures

- RCTs are few and underpowered, and the quality of evidence is generally low. As the risk of acute symptomatic and unprovoked seizures in stroke is low, we do not suggest general use of AEDs in primary prevention after stroke. If treatment is initiated for primary prevention of acute symptomatic seizures, it should be withdrawn after the acute post-stroke phase. Although the risk of unprovoked seizures is considerably higher in patients with large ICH and cortical involvement as well as SVT, primary prevention is rarely justified. Grade C evidence.
- RCTs are needed to assess the benefits of short- and long-term prophylaxis with antiepileptic drugs for prevention of acute symptomatic and unprovoked seizures.

B: Secondary prevention of seizures

- RCTs are absent and quality of evidence generally low. Acute symptomatic seizures have a low risk of recurrence and thus short- and long-term prevention is not suggested. If treatment is initiated for secondary prevention of acute symptomatic seizures, it should be withdrawn after the acute post-stroke phase. Unprovoked seizures carry a high risk of recurrence and based on observational data, long-term AED should be considered. There are no conclusive RCT data specific to post-stroke populations to guide the choice of AEDs. Grade C evidence.

- RCTs are needed, both to assess potential benefit in reduction in risk of seizure recurrence and its consequences, but also in tolerability and adverse effects in this patient population.

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Session No 6

Management of acute stroke (ischaemic or haemorrhagic) under oral anticoagulant therapy

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The Consensus Statement includes two parts, the Consensus Statement itself, and the Recommendation to the European Stroke Organisation (ESO) on revision of ESO Guidelines. Please note that the final text of the Guidelines is decided by ESO and that the recommendation in this document may not be the final guideline version.

I. ESO Karolinska Stroke Update Consensus Statement

The following Consensus Statement was adopted by the 11th ESO Karolinska Stroke Update Conference on November 14th/15th 2016.

The Consensus Statement was proposed by the chairmen of the session, Prof C. Cordonnier and Prof K.R. Lees, and the session secretary Dr E. Eriksson, Stockholm, Sweden, together with the speakers of the session. The statement was then finally approved by the participants of the meeting, after listening to the various presentations. The speakers in this session were Prof B. Norrving (Lund, Sweden), Prof T. Steiner (Frankfurt/Heidelberg, Germany) and Prof R. Veltkamp (London, England).

Issues for the 2016 consensus session:

Introduction

The annual rate of ischaemic stroke or systemic embolism in randomised controlled trials (RCT) on primary or secondary prevention in patients with atrial fibrillation ranges between 1.27% and 1.53% for those taking non-vitamin-K-oral anticoagulants (NOAC) and between 1.60% and 2.4 % for those taking vitamin-K antagonists (VKA, warfarin). [1-4] Compared to warfarin, NOAC had non-inferior efficacy, and superior safety in terms of intracranial haemorrhagic complications.

These findings and the greater convenience of NOACs for patients has led to a steady increase in the use of oral anticoagulants (OAC) in general and of NOACs in particular.[5] Hence, the frequency of emergency events while patients are taking NOACs is expected to increase.

About 46% to 86% of intracranial haemorrhages that occur in association with oral anticoagulants are intracerebral in location (ICH).[6,7] The annual rate of ICH in patients taking VKA ranges from 0.3% to 0.6%. This compares to 0.1 to 0.3% in patients taking NOACs in prospective clinical trials[6,7]. Compared with warfarin, NOACs are associated with a 50% lower rate of ICH.[8] Prior to availability of specific reversal agents for the NOACs, the mortality rate in patients with ICH was similar for NOACs and warfarin in the RCTs (28-64% and 50-64%, respectively).[6,7] The primary drivers of the high mortality in ICH patients are age, the severity of the clinical syndrome, the volume of ICH and haematoma expansion.[9-12]

Theme 1: How should we approach neurological emergencies when patients are on OACs?

Two neurological emergencies need to be considered in patients who are treated with VKA or NOAC: (1) Acute ischaemic stroke (AIS) in need of reperfusion therapy (2) Acute intracerebral haemorrhage (ICH), with the aim to prevent haematoma expansion.

The approach to AIS and ICH depends on whether sufficient information on relevant anticoagulant activity – either actual or expected based on last drug intake and elimination - is available or not (**Error! Reference source not found.**). If this information is unavailable or time until this information will be available is considered too long, specific measures as outlined in themes 2 and 3 should not be delayed.

Anticoagulated patients, and in particular patients taking NOACs, may arrive in the emergency room without relevant residual anticoagulant activity and therefore reversal of anticoagulation may not be necessary. The pharmacokinetic properties of VKAs differ considerably from those of NOACs. The half-life of NOACs ranges from 7 to 17 hours. In contrast, the effective half-life of warfarin is two days and that of phenprocoumon is about 7 days. Consequently, the following factors have an influence on anticoagulant activity and drug levels:

- Type of VKA or NOAC
- Dose taken
- Time when last dose was taken
- Renal function, liver function
- Concurrent medication

If this information is not sufficiently conclusive to suggest absence of relevant anticoagulant activity, coagulation tests may help to determine whether reversal treatment is justified, if indicated. Interpretation of such tests needs to take into consideration time since last drug intake, and speed of elimination.

There are no prospective data available that inform us on any association of drug concentrations with the risk of bleeding complications. We therefore provide the following approach to use of coagulation tests, dividing these into 3 categories (**Error! Reference source not found.**):

A) Global routine tests, that provide qualitative information on whether it is more or less likely that pharmacodynamically relevant drug concentrations can be expected, such as activated partial thromboplastic time (aPTT), prothrombin time (PT), and international normalised ratio (INR).[13,14] These tests are widely available but are neither specific nor sensitive, with the sole exception of INR for VKA.
B) Coagulation tests that are specific but not sensitive like ecarin clotting time (ECT) or factor Xa-activity tests not calibrated to a specific OAC. These tests provide qualitative information.
C) Coagulation tests that are calibrated for a particular OAC and that are both specific and sensitive. Based on calculations from the RELY- and Rocket trials, the Working Group on

Perioperative Haemostasis (GIHP) suggested a NOAC drug concentration lower than 30 ng/ml "as compatible with surgical management, without increasing the risk of bleeding, especially in an emergency".[15] These thresholds were then extrapolated to other factor Xa-inhibitors. Other thresholds like 50 ng/ml have been proposed.[16]

Recommendations

- In AIS, laboratory testing before intravenous thrombolysis is necessary if relevant anticoagulant activity cannot be ruled out by medical history. (KSU Grade C, expert opinion)
- In acute ICH, reversal of anticoagulation should be started as soon as possible after diagnosis of ICH unless relevant anticoagulant activity is regarded unlikely by medical history or has been ruled out by laboratory testing. (KSU Grade C, expert opinion)
- Recommendation relating to "pharmacodynamically relevant (ie active) drug concentrations" (KSU Grade C, expert opinion)
    a. For VKA: In acute stroke patients on VKA, INR should be measured. An INR ≤1.7 allows intravenous thrombolysis in AIS. For ICH patients,
        i. an INR > 2 should trigger reversal treatment with prothrombin complex concentrate (PCC) 30 U/kg.
        ii. an INR > 1.2 should trigger reversal treatment with PCC 10 U/kg.
    b. For NOACs: Relevant drug concentrations in patients on NOACs should be assumed if:
        i. Global routine tests are above normal
            1. aPTT for dabigatran
            2. PT for rivaroxaban and edoxaban; however, PT should not guide therapy in cases involving apixaban
        ii. Non-calibrated tests are above normal
            1. ECT for dabigatran
            2. Factor Xa-activity tests for factor Xa-inhibitors
        iii. *Calibrated tests provide information as below*:
            1. If diluted thrombin time (dTT) for dabigatran indicates concentration > 30 ng/dl
            2. If factor Xa-activity tests calibrated for factor Xa-inhibitors indicate concentration > 30 ng/dl

If calibrated tests are available their thresholds may guide therapy

Theme 2: Management of acute ischaemic stroke and ICH occurring during treatment with Vitamin K-antagonists

2A: Management of acute ischemic stroke and indication for reperfusion therapy during treatment with Vitamin K-antagonists

Patients experiencing AIS while taking VKA can be thrombolysed with acceptable safety if the INR is ≤ 1.7 and therapy can be applied within 4.5 hours after symptom onset based on data derived from large registries.[17,18] These recommendations are supported by an analysis from the Virtual International Stroke Trials Archive (VISTA) that included 9613 stroke patients of

whom 2755 received rt-PA, looking at the questions of thrombolysis in stroke despite contraindications or warnings.[19] The analysis revealed more favourable outcome at 3 months in several subgroups, one being patients on oral anticoagulation with INR ≤ 1.7 (n=157), 1.50 (95% CI, 1.15–1.97), and no excess of risk when compared to other groups.

Thrombectomy is recommended independent of INR levels given that other eligibility criteria including large intracranial vessel occlusion are fulfilled.[20,21] The decision which of these two strategies (thrombolysis, thrombectomy) should be applied first depends on availability of intraarterial therapy in case of thrombectomy and on the INR in case of thrombolysis, respectively. Bridging therapy should be considered if INR ≤ 1.7. An analysis of 456 patients from the national Dutch database on local intra-arterial therapy (IAT: local intra-arterial thrombolysis, mechanical thrombectomy, thrombosuction, acute carotid stenting or a combination) identified 18 patients with an INR > 1.7.[22] The primary endpoint was symptomatic intracerebral haemorrhage (sICH), which occurred in one patient who was not treated with thrombolysis (6%) in the INR > 1.7 and 53 patients (12%) in the INR ≤ 1.7 group (risk ratio 0.49, 95% confidence interval 0.07-3.13). Clinical outcomes did not differ between the two groups.

Recommendations

- In patients with acute ischaemic stroke and indication for reperfusion therapy during therapy with vitamin-K antagonists and an INR ≤ 1.7, thrombolysis should be performed. (KSU Grade C, expert opinion)
- In patients with acute ischaemic stroke during therapy with vitamin K antagonists and an INR > 1.7, thrombolysis should not be performed. (KSU Grade C, expert opinion)
- Patients with acute ischaemic stroke during therapy with vitamin-K antagonists who suffer from large vessel occlusion with indication for reperfusion therapy should be offered thrombectomy. (KSU Grade C)

2B: Management of acute intracerebral haemorrhage during treatment with Vitamin K-antagonists

Introduction

The rationale for anticoagulation reversal in patients experiencing an ICH while taking anticoagulants is that haematoma expansion appears to occur more frequently in anticoagulated than in non-anticoagulated patients.[9,11] Haematoma expansion is among the primary drivers of the high mortality in ICH patients in addition to age, the severity of the clinical syndrome and the volume of the ICH.[9-11] Haematoma expansion (HE) occurs in 30-40% of non-anticoagulated ICH patients presenting within 3 to 6 hours after symptom onset. In ICH associated with VKA, HE was observed in 54% and 36% of patients in a prospective registry (N=183)[11] and retrospective studies of ICH related to VKA (N=853),[23] and occurred over 60 hours after symptom onset.[11] Moreover, 38% of 46 patients in a prospective multicentre study who presented within 24 hours after symptom onset with ICH related to NOAC had haematoma expansion.[9] Therefore, HE appears to be a common complication of OAC-ICH regardless of whether patients are taking VKA or NOACs; taken together, this underlines the

importance of initiating reversal as rapidly as possible after the diagnosis of ICH has been established by imaging.[24]

Management of ICH related to vitamin-K antagonists

The question on the value of prothrombin complex concentrate (PCC) over fresh frozen plasma (FFP) for VKA reversal in patients with ICH was answered by the results of the INCH trial, which compared 4-factor PCC with FFP for normalisation of the INR within 3 hours of admission in 50 ICH patients presenting within 12 hours of symptom onset.[25] PPC or FFP was initiated if the INR was INR ≥ 2. The treatment goal was an INR ≤ 1.2 within 3 hours after start of treatment. If the INR at 3 hours after start of treatment was still between 1.2 and 2.0 then PCC was administered in a dose of 10 U/kg; however, if the INR was > 2 the PCC dose was 30 U/kg. Compared with FFP (20ml/kg), 4-factor-PCC (30 U/kg) more effectively normalised the INR and significantly reduced HE at 3 and 24 hours. There were 5 deaths due to HE within the first 48 hours in the FFP group and none in the group given PCC. These results are supported by 2 other RCTs: first, a clinical trial that compared 4-factor PCC with FFP in VKA-treated patients needing urgent surgical or invasive procedures demonstrated superiority of 4-factor PCC to plasma in normalising the INR and establishing effective haemostasis.[26] Second, a clinical trial that compared 4-factor PCC and FFP in patients with major bleedings while on VKA demonstrated more effective haemostasis in patients treated with 4-factor PCC (72%) vs. FFP (65%), and significantly faster INR normalisation with 4-factor PCC.[27] In all trials, patients were included when the initial INR was 2.0 or higher.

The half-life of coagulation factors included in 4-factor-PCCs ranges between about 2.5 (FVII) and 12 hours (FX). This is thus shorter than the effect of most VKA. Therefore it appears reasonable to administer vitamin-K (10 mg intravenously) in addition to PCC and to re-check INR levels every 12 to 24 hours.[28-30]

Recommendation

1. In adult patients with intracerebral haemorrhage related to vitamin-K-antagonist and with an INR ≥ 2, intravenous 4-factor-PCC in a dose of at least 30 U/kg should be administered to normalise the INR and limit haematoma expansion. (KSU Grade B) Reversal of anticoagulation with PCC may also be initiated at INR between 1.2 to 2.0 with lower PCC-dose of 10 U/kg. (KSU Grade C)
2. Reversal with fresh frozen plasma is not recommended (KSU Grade C)
3. Administration of vitamin-K (10mg, iv) may be considered if the initial INR ≥ 1.2 on repeated measurements. (KSU Grade C)

Theme 3: Management of AIS and acute ICH occurring during treatment with non-vitamin K oral anticoagulants

3A: Management of AIS and indication for reperfusion therapy occurring during treatment with NOAC

Acute stroke patients taking NOAC should be assessed rapidly for a history suggestive of relevant anticoagulant activity at presentation and additionally by suitable laboratory

coagulation tests, if needed. Thresholds of maximum anticoagulant activity in laboratory coagulation assays allowing thrombolysis as safely as in non-anticoagulated patients have not been established. If relevant anticoagulant activity can be excluded based on time since last drug intake or laboratory results, intravenous thrombolysis should be considered. In case of stroke occurring in patients with therapeutic levels of dabigatran, rapid reversal of anticoagulation by injection of idarucizumab followed by intravenous thrombolysis is an option though the evidence for efficacy and safety of this approach is presently very limited.[31] Specific reversal agents for factor Xa inhibitors are not licensed and have not been tested in patients with ischaemic events. Therefore, intravenous thrombolysis cannot be performed in ischaemic stroke occurring in patients having evidence of relevant anticoagulant activity. Limited evidence suggests that thrombectomy is safe in AIS related to NOAC with major intracranial vessel occlusion[16, 32].

Recommendations

- In adult patients with acute ischaemic stroke related to factor Xa-inhibitors and suspicion or evidence of relevant drug concentrations, intravenous thrombolysis should not be performed. (KSU Grade C, expert opinion)
- In adult patients with acute ischaemic stroke related to dabigatran and the suspicion or evidence of relevant drug concentrations intravenous thrombolysis cannot presently be recommended. (KSU Grade C, expert opinion)
- In adult patients with acute ischaemic stroke related to NOACs, thrombectomy should be performed consistent with recommendations for non-anticoagulated patients. (KSU Grade C, expert opinion)

3B: Management of acute ICH occurring during treatment with NOAC

Idarucizumab is a Fab antibody fragment that rapidly and specifically binds and leads to sustained neutralisation and elimination of dabigatran in healthy young and elderly subjects as well as in patients with major bleedings or a need for invasive emergency procedures.[33] Idarucizumab has been licensed for these indications. Bolus injection and infusion of andexanet alpha, a genetically modified analogue of Factor Xa without coagulatory activity, allows rapid binding of all Factor Xa inhibitors. Injection of a bolus followed by an infusion of andexanet-alpha rapidly reversed the anticoagulation by factor Xa inhibitors in patients with major bleeding but partial rebound of anticoagulation after infusion has been observed.[34] Andexanet alpha has not been licensed by regulators as of November 2016. PCC may reverse anticoagulation and stop bleeding in NOAC-related bleedings.[35] Clinical trials for NOAC reversal in ICH patients using PCC have not been performed. Therefore, PCC is an alternative treatment option if specific reversal agents are not available. Because evidence for the effects of specific and non-specific reversal agents on clinical endpoints in NOAC-related ICH are very limited at present, prospective controlled studies are desirable to guide best management in the future.

Recommendations

- In patients with ICH related to dabigatran, idarucizumab 2 x 2.5 g should be injected. (KSU Grade B)
- If idarucizumab is not available, PCC may be infused (30-50 U/kg). (KSU Grade C)
- In patients with ICH-related to apixaban, edoxaban or rivaroxaban, PCC (30-50 U/kg) should be used. (KSU Grade C, expert opinion)
- Reversal of NOAC with fresh frozen plasma is not recommended. (KSU Grade C, expert opinion)

Table and figure

Figure 1: Management algorithm for AIS and ICH in patients on OAC

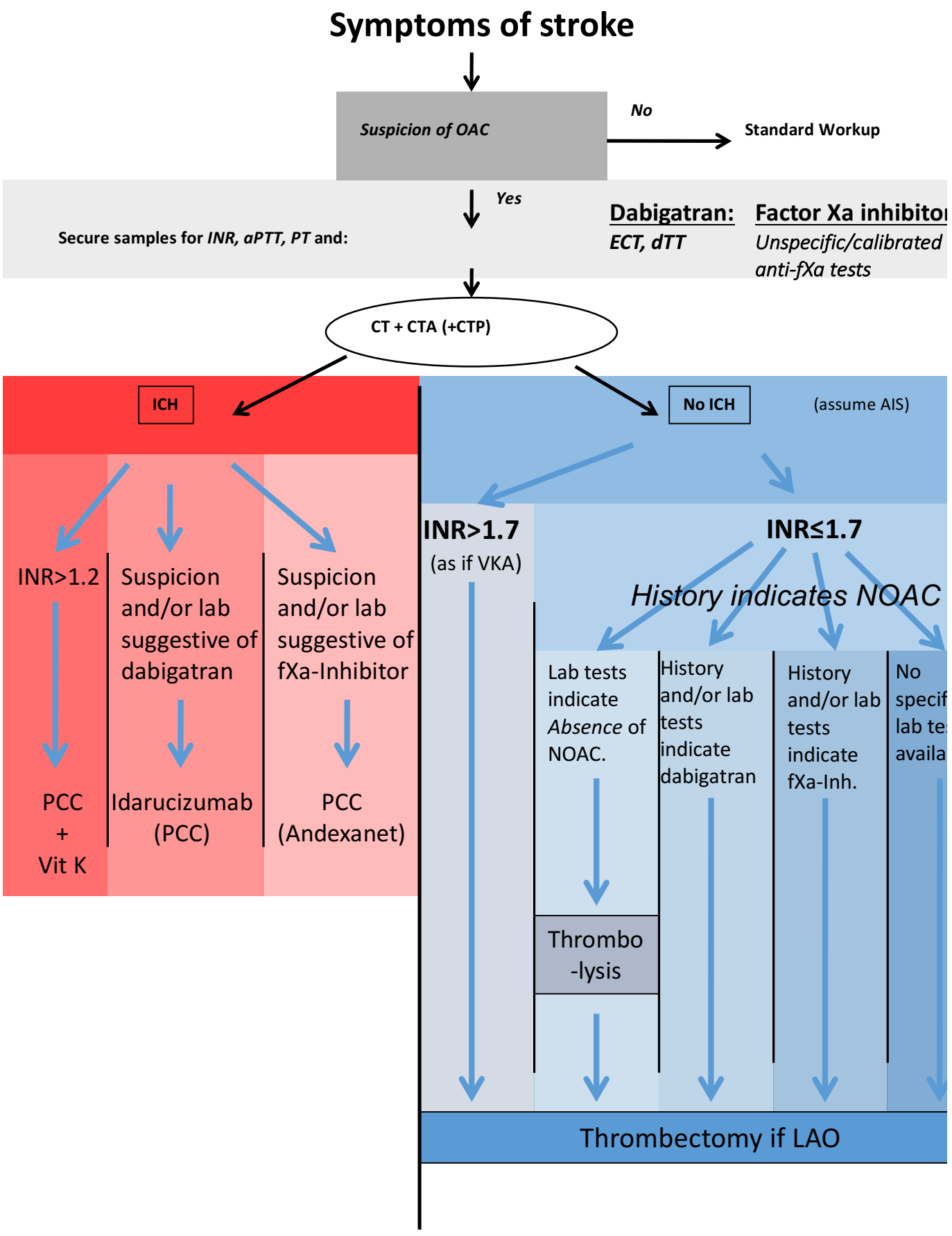
Symptoms of stroke
Suspicion of OAC
No
Standard Workup
Yes
Secure samples for INR, aPTT, PT and:
Dabigatran:
ECT, dTT
Factor Xa inhibitor
Unspecific/calibrated anti-fXa tests
CT + CTA (+CTP)
ICH
No ICH
(assume AIS)
INR>1.2
Suspicion and/or lab suggestive of dabigatran
Suspicion and/or lab suggestive of fXa-Inhibitor
PCC + Vit K
Idarucizumab (PCC)
PCC (Andexanet)
INR>1.7
(as if VKA)
INR≤1.7
History indicates NOAC
Lab tests indicate Absence of NOAC.
History and/or lab tests indicate dabigatran
History and/or lab tests indicate fXa-Inh.
No specif lab te availa
Thrombo -lysis
Thrombectomy if LAO

Table 1: Effects of OACs on coagulation tests and expert recommendation for the indication for reversal agents (modified according to [14])

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	VKA
Global routine tests	Activated partial thromboplastin time (aPTT)	(↑) to ↑	(↑)	(↑)	(↑)	(↑)
	Prothrombin time (PT)	(↑)	↑ to ↑↑	(↑)	↑ to ↑↑	↑↑↑
	INR	(↑)	↑ to ↑↑	(↑)	↑ to ↑↑	↑↑↑
	Guide for indication for reversal agents[a]	Insufficiently sensitive/specific				**INR > 1.2**
Not specific but sensitive tests	Thrombin time (TT)	↑↑↑	Not applicable			Not applicable
	Ecarin clotting time (ECT)	↑↑↑	Not applicable			Not applicable
	Heparin anti-Xa activity	Not applicable	↑↑↑	↑↑↑	↑↑↑	Not applicable
	Guide for indication for reversal agents[a]	**TT < 3 x upper limit of normal[b]**	**Anti Xa < 0.3 U LMWH[c]**			
Sensitive and specific tests		**Diluted thrombin time**	**anti- factor Xa activity calibrated for rivaroxaban**	**anti-factor Xa activity calibrated for apixaban**	**anti-factor Xa activity calibrated for edoxaban**	**INR**
	Guide for indication for reversal agents[a]	**TT < 3 x upper limit of normal[b]**	Functional concentration < 30 ng/ml[d]	Functional concentration < 30 ng/ml[d]	Functional concentration < 30 ng/ml[d]	**> 1.2**

a) These are guidelines only and management must be individualised to each patient.

b) Expert recommendation by the authors.
c) Corresponds to 30 ng/ml; NOAC-calibrated assays should be used whenever possible.
d) If measured > 4 h after drug administration; extrapolated from published recommendations for surgery[25] and supersedes older recommendations.

INR, international normalised ratio; LMWH, low-molecular weight heparin; N/A: Not applicable

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Session No 7

IV thrombolysis – dosing of alteplase

The Consensus Statement includes two parts, the Consensus Statement itself, and the Recommendation to the European Stroke Organisation (ESO) on revision of ESO Guidelines. Please note that the final text of the Guidelines, is decided by ESO and that the recommendation in this document may not be the final guidelines version.

I. ESO Karolinska Stroke Update Consensus Statement

The following Consensus Statement was adopted by the 11th ESO Karolinska Stroke Update meeting on November 14th/15th 2016.

The Consensus Statement was proposed by the chairman of the session, Professor Martin Dichgans, and the session secretary Dr Konstantinos Kostulas, Stockholm, 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 Professor Thompson Robinson, Leicester, UK, and Professor Werner Hacke, Heidelberg, Germany.

Issues for the 2016 consensus session:

- Do the results of the ENCHANTED study support a recommendation of a dose of 0.6 mg/kg of alteplase for iv thrombolysis for an Asian population?
- Do the results of the ENCHANTED study support a recommendation of a dose of 0.6 mg/kg of alteplase for iv thrombolysis for a European population?

Implications for all populations of the results of the ENCHANTED study

A lower dose of intravenous alteplase (0.6mg/kg body weight; maximum 60 mg) is approved for the treatment of acute ischaemic stroke (AIS) within 3 hours of onset in Japan. Many neurologists in other Asian countries have also adopted use of low-dose alteplase because of a perceived reduction in bleeding risk and lower cost, although observational studies have produced conflicting findings and no previous randomised trials have been conducted. The ENhanced Control of Hypertension And Thrombolysis strokE stuDy (ENCHANTED) was an international, multi-centre, prospective, randomised, open-label, blinded-endpoint trial of low- versus standard-dose (0.9mg/kg body weight; maximum 90 mg) for patients with thrombolysis-eligible acute ischaemic stroke within 4.5 hours of symptom onset (1). Low-dose alteplase did not meet the non-inferiority criteria compared to standard-dose with respect to the conventional 90-day binary clinical outcome measure of death and disability (modified Rankin scale scores (mRS) 2 to 6).

However, the lower dose was non-inferior with respect to an ordinal analysis of the mRS and produced significantly fewer symptomatic intracerebral haemorrhages (sICH) across a broad range of definitions.

Moreover, there was consistency of these findings between the Asian (n=2079) and non-Asian (n=1212) participants, as well as across several pre-defined subgroups.

Conclusions

- AIS patients, regardless of ethnicity, in whom treatment can be started within 4.5 hours of stroke onset should be treated with alteplase.
- Low-dose alteplase is NOT non-inferior to standard-dose with respect to a regulatory measure of clinical outcomes - 90-day death and disability (mRS 2 to 6).
- Low-dose alteplase is safer with respect to sICH.
- Low-dose is non-inferior to standard-dose with respect to overall functional outcomes defined by an ordinal analysis of mRS.
- There is consistency of these findings between Asian and non-Asian ethnic groups.

II. Summary of updated recommendations to ESO Guidelines Committee

Recommendations

- Standard-dose intravenous alteplase (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by a 60-minute infusion, is recommended within 4.5 hours of onset of ischaemic stroke (Class I, Level A).
- Ethnicity should not be used as a reason for not offering best treatment, i.e. standard-dose alteplase (Class 1, Level B).
- Where there is concern over sICH risk, further RCTs are required to define the patient populations in whom low-dose intravenous alteplase (0.6 mg/kg body weight, maximum 60 mg) may be considered (Class 2, Level C).

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Session No 8

Management of symptomatic intracranial stenosis

This topic will be discussed at the Karolinska Stroke Update Conference for the first time. The ESO stroke guidelines from 2008 recommended that endovascular treatment may be considered in patients with symptomatic intracranial stenosis (Class IV, GPC).

The Consensus Statement includes two parts, the Consensus Statement itself, and the Recommendation to the European Stroke Organisation (ESO) on revision of ESO Guidelines. Please note that the final text of the Guidelines is decided by ESO and that the recommendation in this document may not be the final guidelines version.

I. ESO Karolinska Stroke Update Consensus Statement

The following Consensus Statement was adopted by the 11th ESO Karolinska Stroke Update Conference on November 14th/15th 2016.

The Consensus Statement was proposed by the chairman of the session, Professor David Russell, Oslo and the session secretary Dr. Magnus Thorén, 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 Professor Peter Ringleb, Heidelberg, Germany and Professor Michael Söderman, Stockholm, Sweden.

Issues for the 2016 consensus session:

- Is intensive medical management the primary recommended therapy for the management of symptomatic intracranial stenosis?
- If so, are there subgroups of patients for which angioplasty and/or stent placement would offer a better or equivalent alterative?

Theme 1: Update on management of symptomatic intracranial stenosis.

Intracranial atherosclerosis (ICS) causes 10–29% of brain ischemic events, depending on the studied population (Hartmann 2005). ICS is particularly prevalent in black, Asian, Hispanic, and Indian populations, and in some Arabic countries, which suggests that the global burden of stroke from ICS is likely to grow (Holmstedt 2013).

The recurrent stroke risk with severe (≥70%) symptomatic intracranial stenosis (sICS) may be as high as 23% at 1 year, despite medical therapy (Chimowitz 2005).
Traditional risk factors associated with ICS include hypertension, smoking, diabetes mellitus, and hyperlipidaemia. In the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial, the most important modifiable risk factors for an increased risk of recurrent stroke and vascular events associated with ICAS were raised systolic blood pressure greater than 140 mm Hg and mean cholesterol concentration >200mg/dL (5.20 mmol/L)(Chaturvedi 2007). The WASID trial was designed to

compare warfarin (targeted INR 2.0-3.0) and a high dose (1300mg/day) aspirin in patients with symptomatic 50-99% sICS (Chimowitz 2005). The study with 569 included patients showed no benefit of warfarin over aspirin for the prevention of stroke and vascular death in patients with ICS. However, aspirin was safer than warfarin, with a lower rate of death and major haemorrhage. In addition, findings from the WASDIN study showed that there was also no benefit from oral anticoagulation in subgroups with a presumed higher recurrence risk, such as those with severe (70–99%) stenosis, vertebrobasilar stenosis, or previous stroke symptoms on antithrombotic therapy (so-called medical failures) (Turan 2009).

So far, two randomized controlled trials the “Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis” (SAMMPRIS; Chimowitz 2011) study and the “Vitesse Intracranial Stent Study for Ischemic Stroke Therapy” (VISSIT; Zaidat 2015) study have evaluated endovascular intervention with stenting for sICS. The SAMMPRIS study included 451patients with a recently (<30 days) symptomatic (transient ischemic attack or minor stroke) 70% to 99% ICS. These patients received either optimized medical therapy (OMT) or OMT plus percutaneous transluminal angioplasty and stenting (PTAS). OMT consisted of 325 mg aspirin per day plus 75 mg clopidogrel per day for the first 90 days, rosuvastatin (target low-density lipoprotein <70 mg/dL [<1,8 mmol/L]), antihypertensives (systolic blood pressure <140 mmHg or <130 mmHg for diabetics), and lifestyle modification. PTAS were carried out using the Wingspan stent system (Stryker Inc). Enrolment was stopped early because the 30-day rates of stroke and death were significantly higher in the PTAS-group (14.7% (10.2% ischemic, 4.5% hemorrhagic) versus 5.8%; P=0.002). The 30-day risk of PTAS was therefore nearly twice as high as previously assumed and the 30-day risk under OMT ‘alone’ was approximately half of that what was expected (Abou-Chebl 2012). This difference also persisted for a longer observation period (Derdeyn 2015). During a median observation period of 32.4 months, 15% of the patients in the OMT-group compared to 23% in the PTAS-group had a primary endpoint event (stroke or death within 30 days after enrolment, ischemic stroke in the territory of the qualifying artery beyond 30 days of enrolment, or stroke or death within 30 days after a revascularization procedure of the qualifying lesion during follow-up). Beyond 30 days, 10% in the OMT-group and 10% in the PTAS-group suffered from a primary endpoint event. The absolute differences in the primary endpoint rates between the two groups were 7.1% at year 1 (p=0.043), 6.5% at year 2 (p=0.07) and 9.0% at year 3 (p=0.020). A subgroup analysis of the SAMMPRIS trial did not find any patient specific factor supporting PTAS in favour of OMT in a specific cohort of patients with ICS (Lutsep 2015b). In addition, SAMMPRIS-patients, on antiplatelet therapy at the time of the index event, did not benefit from PTAS compared to OMT (Lutsep 2015a).
The VISSIT study was initiated soon after the start of SAMMPRIS, but differed amongst others in the type of intracranial stent used (Zaidat 2013). An interim analysis was performed after the publication of the SAMMPRIS results, and the study stopped prematurely. Overall 112 patients (18-85years of age) with severe (70%-99%) intracranial (internal carotid, middle cerebral, intracranial vertebral, or basilar artery) and symptoms (hard TIA or stroke) within 30 days prior enrolment were included (Zaidat 2015). OMT was similar to the one used in SAMMPRIS. However, LDL-Cholesterol target was <100 mg/dL [<2.6 mmol/L] and no specific statin was used. The primary safety measure was a composite of any stroke, death, or intracranial

haemorrhage within 30 days of randomization and any hard TIA[1] between days 2 and 30 of randomization. This endpoint occurred in more patients in the stent group (14/58; 24.1%) compared to the OMT-group (5/53; 9.4%) (p = 0.05). The 1-year primary outcome of stroke or TIA occurred in more patients in the PTAS group (36.2%) vs. the OMT group (15.1%) (p=0.02). The authors concluded that these findings did not support the use of a balloon-expandable stent for patients with symptomatic intracranial arterial stenosis.

Conclusions

- Intracranial atherosclerotic stenoses are one of the most common causes of stroke worldwide and are associated with a high risk of recurrent stroke
- Strict risk factor management including systolic blood pressure reduction to <140 mmHg, reduction of LDL-cholesterol to <70 mg/dl [1.8 mmol/L], and smoking cessation is mandatory for secondary prevention
- For patients with moderate (50-69%) stenosis or symptoms more than 30 days old, antiplatelet therapy with aspirin is more effective than oral anticoagulation.
- In patients with severe (>70%) and recently (<30day) symptomatic ICS dual antiplatelet therapy with 75-100 mg aspirin and 75 mg clopidogrel daily is recommended for three months. After this period, aspirin therapy should be continued.
- It's not recommended to prolong the duration of dual antiplatelet therapy more than three months (based on MATCH and CHARISMA).

Theme 2

SAMMPRIS, VISSIT and other studies and registries show that an unselected population with symptomatic intracranial stenosis >70% will do better with OMT than with angioplasty and stenting or with angioplasty alone. However, even with OMT the recurrent stroke rate can be as high as 13% the first year after the initial event (Chimowitz 2011).
The major issues with angioplasty and stenting are the high peri-procedural complication rate, up to 14%, the fact that despite successful stenting the patient has still some risk for stroke, the need for double antiplatelet therapy and finally the risk for restenosis (Chimowitz 2011, Gröschel 2009, Zaidat 2015). However, in for example the WINGSPAN study, the 30-day complication rate was lower, only 4.5% and the 6 months ipsilateral stroke rate 7% (Bose 2007).

Are there subgroups of patients where, despite these disappointing results, intracranial stenting may be considered? i.e. where the natural history is very poor, and where medical therapy is less effective or angioplasty and stenting less dangerous? These subgroups could be:

Patients with recurrent thromboembolic events while on OMT. There is today no other treatment option. However, a sub-analysis of the SAMMPRIS trial showed that in patients with perforator strokes there was a high risk for further stroke due to perforator

[1] defined as a transient episode of neurological dysfunction caused by focal brain or retinal ischemia that lasts for at least 10minutes but resolves within 24 hours

occlusion at the time of angioplasty (Fiorella 2012). This must be taken into account when considering the treatment risk balance.

Patients with acute symptomatic vessel occlusion. In these cases, there are no other treatment options.

Patients with severe symptomatic regional hypoperfusion. A sub-analysis of the WASID trial patients showed that abundant collateralisation was protective against further stroke The relative recurrent stroke risk was six fold higher in patients with poor collaterals (Liebeskind 2011). This could be because the presenting event was hemodynamic, or because a good collateralisation is protective also against embolic events. Patients with severe symptomatic hypoperfusion may not have time to benefit from OMT, where statins play a significant role in plaque reduction.

Conclusions

- Symptomatic intracranial arterial stenosis should be treated with strict risk factor management and optimal medical therapy.
- Although there is no clear evidence, the role of angioplasty and stenting, carried out by experienced personnel, may be considered in a few special situations, such as:
    - Patients with recurrent thromboembolic events while on OMT.
    - Patients with severe symptomatic regional hypoperfusion
    - Patients with acute symptomatic vessel occlusion.

II. Summary of updated recommendations to ESO Guidelines Committee

Recommendations

- Strict risk factor management and optimal medical therapy is the primary recommended treatment for the management of symptomatic intracranial stenosis (Grade B evidence)
- There is not enough evidence to recommend situations where angioplasty and/or stent placement would offer a better or equivalent alterative. Although there is no evidence, the role of angioplasty and stenting, carried out by experienced personnel, may be considered in a few special situations (Grade C evidence).
- RCTs or prospective registry studies are therefore required.

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Session No 9

How to reach a cognitive endpoint in stroke trials

The Consensus Statement includes two parts, the Consensus Statement itself and the Recommendation to the European Stroke Organisation (ESO) regarding the design of future clinical trials ESO Guidelines. Please note that the final text of the Guidelines has to be accepted by the ESO Guideline Committee and that the recommendations included in this document may not be the final guideline version.

I. ESO Karolinska Stroke Update Consensus Statement

The following Consensus Statement was adopted by the 11th ESO Karolinska Stroke Update Conference on November 14th/15th 2016.

The Consensus Statement was proposed by the chairmen of the session, Dr Valeria Caso, Perugia, Italy and the Session Secretary Dr Ioanna Markaki, Stockholm, Sweden, together with the speakers of the session. The statement was then finally approved by the participants of the meeting, after evaluating the different presentations. The speakers in this session were Prof. Michael Brainin, Krems, Austria, and Prof. Didier Leys Lille, France

Aims for the 2016 consensus session:

- Strategies that guarantee that cognitive endpoints are included in future major stroke studies/trials
- Neuropsychological tests for best identifying cognitive endpoints
- Appropriate tailor strategies for the education of clinicians and researchers on the interplay between stroke and dementia

Theme 1: Why is the integration of cognitive endpoint in stroke trials important?

In 2013, there were almost 6.5 m deaths from stroke, 113 m Disability-Adjusted Life Years (DALYs) lost due to stroke and 10.3 m of people with new strokes. Knowledge on the implications of vascular damage associated with dementia onset and progression remains insufficient as most research on stroke prevention and risk factors has failed to adequately investigate primary and secondary prevention strategies for cognitive impairment.

The most common vascular contributor to vascular dementia is cerebral small vessel disease (SVD) [1], a condition that affects perforating vessels, therein white and grey matter, and neuro- degenerative processes, more than often manifesting in stroke, cognitive decline and dementia, as well as neuropsychiatric symptoms [2,3]

In 2006, the National Institute for Neurological Disorders and Stroke along with the Canadian Stroke Network convened a multidisciplinary research group to recommend standards for the study of vascular cognitive impairment [4]. In 2013, the Alzheimer's Association set up an expert working group, which reviewed the state of vascular cognitive impairment science and identified areas where knowledge is lacking [5]. However, despite evidence of vascular cognitive impairment on both dementia patients and their caregivers [6], most research has largely excluded or overlooked vascular disease as a possible contributor to cognitive decline. The inclusion of cognitive outcomes in stroke studies has been the exception rather than the rule. A survey has shown that out of 8,826 stroke studies, only 488 (6%) included a cognitive or mood outcome [7]. This reflects the need for a change. Outcome measures of cognition need to be greater prioritized by stroke researchers by including cognitive and emotional endpoints as primary endpoints in stroke studies, replacing combined outcome event endpoints that collectively investigate on the occurrence of recurrent stroke, MI, vascular death, death of all causes and re-hospitalization. These specific endpoints are often considered hard endpoints, whereas cognitive/emotional measures are often considered soft, less harmonized, and therefore not well suited for international purposes.

Based upon the above-mentioned hypotheses on interactions between stroke and dementia, some stroke researchers have begun to grasp that cognitive and emotional endpoints could play an important underlying role in stroke outcome. In fact, the human brain cortex is made up of motor and non-motor areas) mostly the latter. This is especially true for the frontal brain areas, which are the most frequent sites of stroke lesions.

Motor function impairment, especially sensorimotor hemiparesis, has been reported to be the leading symptom of brain dysfunction at 80%, followed by dysexecutive syndrome (43%) dysarthria (34.5%), memory disorder (33.1%), aphasia (29.1%), depression (23.6%), hemineglect (19.6%), and disorientation (18.9%), agraphia (14.2%), acalculia (13.5%), alexia (8.2%), panic reaction (5.4%), anosodiaphoria (5.4%), anosognosia (4.7%), psychotic syndromes (2.7%), and akinetic mutism (0.7%) [8]. It has been now accepted that the dysexecutive syndrome is the most frequent non-motor disturbance, but its role in early stroke-related deficit has not been sufficiently recognized. Therefore, clinical trials of stroke should include cognitive endpoints, especially the dysexecutive syndrome as well as related outcomes [9].

Nevertheless, most studies have failed to include these cognitive endpoints and this is most likely influenced by the fact that currently available scales for measuring outcome, following stroke, are often inappropriate for this utilization. The time-honoured Barthel Index, for example, is not at all appropriate for stroke patients, as it was developed for hip surgery patients and does not include assessments for cognitive and emotional states [10]. In addition, the Barthel Index as well as other scales including the FIM, have pronounced floor and ceiling effects [11]. Recommendations for stroke research have highlighted the importance of cognitive outcome measures for RCTs as a prerequisite for improving our standards of clinical research [12].

In light of this issue, recent studies on prevention or on recovery have assessed cognitive outcomes using composite z-scores that provide a summary score of neuropsychological test results over several cognitive domains [13,14]; a consensus group has detailed

recommendations such as the Vascular Cognitive Impairment Harmonization Standards [5]. Additionally, the DSM-5 classification now includes post-stroke cognitive deterioration as a separate condition, thus giving this condition a well-defined basis. It is now recognized as a separate and defined disease category, which should enable the development of licensed therapies. The major or mild vascular neurocognitive disorder now represents a disease entity which enables our stroke community to develop new trials with recognized outcomes focused on the dysexecutive syndrome and related impairments.

There are ongoing discussions whether all future large clinical trials (not only those studying brain diseases) should have at least one cognitive outcome measure along with the standardly used QOL measurements. This is because new drugs and new dose recommendations might bear an increased risk of neurological side effects not revealed in the trial phases. Recent examples for this include the finding that, propanozol might promote dementia [15] and high dose statins seem to increase the risk of intracerebral hemorrhage [16].

Theme 2: How to integrate cognitive endpoints in stroke trials

Integrating cognitive endpoints in acute as well as recovery stroke trials is important.

Objective of acute treatments

The objective of acute stroke treatment is to increase the proportion of patients who survive without handicap i.e. with a modified Rankin Scale [mRS] [17] 0-1, and without dependency (mRS 0-2). In severe strokes, such as those with malignant infarcts, the objective may be to increase the proportion of patients who survive without severe dependency (mRS 0-3 or mRS 0-4). The mRS may be used in a dichotomised analysis, but the European Stroke Organisation (ESO) outcome working group recommended using a shift analysis [18]. The mRS evaluates handicap and dependency irrespective of their underlying mechanism (physical, cognitive, behavioral, etc.).

Evaluation of the pre-existing cognitive status

Including an evaluation of the pre-existing cognitive status is important because (i) pre-existing dementia is frequent in stroke patients [19]; (ii) patients with pre-existing cognitive impairment but no dementia are more likely to be dependent and to require institutionalizing during the follow-up [20]; and (iii) patients with pre-existing dementia are more likely to have a bad outcome after an acute stroke with more seizures [21], delirium [22]), and a higher mortality rate at the acute stage [23], both in ischemic and in haemorrhagic strokes [24].

The global clinical impression, based on the clinical judgement of the physician after an interview with relatives, can provide some information [25], but such an interview needs to be structured to guarantee reliability. A systematic approach with the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) [26] provides reliable and reproducible results. The original (long) version, of the IQCODE consisted of 26 questions regarding changes experienced by the patient over the last 10 years in various aspects of daily behavior that require memory and other intellectual abilities [27]. The participation of the patient is not required: the IQCODE can, therefore, be used when the neuropsychological

evaluation is possibly influenced by stroke, or is not feasible because of coma or severe aphasia. The short version of IQCODE is now available, and contains 16 of the most relevant questions from the long version [27], and has been validated in many languages [28]. Patients are classified as previously demented when they have an IQCODE score of 104 or more (long version) or 64 or more (short version), and cognitively normal when they have an IQCODE score of 78 (long version) or 64 (short version). The results from the IQCODE had an excellent correlation with those of the mini-mental state examination when tested in the community [29]. The limitations of the IQCODE are that a reliable informant who meets the patient at least once a week must be interviewed, and the test must be given within 48 hours after admission to prevent any influence of the relative by the current status of the patient [29]. These limitations explain that the IQCODE cannot be used in approximately 20% of patients [30]. Another limitation is that the IQCODE is time-consuming.

Evaluation of post stroke cognitive status

Cognitive impairment after stroke has not been systematically assessed as outcome in acute trials [31]. Integrating cognitive measures during the follow-up of patients recruited in acute stroke trials is important because: (i) stroke is associated with an increased risk of dementia [19], and therefore acute stroke treatment should influence cognitive outcomes, and (ii) cognitive impairment accounts for a part of the functional outcome [32]. The evaluation of cognition is of special interest in patients who are independent and in patients who are dependent after stroke despite minimal physical disability [32].

Evaluation of the post-stroke cognitive state should cover relevant cognitive domains and, simultaneously have a reasonable duration. Five domains should be assessed by at least one test, and coupled with an evaluation of mood and behavior. Widely used tools to screen for dementia are the MMSE [33] and MoCA [34]. The MMSE is more sensitive to memory disorders. The MoCA is more sensitive to executive functions impairments [35] A subset of 4 item of the NIHSS has been proposed to assess cognitive function nearly (orientation, executive function, language, and inattention) and may act as a surrogate; this remains to be confirmed by an ongoing analysis of trials in the Virtual International Stroke Trials Archive (VISTA) archive [36]. The confounding effect of language impairment on cognition and mood should be taken into account when interpretation cognitive outcomes [32].

II. Summary of recommendations to ESO Guidelines Committee:

Recommendations

- Cognitive endpoints should be included in all stroke trials.
- IQCODE or equivalent should be included in acute stroke trials to be sure that groups are balanced for pre-existing cognitive impairment.
- Two versions of neuropsychological test batteries may be considered within three to six months post stroke: a short version that can be conducted by trained nurses or physicians, and a more comprehensive long version that has to be performed mostly by trained neuropsychologists.
  The short test battery could include the MoCA, the Trail Making Test A and B and the digit span forward and backward.
  An extended test battery should assess multiple domains and be composed of

validated neuropsychological tests fulfilling different criteria regarding psychometrics, usability, costs, time, language and culture.

- Sample sizes and duration of follow-up should be taken into account in prevention trials to evaluate cognitive outcomes.
- It is advisable to include also a short depression scale, a self-rating scale such as the Beck Depression inventory or the Center of Epidemiologic Studies Depression scale.
- Focus on longstanding effects of interventions should also consider assessment of fatigue and apathy, as well as caregiver status.

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Session No 10

Prehospital triage for mechanical thrombectomy

The Consensus Statement includes two parts, the Consensus Statement itself, and the Recommendation to the European Stroke Organisation (ESO) on revision of ESO Guidelines. Please note that the final text of the Guidelines, is decided by ESO and that the recommendation in this document may not be the final guidelines version.

I. ESO Karolinska Stroke Update Consensus Statement

The following Consensus Statement was adopted by the 11th ESO Karolinska Stroke Update Conference on November 14th/15th 2016.

The Consensus Statement was proposed by the chairman of the session, Professor Urs Fischer, Department of Neurology, University Hospital Bern, Switzerland, and the session secretary Dr. Michael Mazya, Karolinska University Hospital, Stockholm, 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 Professor Grethe Andersen, Arhus, Denmark, Professor Antoni Davalos, Barcelona, Spain, and Dr. Michael Mazya, Stockholm, Sweden.

Issues for the 2016 consensus session:

- Prehospital triage may save brains – get started!
- How can we find the best triage criteria?
- Prehospital triage may cause problems for some patients – randomise!

Theme 1: Clinical identification of stroke patients with large vessel occlusion: current evidence and limitations

The beneficial effects of endovascular thrombectomy (EVT) are time-dependant, decreasing with increasing time from symptom onset to initiation of treatment.[1, 2] The currently established practice for emergency prehospital medical services is to transport the patient with acute stroke symptoms to the nearest emergency hospital. There, the patient undergoes initial diagnostic work-up including vessel imaging as indicated, aiming to assess the patient's eligibility for intravenous thrombolysis (IVT) and EVT. If there is an indication for EVT and the initial hospital cannot deliver such treatment, patients are taken by secondary transport to an EVT-capable facility. Secondary transport, while necessary, delays the initiation of EVT by up to two hours compared to a situation where the patient arrives primarily at an EVT-capable hospital (exact time differences: ESCAPE, 51 minutes[3]; SWIFT PRIME, 57 minutes[4]; REVASCAT, 67 minutes[5]; EXTEND-IA, 93 minutes[6]; German observational registry study by Weber et al, 83 minutes[7]; Danish before and after cohort study 49 minutes (Mohamad NF et al. European Stroke Journal 2016;1:85-92); Catalonia area 82-120 minutes (ref 10 from part B) In order to avoid this delay to EVT, a need has materialised of prehospital triage tools which can rapidly and reliably identify patients whose

symptoms are most likely to be caused by a large arterial occlusion.

Higher stroke severity has been associated with a higher likelihood of LVO in patients with acute stroke undergoing vascular imaging. Heldner et al demonstrated in 2013 that NIH Stroke Scale scores ≥12 were associated with a 91% positive predictive value to find an occlusion of the internal carotid artery (ICA), M1 or M2 segment of the middle cerebral artery, or the basilar artery LVO.[8] Further studies have shown that the optimal stroke severity cut-off for predicting LAO is a function of time, decreasing from NIHSS 12 within the first hour to 10 between 3 and 4,5 hours in a recent publication from SITS by Cooray et al[9]. NIHSS ≥9 has been reported to be associated with a PPV for LVO of 86.4% within 3 hours of onset, while a lower NIHSS score ≥7 was associated with a similar PPV for LVO of 84.4% between 3 and 6 hours of stroke onset.[8] However, the full 13-item NIHSS is generally perceived as impractical in the pre-hospital setting. To address this issue, a number of simplified clinical scales for prediction of LAO, either directly or via association with severe stroke, have been developed.[10-21].

In the scores which have been subjected to validation studies, most have been retrospectively applied to selected in-patient cohorts of patients with a diagnosis of ischemic stroke. Only two triage instruments have been tested in the prehospital setting. One, a binary presence / non-presence of severe hemiparesis or hemiplegia, was used to select patients for helicopter transport to a comprehensive stroke centre (CSC), with 27% of triage-positive patients undergoing EVT, 7% having an endovascular procedure for a neurosurgical indication and 13% being treated with IVT alone.[20] However, this study was based on 45 patients only. A yet unpublished study validated the hemiparesis rule in Stockholm with better results.

The RACE (Rapid Arterial Occlusion Evaluation) scale is the only one to-date with reported sensitivity, specificity and accuracy for LAO validated in a pre-hospital setting. It has been implemented in routine practice in Catalonia, Spain, and has an accuracy to predict LAO of 76%.[19, 22]

Overall, the predictive scales published to-date have similar predictive performance, showing an overall accuracy in the range of 70-80% in retrospective in-hospital validation cohorts.[23-25]

	3I/SS	LAMS	C-STAT	VAN	PASS	FAST-ED	RACE	Hemi-paralysis
LoC	0/1/2		0/1		0/1			
Gaze / head deviation	0/1/2		0/2	0/1+Visfield	0/1	0/2	0/1	
Facial palsy		0/1				0/1	0/1/2	
Arm motor	0/1/2	0/1/2	0/1	0/1	0/1	0/2	0/1/2	0/1
Grip strength		0/1/2						
Leg motor							0/1/2	0/1
Aphasia				0/1		0/2	0/1/2	
Neglect				0/1		0/2	0/1/2	

3I/SS: 3-Item Stroke Scale; CPSSS: Cincinnati Prehospital Stroke Severity Scale;

FAST-ED: Field Assessment Stroke Triage for Emergency Destination; LAMS: Los Angeles Motor Scale; PASS: Prehospital stroke severity Scale, RACE: Rapid Arterial Occlusion Evaluation; and VAN: Vision, Aphasia, Neglect. Hemiparalysis rule: presence of NIHSS ≥ 2 points in ipsilateral arm and leg.

It is likely that increasing complexity of a scale will reduce the frequency, as well as the reliability with which it is used in the prehospital setting. Moreover, it is likely that the preferred cut-off level of any triage score would differ depending on geography and population density (as well as "hospital density"). In large urban areas with several comprehensive stroke centers, a cut-off level associated with a higher sensitivity (lower false-negative rate) may be preferred to allow the maximum number of patients to achieve low onset-to-thrombectomy times, bypassing primary stroke centres. Conversely, in areas with lower population, with one remote CSC, a cut-off with a higher specificity (lower false-positive rate) may be preferred, to reduce numbers of patients without LAO taken to the CSC, and avoiding increasing the onset-to-IVT time in eligible patients, who would be treated more rapidly in the nearest PSC.

Conclusions

- Studies validating the predictive performance of currently available LAO prediction scores should be performed in pre-hospital settings in unselected patients with a suspicion of stroke following initial contact with emergency medical services.
- Several published scores appear to have similar predictive performance in the range of 70-80%, resulting in 20-25% of LAO patients being missed at optimal score cut-off levels. At the same cut-off levels, 12-25% of triage positive patients would not have an LAO. Attempting to reduce false negative LAO rates will lead to transportation of nearly all patients with suspected stroke to comprehensive stroke centres, which in many areas is unfeasible.
- If implemented in the pre-hospital setting, the scores would likely result in triage positive patients with LAO receiving EVT with a shorter onset to treatment time, than is possible with current practice of "nearest IVT-capable hospital first".
- The current level of evidence is insufficient to recommend one score over the other. The choice is contingent on the perception of ease-of-use, and preference for high specificity or high sensitivity, which depend on local circumstances related to geography, population density and hospital infrastructure.
- If a stroke triage procedure is implemented incorporating an LAO prediction score within a study framework or otherwise, efforts should be directed toward ensuring that the quality of care in triage positive patients taken to CSC and discovered to lack an indication for EVT, is not diminished. Conversely, it is imperative that triage negative patients taken to a primary stroke centre be taken care of on a first priority alarm basis and undergo vessel imaging immediately, in order to rapidly initiate secondary transfer to CSC if indicated by clinicoradiological findings.
- EMS systems should implement validated prehospital tools to identify patients with a LVO or participate in the validation of those yet unvalidated in the prehospital setting.

Theme 2: Mechanical thrombectomy: "Drip and ship" or "load and go"?

Models of prehospital stroke care/organization of stroke care within a certain area. Strengths and weaknesses of these models.

Drip and ship model: transfer to the nearest Primary Stroke Center (PSC) where initial specialized attention and iv tPA, if eligible, can be offered, followed by transfer to an Comprehensive Stroke Center (CSC) of patients candidates for EVT. This model prevails worldwide since decentralized stroke networks favoring early iv-tPA administration have been implemented in many countries.

Advantages:

- Early initiation of iv-tPA. Although benefit of iv-tPA in patients with large artery occlusion (LAO) is limited, with rates of recanalization lower than 20%, odds of recanalization and good outcome are higher if started within the first 60-90 minutes from symptom onset.[1] In recent EVT clinical trials[2] more than 70% of patients with LAO were eligible for iv-tPA.
- Selection of patients eligible for EVT based on vascular neuroimaging or stroke severity, ruling out patients with intracerebral haemorrhage and avoiding long transfers to a CSC of patients who are not candidates for EVT.

Disadvantages:

- Delay of EVT due to in-hospital attention at the PSC and interhospital transfer. Data coming from recent clinical trials show that time from onset to randomization was about two hours longer for patients transferred from other centers.[3] *Picture to puncture* time has been proposed as the time metrics for the primary evaluation at local stroke centers and transfer.[4] Delays in picture-to-puncture times for interhospital transfers reduce the probability of good outcomes among treated patients.

Mother ship model: direct transfer to a CSC, bypassing PSC.

Advantages:

- Higher proportion of patients treated with EVT and earlier initiation of EVT by avoiding time consumption at the PSC and during interhospital transfer. Two observational studies before-and-after interventions have shown higher proportion of patients treated with EVT and shorter treatment times after implementing a local mother ship model with different prehospital triaging tools.[5,6]
- There are some few data about the benefit of treating hemorrhagic stroke at a CSC.[7]

Disadvantages:

- Transfer of patients not eligible for EVT. Using current pre-hospital selection tools, this model would result in many endovascular ineligible patients transferred to a CSC. For example, triaging patients with RACE>4 would include about 25% hemorrhagic stroke patients and 25% acute ischemic stroke patients without LAO.[8]

- Delay or deny of intravenous thrombolysis. This model may result in delay on the initiation of iv-tPA or even denying iv-tPA in cases attended by EMS close to the 4.5h time window, missing their treatment opportunity at the closer facility. This fact may have clinical outcome consequences, in particular in patients without LAO who have a higher rate of IV t-PA response.
- Risk of neurological deterioration during long transfers.

Mobile stroke units (drip during ship model): medical attention, neuroimaging-vascular diagnostic and iv-tPA administration at the ambulance, followed by transfer to a CSC of patients candidates to EVT.

Mobile stroke units (MSU), equipped with a CT scanner, point of care laboratory, telemedicine connection and a prehospital stroke team, have been implemented in few areas around the world.[9] This model of care has been demonstrated to be safe and allows a reduction on the time from EMS alert to iv-tPA by 25 minutes compared with the usual care at a PSC. Mobile stroke units could be used as an intermediate model between the drip and ship and the mother ship models, by offering the opportunity of administering early iv-tPA, selecting patients eligible for EVT based on neuroimaging (CT angiography) and avoiding the transfer of patients without LAO to a CSC. However, the low availability, the high cost and variable geographical situations limits its use worldwide.

Conclusions

- For patients with a suspected LAO based on current clinical tools on field, there is equipoise between drip and ship (that prioritizes early iv-tPA and other standard of care therapies) and mother ship (that prioritizes early EVT) models. Data based on randomized controlled trials is needed to determine the most beneficial model for each particular patient (eligible or not to iv-tPA) in different geographical regions and to establish isochrones where a particular model may be beneficial.

In the meanwhile:

- for patients considered eligible to tPA in the field, if estimated transfer time to the nearest PSC is considerably shorter than time to a CSC (more than 15-30 minutes), the drip and ship model would be recommended.
- in a scenario where a PSC and CSC are equidistant (not more than 15-30 minutes apart) or when absolute contraindication to tPA is known in the field, patients with suspected LAO on field should be transferred directly to a CSC, bypassing closer PSC.

II. Summary of updated recommendations to ESO Guidelines Committee:

A. Clinical identification of stroke patients with large vessel occlusion: current evidence and limitations
B. Mechanical thrombectomy: "Drip and ship" or "load and go"?

Recommendations

- Several published clinical scores to predict large artery occlusion appear to have similar predictive performance in the range of 70-80%, resulting in 20-30% 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. Evidence grade (C).
- Studies validating the predictive performance of currently available large artery prediction scores should be performed in pre-hospital settings in unselected patients with a suspicion of stroke following initial contact with emergency medical services. Evidence grade (C).
- For patients with a suspected large artery occlusion based on current clinical tools on field, there is uncertainty about the equipoise between drip and ship (that prioritizes early iv-tPA and other standard of care therapies) and mother-ship (that prioritizes early EVT) models. Data based on randomized controlled trials is needed to determine the most beneficial model for each particular patient (eligible or not for iv-tPA) in different geographical regions and to establish isochrones where a particular model may be beneficial. Evidence grade (Expert opinion).
- In the absence of evidence, for patients considered eligible to intravenous thrombolysis in the field, if estimated transfer time to the nearest primary stroke center is considerably shorter than time to a comprehensive stroke center (approximately more than 30-45 minutes), the drip and ship model should be considered. Evidence grade (Expert opinion).
- In the absence of evidence, in a scenario where a primary stroke center and comprehensive stroke center are equidistant (approximately not more than 30-45 minutes apart) or when contraindications to intravenous thrombolysis are known in the field, patients with suspected large artery occlusion in the field, should be considered for transfer directly to a comprehensive stroke center, bypassing any closer primary stroke centers. Evidence grade (Expert opinion).
- In case of primary admission to a non endovascular-capable center, evaluation and treatment for patients with a possible large artery occlusion must be expeditious, to ensure a rapid secondary transfer to a comprehensive stroke center, avoiding any sources of delay such as complex neuroimaging studies (i.e. perfusion studies) or waiting for effect of intravenous thrombolysis. First picture to puncture time should be less than 90 minutes. Evidence grade (A).

Rationale for a future randomized trial (Appendix)

The access of patients with LAO for endovascular treatment (EVT) is limited by their geographical location. For patients living in remote areas, transfer from local centers to a CSC is time-consuming and may cause a loss of effectiveness of EVT. In the meta-analysis of individual patients' data from recent thrombectomy trials (HERMES collaboration), the benefit of EVT declined with longer time from symptom onset to arterial puncture, being the ORs 2.79 at 3 hours (absolute risk difference for OR 0-2 39.2%), 1.98 at 6 hours (absolute risk difference 30.2%) and 1.57 at 8 hours (absolute risk difference 15.7%). The relative risk reduction of functional independence by 60 minutes delay in time to reperfusion was 19% and favorable outcome disappeared roughly after 7 hours.[3]

Access to EVT continues to be very unequal according to the patient's geographical location at stroke onset. In a recent population study in Catalonia, Spain, EVT rates by 100 000 inhabitants/year in 2015 were 10.5 in health areas primarily covered by CSC, 3.7 in areas primarily covered by local stroke centers located less than hour away from a CSC, and 2.7 in areas primarily covered by local stroke centers located more than hour away from a CSC.[10] Median time from symptom onset to groin puncture were 230, 312 and 350 minutes, respectively ($p<0.001$). There were, however, no differences in symptomatic hemorrhagic transformation, postprocedure complete recanalization, functional outcome, and mortality rates at 3 months by geographical areas. Although this study did not investigate the reasons for lower rate of EVT in patients from referring centers, large ischemic core on arrival at CSC and long time from symptoms onset has been ascribed to 32% of excluded cases.[11]

The HERMES group showed almost two hours longer onset to reperfusion time in patients who were transferred from local centers compared to those with direct admission at a CSC.[3] Onset to reperfusion time was the key determinant of outcome, regardless of whether the patient went directly to the endovascular hospital or transferred from an outside hospital. Therefore, EVT effect on functional outcome was comparable between the two models of stroke care when onset to reperfusion time was similar.

SWIFT PRIME looked at the treatment effect by system of care on functional outcome (mRS 0-2). There was no evidence of treatment heterogeneity between *Direct* (patients who received IV tPA at the EVT-SC) versus *Transfer* (patients treated with IV tPA at local hospitals) subgroup analysis. The RRs for improved mRS 0-2 rates were quite similar, 1.6 versus 1.7, indicating that the proportional benefit of thrombectomy was similar in both groups. However, overall the proportion of patients with functional independence (mRS 0-2) was higher among the Direct group (64%) than among the Transfer group (49%) suggesting that Direct arrival at a CSC is an important prognostic variable whatever treatment is given.[12]

Recent guidelines recommend direct transfer of patients with suspected LAO and eligible for IV tPA to CSC, bypassing closer facilities without this capability if the transport difference to the closer facility is less than 15-30 minutes. In patients not eligible for IV t-PA recommend direct transfer to a CSC with endovascular treatment capability.[13] In case of primary admission at a non-endovascular-capable center, evaluation and treatment must be expeditious for a rapid secondary transfer to a CSC avoiding potentially catastrophic sources of delay such as complex neuroimaging studies. Picture to puncture time should be less than 90 minutes.[13]

CSC are frequently located into the metropolitan areas of the big cities but not uniformly distributed covering equidistant population areas in developed countries.[14] Consequently, most patients suffer the acute stroke at long distances from the nearest CSC requiring more than 30 minutes or 1-hour transportation.[10] Whether the direct transfer to a CSC is more effective and safer than the first admission at local SC is unknown with the present scientific published evidence. The next major clinical trials in acute stroke therapeutics should test out-of-hospital strategies to improve outcomes with thrombectomy by substantially reducing times to reperfusion.[15] The benefit and safety of direct transfer to an endovascular center should be compared with first attention at the closest hospital for acute stroke patients with severe symptoms

attended by emergency medical services. This trial is needed to answer if a pre-hospital triage system allowing expert remote evaluation to determine best primary destination center would allow an increased efficiency of revascularization treatments and long term clinical benefits, the safety of long distance transfer before they access a hospital and the distance beyond which there is no or very limited benefit from a direct transfer to a CSC, and if the benefits of a primary transfer to a CSC would only apply to patients with LAO and may unnecessarily delay treatment in all others.

There is important room for improvement since the rate of acute stroke patients who may be eligible for EVT is estimated ranging from 8.6 to 30 EVT/100,000 inhabitants/year,[16] but in distant to CSC geographical areas, the rate of patients treated with EVT is markedly reduced.[10] Conversely, about 60% of these patients are treated with iv-tPA at IPSC.[10] Therefore, primarily transferring these patients to a CSC by-passing the closet PSC may result in a delay in iv-tPA infusion in 60% of these patients. Whether the harm caused by this delay is counterbalanced by the potential benefit of a direct transfer to a CSC increasing the chances to receive EVT is a crucial goal of future research. One study has shown that the effect of IV tPA on recanalization may decrease over time; treatment after 270 minutes predicted a lack of recanalization, especially in distal occlusions.[1] Consequently, delay in IV tPA treatment during transfer might prevent treatment effect in patients with distal occlusions.

The uncertainty about equipoise between the two models of care support the rationale for a controlled trial of acute stroke patients with suspected LAO living in geographical areas in which the reference stroke center is a hospital not capable to offer endovascular treatment (Primary stroke Center or Telestroke Center). Patients should be identified by emergency medical services at first assistance on the field, validated by a stroke neurologist by teleconsultation and allocated to a specific intervention according to a pre-established temporal sequence. Two strategies should be compared under usual care conditions: transfer to the closest PSC versus direct transfer to a CSC. Functional outcome at 90 days should be evaluated by a blinded central assessor in ischemic stroke patients and safety variables in the total included stroke patients. The complexity of this design involves EMS technicians and dispatchers, public health authorities, local and comprehensive stroke centers, telestroke consultants and a stroke network.

Conclusions

- The access of patients with LAO for EVT is limited by their geographical location. Patients living in areas distant to CSC are less frequently treated and with longer times from onset to reperfusion. The benefit of EVT declined with longer time from symptom onset to arterial puncture.
- There is no evidence of EVT heterogeneity between patients directly admitted at CSC and patients transferred from local stroke centers. However, direct arrival at a CSC may be an important prognostic variable whatever treatment is given.
- It is unknown whether the direct transfer to a CSC is more effective and safer than the first admission at PSC.
- For patients with an LAO, EVT is highly effective even though when it is administered in longer windows than IV tPA. However the effect of tPA on recanalization may decrease over time especially in distal occlusions.

- The uncertainty about equipoise between the two models of care support the rationale for a controlled trial of acute stroke patients with suspected LAO living in geographical areas in which the reference stroke center is a hospital not capable to offer endovascular treatment (Primary stroke Center or Telestroke Center).

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