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Neurochirurgie
Neurologie
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Neuroradiologie
Psychiatrie

www.strokecenter.ch

Version 2024

Stroke Guidelines

of the Bern Stroke Network

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Stroke-Team Bern

Physicians on duty	**Phone number**	**Miscellaneous**	**Phone number**
Neurology		Resuscitation (CPR)	
Neuroradiology		Laboratory results	
Neurosurgery		Stroke Unit	
Radiology		Rehab	
Anesthesia			
Intensive Care Unit			
Cardiology			
Internal Medicine			
Infectious Diseases			

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Apps by Stroke Center Bern

Links to additional documents including pediatric stroke guidelines

www.strokecenter.ch

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Ambulance SOP

Case history	Diagnostics
• Symptom onset or last-seen-well time • Previous history/medication? • Relevant pre-existing condition/impairment? • Pacemaker/artificial heart valve? • Phone number of GP/next of kin	• ABC scheme • Glucose • Temperature • GCS • RACE or G-FAST score

Triage

See chapter on patient triage
Early information transmitted to Stroke Centre/Unit to decide triage, fastest transportation

Position

⇒ Supine position – max. 30° if possible
(when indicated due to other reasons higher positions are possible, e.g. if patient has respiratory problems)

Therapy

⇒ Venous line
⇒ Aim blood oxygen saturation > 92%
⇒ BP aim 120–220 mmHg syst, < 120 mmHg diast
> 220 mmHg syst. or > 120 mmHg diast: lower carefully
< 120 mmHg syst: 500 ml NaCl
WARNING Do not administer aspirin, heparin or similar medication

Patient triage

Symptom onset < 4.5 h	**RACE score < 5** → admit to nearest Stroke Unit (if IVT can be initiated within 4.5 h) consider IVT and transport to stroke center in case of large vessel occlusion: ICA, Carotid T, M1, M2, BA, P1, A1 **RACE Score ≥ 5** Distance to Stroke Center < 20 min longer than to Stroke Unit → admit directly to Stroke Center Distance to Stroke Center > 20 min longer than to Stroke Unit → admit to Stroke Unit, IVT if indicated and transport to Stroke Center in case of large vessel occlusion: ICA, Carotid T, M1, M2, BA, P1, A1
Symptom onset 4.5–24 h	→ admit to nearest Stroke Center
- Unclear symptom onset - Wake-up stroke - Contraindication for IVT	→ admit to nearest Stroke Center
Symptom onset > 24 h	→ admit to nearest Stroke Unit or Stroke Center

Stroke Unit: availability of IVT, Stroke Center: availablity of IVT + EVT
IVT: intravenous thrombolysis, EVT: endovascular treatment
ICA: internal carotid artery, BA: basilar artery, M1-2: middle cerebral artery, A1: anterior cerebral artery, P1: posterior cerebral artery

RACE Score

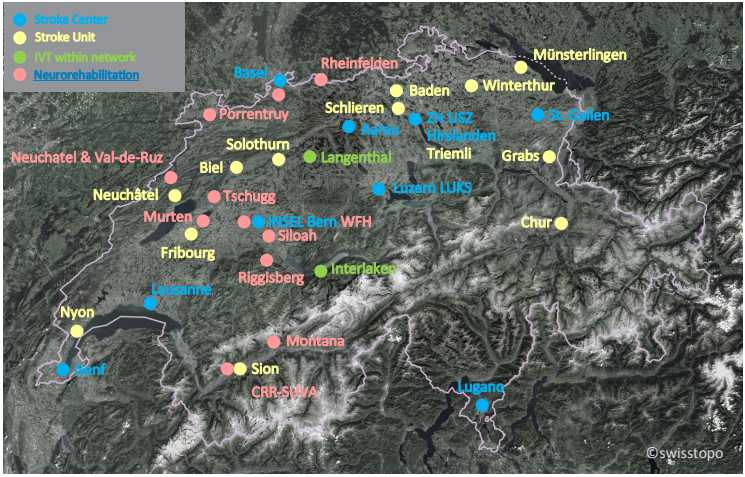
Stroke Amb

	**"Show me your teeth"**	
	No palsy (symmetrical movement)	0
	Mild (slight asymmetric)	1
	Moderate to severe (complete asymmetry)	2
	**"Extend your arms and hold them there" (supine 45°, otherwise 90°)**	
	Normal to mild: arms held out > 10 sec	0
	Moderate: one or both arms held out < 10 sec	1
	Severe: unable to raise arm(s) against gravity	2
	**"Extend your legs and hold them there" (30° in supine position)**	
	Normal to mild: legs raised for > 5 sec	0
	Moderate: one or both legs raised for < 5 sec	1
	Severe: unable to raise leg(s) against gravity	2
	**Gaze deviation**	
	Absent	0
	Deviation of eyes or head	1
If palsy is right-sided 	**"Close your eyes" + "Make a fist"**	
	Normal, both commands followed	0
	Moderate: one command not followed	1
	Severe: neither of the commands followed	2
If palsy is left-sided 	**"Whose arm is this?" + "Does your arm feel weak?"**	
	Normal: recognizes arm, aware of impairment	0
	Asomatognosia or anosognosia	1
	Asomatognosia AND anosognosia	2

Perez de la Ossa Stroke 2014

Probability of large vessel occlusion depending on summed score					
1	8%	4	34%	7	72%
2	14%	5	47%	8	81%
3	22%	6	61%	9	86%

Swiss Stroke centres, Stroke Units & Rehab



In-Hospital Stroke specific management

Pediatric Stroke specific management

be FAST SAFE STROKE PATH

Registration	**? Symptoms, Symptom Onset** **? ABCDE** **? Arrival time**
ED/trauma room	Inform ED or trauma room
Prenotification	**CT/MRI, Anaesthesia**
Drip & ship?	**Notify team in case of drip and ship, angio suite free?**
ED arrival	**Start Stroke Clock App** **Blood tests, 2nd venous line** **Monitoring?** criteria———→ **NIHSS** (do not waste time) **ECG?** only if chest pain or other clear indication **Monitoring until CT/MRI if** Unstable during transport to ED O_2 >2l/min BP sys >200 or <100 HR > 110 or < 50 Relevant disturbance of consciousness
Acute care nurse	**Acute care nurse accompanies every patient** **If not available:** Anaesthesia if monitoring is indicated
CT or MRI	**CT if** • Pacemaker • Implants not MR compatible • Consciousness↓/Agitation/Vomiting • History of implants not clear (e.g. aphasia, severe dementia) **+ pregnancy ??** (→MR without contrast agent)
Imaging priority?	**Priority 1** ASAP IVT/EVT indication Symptom onset <12h **Priority 2** within 20 min Presumably no IVT/EVT indication Symptom onset 12– 24h **Priority 3** within 3h TIA > 2h otherwise P2 Symptom onset > 24h
Arrival CT/MR	**MR questionnaire**
Monitoring MR	**Monitoring during MR** O_2 needed for Biox >92% BP sys > 165 or < 100 HF > 110 or < 50 Pat. cannot ask for help by him/herself **Acute care nurse in MR if** Patient cannot ask for help by him/herself Patient agitated
Physician presence	**Obligatory in case of** Priority 1+2: always Priority 3: if criteria for monitoring in MR are fulfilled (exception O_2 < 4l) **Not required if** DWI/SWI/TOF negative + no other indication for surveillance by physician
Therapy decision	**IVT** only if BP <185/105, CAVE fever endocardtis!), see chapter on contraindications for IVT **EVT** decision on intubation together with interventionalist
IVT/EVT	**IVT** start bolus after native imaging **EVT** Transfer of patient to interventionalist + anaesthesia in NeuroAngio
Stroke Unit /ICU	**Request a bed SU/ICU**
Arrival SU/ICU	**ECG**

max 10′

max 15`

Indications and choice of therapy

Presentation
NIHSS Score ≥ 4
or
NIHSS < 4 with relevant disabling deficit (e.g. aphasia, hemianopia, distal paresis)
or
Consider for persistent vascular occlusion with minor deficits and/or rapid clinical improvement

+

Vessel occlusion	Time & Imaging		
	< 4.5 h **also treatment if no infarct core perfusion/ FLAIR mismatch can be detected**	**4.5 - 11 h**	**Wake up/** **Unknown onset/ or >11h - 48h:**
ICA, Carotid-T, M1, prox. M2	Bridging (especially if up to 140 min after onset)	EVT usually independent of core/perfusion or core/clinical mismatch§, consider bridging IVT (for transfer patients)#	EVT depending on ASPECTS and including mismatch/collaterals@
P1, A1, VA	IVT und ggf. EVT (DISTAL trial P1, A1)	EVT or IVT if mismatch#	EVT if Mismatch*§
Dist. M2 (<1/3 MCA-territory), M3/4, P2/3, A2/3/4	IVT, consider i.a. lytics or distal EVT* (DISTAL trial)	IVT if mismatch# or i.a. thrombolytics or distal EVT* (DISTAL trial)	IVT if mismatch/collaterals# or i.a. thrombolytics or distal EVT* (DISTAL trial)
BA	Bridging	EVT §	EVT depending on pcASPECTS and considering mismatch@, §
No detectable vessel occlusion	IVT	IVT if Mismatch#	IVT if Mismatch#
Spinal Ischemia	IVT	Consider IVT up to 6h	

*** Individual decision depending on infarct core-perfusion mismatch**

 # Diffusion FLAIR mismatch (no or incomplete FLAIR demarcation of the DWI lesion) or **perfusion infarct core mismatch** (up to approx. 70mL infarct core, mismatch ratio >1.2)

§ If EVT is not technically possible, IVT can also be considered for large vessel occlusion beyond 4.5h in case of mismatch (see #)

@ If (pc)ASPECTS >5 always EVT regardless of perfusion, if (pc)ASPECTS <6 relative indication depending on patient's wishes with overall poor prognosis (age, pre-mRS, comorbidity). In the presence of collaterals in multiphase CTA rather proactive.

IVT: intravenous thrombolysis, EVT: endovascular treatment, BA: basilar a., M1-4: middle cerebral a., A1-2: anterior cerebral a., VA: vertebral a., P1-2: posterior cerebral a.

Contraindications

IVT	EVT	
Absolute	Relative	Septic embolization, endocarditis, encephalitis, pancreatitis
		Intracranial haemorrhage
		INR > 1.7
		Surgery at non-compressible sites within the past 10 days
		Clinical picture of CAA **AND** cortical superficial siderosis OR >15 merely cortical microbleeds
		Severe trauma or recent head trauma
		Intraparenchymal haemorrhage within the past 3 months
		Delivery within the past 14 days
		Gastrointestinal haemorrhage within the past 21 days
		Blood pressure above 185 mmHg sys./105 mmHg dias. after BP treatment
Relative		Coagulopathy, incl. tumour-associated (e.g. in patients with leukaemia) and prolonged aPTT
		Thrombocytopenia < 100,000
		Pregnancy (IVT may be considered as off-label treatment)
		Ischaemic stroke within the past 2 months
		Septicaemia
		Hypoglycaemia < 2.7 mmol/l or hyperglycaemia > 22.2 mmol/l
		Sodium < 120 mmol/l or > 150 mmol/l
		Lumbar puncture < 24h
		Severe underlying disease, short life-expectancy

Notes

- **IVT in patients previously treated with antiplatelet aggregation therapy**
  - Monotherapy: aspirin/clopidogrel/aspirin+dipyridamole/ticagrelor: no restrictions
  - Dual therapy: aspirin+clopidogrel: no restrictions; other combinations: consider IVT carefully
  - Monotherapy or combination therapy with prasugrel: consider IVT carefully
  - Triple therapies: no IVT
- **Bridging (IVT + EVT)**
  - normally full dose alteplase 0.9 mg/kg KG continue to run without interruption - even after complete recanalization during thrombectomy
  - normally no control imaging before EVT except in the case of clinical deterioration

- **Large infarct core DWI/CBV (> 150 mL):** consider EVT in younger patients (< 75 years, and especially if < 60 years)
- **IVT for non-disabling deficits in the early time window NOT recommended, then DAPT with loading is preferred**
- Prognosis assessment for participatory decision-making for borderline thrombectomy decisions

Sedation for agitation (ED, imaging)

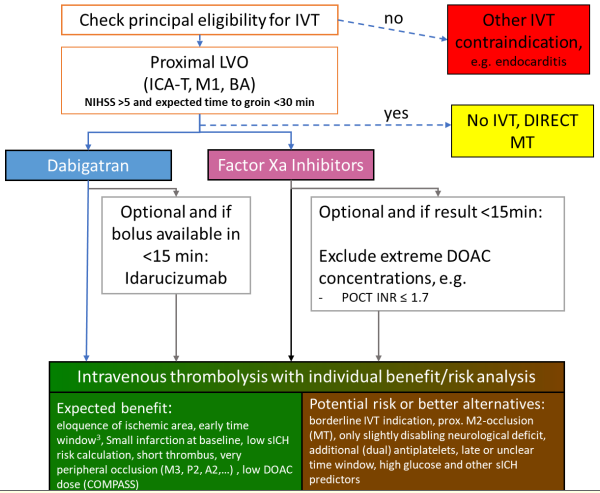
Medication	Dose	Note
Midazolam (Dormicum®)	1mg test dose, sedation usually with 1-10mg	Antidote: Flumazenil (Anexate®) 0.2mg over 15 sec, then repeat potentially every 60 sec, max. total dose 1mg
Propofol (Propofol®)	Only in presence of anesthesia	

IVT dosage

Weight	Alteplase (Actilyse®)			Weight	Tenecteplase (Metalyse®)
(kg)	**Sum dose** 0.9 mg/kg	**Bolus** 10% in 1 min	**Perfusor** 90% over 60 min	(kg)	**Apply as bolus within 5–10 sec**
44–47	40 mg = 40 ml	4 ml	36 ml/h	60	15mg
48–51	44 mg = 44 ml	4 ml	40 ml/h	70	17mg
52–54	47 mg = 47 ml	5 ml	42 ml/h	80	20mg
55–57	50 mg = 50 ml	5 ml	45 ml/h	90	22mg
58–62	54 mg = 54 ml	5 ml	49 ml/h	≥90	25mg
63–67	59 mg = 59 ml	6 ml	53 ml/h		Dose must be calculated exactly
68–72	63 mg = 63 ml	6 ml	57 ml/h		to the kg body weight
73–77	68 mg = 68 ml	7 ml	61 ml/h		
78–82	70 mg = 70 ml	7 ml	63 ml/h		
83–88	77 mg = 77 ml	8 ml	69 ml/h		
89–92	80 mg = 80 ml	8 ml	72 ml/h		
93–97	86 mg = 86 ml	9 ml	77 ml/h		
≥98	90 mg = 90 ml	9 ml	81 ml/h		

Note: when administering 2/3 of the dose, stop the perfusor after 40 min.

IVT in patients with recent DOAC intake



If last intake >48h (normal renal function) IVT generally possible. 1) Idarucizumab (2x2.5 g i.v. before IVT); 2) POC INR to exclude other coagulopathy. Waiting for levels optional. 3) Only applicable in the early time window (<4.5h). In case of unclear benefit/risk situation consult stroke specialist.
In case of stroke under DOAC, always order substance-specific levels (compliance).

Monitoring during IVT + EVT

IVT

1. **Measure BP every 5 minutes:** target sys. ≤ 185 mmHg, diast. ≤ 105 mmHg
   - in the case of > 185/105: re-check after 5 minutes
   - if BP persists > 185/105: BP lowering (see Antihypertensive medications, below)
2. **Respiration:** control of oxygen saturation: target Biox > 92%
3. **Evaluation of pupils:** 3 × per hour

- **in case of clinical deterioration**: stop alteplase; CT: haemorrhage?
- **in case of allergic reaction**: stop alteplase, administer clemastine 2 mg, methylprednisolone 250 mg i.v. for extreme anaphylaxis: adrenalin 0.3–0.5 mg s.c.; for very extreme anaphylaxis: adrenalin 0.05–0.1 mg i.v.
- **For orolingual angioedema**: adrenaline (0.1%) 0.3 mL s.c. or 0.5 mL nebulized, early contact anesthesia (fiberoptic intubation) if base of tongue, pharynx, larynx affected, Icatibant 30mg s.c. (abdominal), repeat up to 2x in 24h
- **in case of plasma glucose > 11 mmol/l**: reduce carefully with insulin

EVT: during EVT MAP relatively stable at baseline; after thrombectomy: ≤180/105; raise RR only if hemodynamic symptoms or infarction

Antihypertensive medication (iv)

Use (standard values)	Medication	Dosage	Maximum effect	Warnings/Side effects
bolus administration	**Urapidil** 50 mg/vial	2.5–10 mg (1 ml = 5 mg) max 50 mg/d	10 min	Vertigo, headache, dyspnoea, arrhythmia (tachycardia or bradycardia)
bolus administration for HR > 70/min	**Labetolol** 100 mg/vial	5–10 mg (1 ml = 5 mg) max 200 mg/d	15 min	Bradycardia, AV-block, hypotension, vertigo, nausea, paresthesia, bronchial spasm
bolus administration for HR > 70/min	**Metoprolol** 5 mg/vial	1–2.5 mg (1 ml = 1 mg) max 15 mg/d	5 min	Bradycardia, AV-block, low output syndrome, bronchial spasm
bolus administration for HR < 70/min	**Dihydralazin** 25 mg/vial	6.25 mg slowly over 2 minutes (1 ml = 12.5 mg) max 100 mg/d	20 min	Oedema, tachycardia, angina pectoris; excercise caution in the case of liver or renal failure
Perfusion therapy	**Urapidil** 50 mg/vial	5–10 mg/h max. 40 mg/h	–	Restricted to 48 h therapy
Perfusion therapy	**Labetolol**	10–40 mg/h max 100 mg/h (1 ml = 1 mg)	–	Bradycardia, AV-block, hypotension, vertigo, nausea, paresthesia, bronchial spasm
Perfusion therapy	**Cleviprex ●** **Clevidipin**	2-16 mg/h max 32 mg/h (1 ml = 0.5mg)	-	Only short time! At the same time initiate oral medication Headache, afib, tachycardia, dizziness, hypotension, **Contraindication:** allergy (soy, egg), critical aortic stenosis

Vasopressor therapy (iv)

Use (standard values)	Medication	Dosage		Warnings/Side effects
Perfusion therapy	**Noradrenalin●** 10 mg/vial	Start with 0.01 µg/kg BW/min then titrate		CI: Hyperthyreosis, tachycardia arrhythmias, angle-closure glaucoma, pheochromocytoma, cardiomyopathy (esp. hypertrophic) Compensate hypovolaemia first

Stroke Unit treatment

First neurological examination immediately after arrival
Cardiovascular monitoring:
- BP upper limits during the early phase (especially first 24h):
  ≤ 180/105mmHg after IVT or EVT
  ≤ 220/110mmHg if medical management
- BP lower limit: only in selected cases in case of hypoperfusion/symptom worsening with drop of BP => to increase BP: only temporary administration of a limited volume of infusion solution (max. 500 ml); in other cases use vasopressors (e.g. Noradrenaline)

- Tachycardia > 100 bpm => usually beta blockers; in case of tachycardic atrial fibrillation consider adding digoxin
- Frequent ventricular extrasystole => magnesium 2 g i.v.
- Bursts of ventricular extrasystole (more than 3 beats): usually beta blocker + magnesium;
≥10 beats or polymorphic or >120/min or clinically symptomatic => consultation with cardiologist
- Bradycardia: during sleep in asymptomatic patients, usually up to 35 bpm is tolerable
- Pause > 3 seconds => consultation with cardiologist

Respiration: target Biox ≥ 92; screening for sleep apnoea
- If > 4l O_2/min is necessary or respiration frequency > 20 => clinical examination, arterial blood gas analysis, chest X-ray (pulmonary embolism? cardiac failure? pneumonia?)
- If respiration frequency > 25–30 there may be a danger of respiratory exhaustion

Body temperature: ≥ 38° -> antipyretics (1st choice paracetamol) + 2x2 blood cultures, empirical/causal treatment

Neurological evaluation: usually every 2h during the first 24h after IVT/EVT or symptomatic stenosis, otherwise every 6h
Clinical general medical evaluations: cardiac compensation, lungs, abdomen to be checked daily

Prescription of medication:
- Do not prescribe antiplatelet aggregation therapy after IVT/i.a Urokinase before exclusion of haemorrhage in control CT/MRI after 24h
- General cardiac premedication should be continued, with potential reduction of dose (WARNING cardiac failure/rebound tachycardia after stop)
- Stop any antihypertensive medication in the case of haemodynamic stroke

Laboratory controls: (24h after IVT/EVT)
- Hb, Lc, Tc, CRP, glucose, Na, K, creatinine, INR
- hs-Troponin T and ECG after 3 h if initially abnormal
- Anaemia: transfusion if Hb < 90 g/l
- Tc daily under heparin therapy; further laboratory examinations individually determined

Neuroradiological control:
- 24h after IVT/EVT, MRI (or CT), including MRA (CTA) except in patients with severe renal insufficiency
- In case of neurological deterioration (usually NIHSS worsening of 2 points or more) immediately

Swallowing: in case of dysphagia, reduced consciousness , facial palsy or relevant neuropsychological deficits: swallowing test (GUSS: Gugging Swallowing Screen) —> if suspicious or brain stem ischemia: FEES

Nutrition and fluid balance:
- Daily fluid intake requirement: 30–35 ml/kg body weight: If volume administration is necessary: infusion as bolus (either 500 ml i.v. or as free water via ng tube); if volume status unclear: ultrasound (inferior vena cava, lungs, bladder)
- Daily energy demand: 35 kcal x body weight
- If sufficient oral energy supply cannot be given within 3 days after stroke: enteral feeding via nasogastric tube with high caloric fibrous enteral feeding as bolus application 3–4x/d; control of electrolytes (incl. magnesium and phosphate)
- If fasting period > 7 days: delayed feeding (WARNING refeeding syndrome)

Mobilization

Day 0	Day 1 and thereafter
Subacute stroke > 2d	
TIA without vessel occlusion	
Small infarcts, without symptoms, without vessel occlusion, conservative treatment	
Infarct, NIHSS ≥ 1, without vessel occlusion, conservative treatment	
Stroke pontine/internal capsule	
Vessel occlusion/haemodynamic watershed infarcts/ symptoms, conservative treatment *	No penumbra , not pontine/internal capsule stroke
	Persistent penumbra, severe hypoperfusion, haemodynamic watershed infarcts/symptoms
IVT/EVT/Bridging	Reperfusion, not pontine/internal capsule stroke
	Persistent penumbra, hemodynamic or fluctuating infarcts/symptoms
Mobilization without restriction Mobilization delayed (possibly slower in case of persistent penumbra or mobilization-dependent symptoms) 30°, up to max. 60° (*supine position if possible)	**Mobilization delayed** Level 1: 30°, up to max. 60° Level 2: sitting Level 3: walking with assistance, if patient is steady then free mobilization is possible

Daily checklist – visiting stroke patients

1	**Neurological evaluation**	NIHSS and symptom-orientated functional examination (results of physio-, ergotherapy, speech therapy); depression? sleep-wake disorder?
2	**Clinical evaluation**	Cardiac compensation, lung, abdomen, fever?
3	**Monitoring**	Relevant rhythmic disorders (regarding reason, haemodynamic, cardiac pathology) BP target value? BP actual value?
4	**Mobilization?**	
5	**Nutrition, dysphagia?**	
6	**Laboratory controls?**	Especially electrolytes, inflammation parameters, kidney, haemostasis
7	**Medication**	Antithrombotic therapy? Deep vein thrombosis prophylaxis? BP therapy?

Systematic monitoring

1. graphical 24h-Spectrum of heart rate
2. Identify and analyze sudden raise/drops
3. Identify and analyze abrupt volatility in amplitude of the heart rate variability
4. Analyze episodes with heart rate >120/min or <40/min
5. Evaluation of all detected arrhythmia episodes by the automatic ECG analysis software
6. Chronological analysis of beat-to-beat irregularities in RR intervals and atrial fibrillation

Kallmünzer et al. Stroke 2012

DD Neurological deterioration

? Reinfarction
? Infarct localization: e.g. secondary deterioration more frequent in internal capsula or pontine infarctions
? Haemodynamic: BP associated? Associated with mobilization?
? Bleeding
? Rising ICP
? Epileptic seizure / non-convulsive status epilepticus
? **Infection**
? **Sedation**
? Psychogenic
and other less frequent causes

Alteplase-associated ICH

In the case of symptomatic ICH or neurological deterioration within 24 after Alteplase administration:
→ Stop Alteplase
→ **Blood tests**: thrombocytes, INR, aPTT, fibrinogen, type and cross-match
→ **CT**; in case of bleeding:
→ **Fibrinogen (Haemocomplettan P)** or **Prothrombin complex concentrate** (involve haematology)
→ **Tranexamic acid** (Tranexam OrPha) i.v. 1000 mg, apply over 10min
→ BP aim ≤ 140/90 mmHg

Prevention of deep vein thrombosis

- In case of IVT, bridging, Urokinase initiation: after exclusion of cerebral haemorrhage in the follow-up-imaging
- After mechanical thrombectomy without IVT and with conservative therapy: start immediately
- Under heparin Tc control on day 1, then every 3 days (HIT?, 4Ts score)
- Pneumatic compression stockings may be an alternative if LMWH is contraindicated

DD Myocardial inf. DD stress cardiomyopathy

hsTnT-elevation in approx. 20% of ischaemic stroke patients, DD: MI, stress cardiomyopathy (SCM), renal failure, hypertensive crisis, tachycardia, aortic dissection

Variable manifestation of SCM: hsTnT ↑ < regional hypokinesia < transient apical ballooning

- The extent of hsTnT-elevation does not discriminate between MI and SCM
- SCM is an exclusion diagnosis
- In case of doubt consider cardiac MRI (best discrimination)

Possible practical approach in case of hsTnT-elevation:
- Clinical correlate for MI (repolarization disturbance, wall motion abnormalities, angina pectoris) → coronary angiography
- No clinical correlate: repeat ECG and hsTnT after 1 and 3 h, and, if necessary, after 6 h:
  - hsTnT without relevant change (<20%): renal failure? heart failure? hypertensive state?
  - hsTnT change >20%: consider cardiac MRI or coronary angiography

Malignant infarcts

General
- Usually 30° supine position
- BP aim: MAP > 85 mmHg, sys. < 220 mmHg
- **In case of imminent craniectomy: stop antiplatelet therapy**
- Pneumatic compression stockings for prevention of deep vein thrombosis
- Consider as emergency medication until craniectomy:
  - mannitol/hypertonic saline solution (dosage control of mannitol via osmotic gap, hypertonic saline solution via Na and osmolality)
  - Hyperventilation

Decompressive craniectomy
- **Craniectomy if possible within 24–48 h** and before relevant neurological deterioration
- Critical phase with risk for neurological deterioration: 24–96 h (rarely up to as late as 10 d)
- Signs of rising ICP: decreasing consciousness, disturbance of pupillomotor function usually with dilatation in case of supratentorial swelling, and miosis in case of infratentorial swelling, increasing paresis, new ipsilateral paresis, pathological breathing pattern, rhythmic disorders
- **Possible practical approach:**
  - o general actions see above
  - o frequent clinical control and early CT control (e.g. 12 h after stroke) in case of infarct >2/3 middle cerebral artery territory or larger infratentorial stroke (e.g. complete PICA infarct or larger)
  - o aim: preventive planned decompression! An emergency rescue decompression only in exceptional circumstances since it is associated with worse outcome

Malignant infarctions of the middle cerebral artery territory

Predictors for malignant infarction: young patient, no atrophy, persistent vessel occlusion, early midline shift ≥ 4mm, critical infarct volume dependent upon age/atrophy but >>80 ml or >1/2 media territory, additional infarction in anterior or posterior territory

Indications for craniectomy
1. Usually < 60 years, individually consider also in older patients
2. Symptom onset within the past 48 h (in exceptional cases this may be longer)
3. Infarction of at least half of the middle cerebral artery territory
4. Consent of patient or family
5. Indication independent from affected hemisphere (dominant vs. non-dominant)

Contraindications
1. Bilateral fixed pupils and coma
2. More than 3 of the following unfavourable prognostic factors:
   a. age >50 years
   b. infarction extends beyond the middle cerebral artery territory
   c. unilateral dilated pupil
   d. GCS <8
3. Severe comorbidity; severe preexisting disability

Malignant cerebellar infarctions

Predictors for malignant infarction: young patient, persistent vessel occlusion, bilateral infarction, the size has less predictive value because small infarcts may induce large oedema

Indications for craniectomy
1. Larger infratentorial ischaemia (e.g. complete PICA stroke)
2. Imaging shows space-occupying infarction with progression in short term follow-up imaging
3. Consent of patient or family

Contraindications
1. Clinical or imaging signs of severe irreversible brainstem damage
2. Severe comorbidity, severe preexisting disability

Agitation/delirium

General

- Screening: CAM (Confusion Assessment Method) or IDCSC or 4-AT
- Follow-up parameter: **RASS** (Richmond Agitation Sedation Scale):

+4 combative	+3 very agitated	+2 agitated	+1 restless	0 alert and calm
–5 unarousable	–4 deep sedation	–3 moderate sedation	–2 light sedation	–1 drowsy

Diagnostic criteria ICD-11

Required:
- **Disturbance of attention, orientation and consciousness** that develops within a short period of time (e.g. within hours or days) and **usually fluctuates**.
- **Change compared to the previous state**.
- **Not better explained by pre-existing disorder** (e.g. MCI / dementia or psychiatric illness) or intoxication.
- **Trigger**: disease, substance or medication, withdrawal, multiple or unknown factors

Additional possible clinical features:
- Global cognitive impairment (multiple domains)
- Impaired perception (illusions, delusions or hallucinations)
- Emotional disorders (anxiety, depressive mood, irritability, anger, euphoria or apathy)
- Behavioral symptoms (e.g. restlessness, agitation, impulsivity, sleep-wake rhythm)

Treatment

1. **Eliminate/treat cause**
2. **Non-drug therapy measures**
   - circadian rhythmization
   - Stimulus reduction

Symptomatic therapy

In case of alcohol withdrawal delirium, 1st choice is benzodiazepines, otherwise use the following scheme:

Level 1: **Pipamperone** 20 mg stepwise (maximal dose 360 mg/d)
or **Quetiapine** 12.5 mg stepwise (maximal dose 800 mg/d)
or/and Risperidone 2×0.5 mg/d (maximal dose 16 mg/d)
or exceptional Haloperidol (Haldol®) 0.5–1 mg stepwise (maximal dose 60 mg/d)
WARNING: arrhythmia → apply i.v. only exceptionally under monitoring

Level 2: **Clonidine:** 25–50 µg as bolus, then 25–150 µg/h perfusion therapy (maximal dose 150 µg/h)

Level 3: Dexmedetomidine (Dexdor®): 0.2-1.4µg/kgKG/h (starting dose 80kg = 40µg/h = 5ml/h)
CAVE: contraindication hypotonia, bradycardia, AV-block II/III°

Level 4: Propofol perfusion in ICU

Special case, delirium in patients with stroke and Parkinson's disease
→ **Quetiapine (Seroquel®)** 25–100 mg p.o., max. 300 mg/d
→ **Clozapine (Leponex®)** 6.25–12.5 mg, max. 100 mg/d; 2/3 of the dose at night, 1/3 throughout the day

Special case, delirium in patients with stroke and alcohol withdrawal
→ **Primarily benzodiazepines + thiamine substitution**

Delirium due to alcohol withdrawal: → **primarily benzodiazepines + thiamine substitution**
Diazepam (Valium®) 5mg intravenously (increase possible up to 10mg intravenously)
or midazolam (Dormicum®): 2.5-5mg as a bolus (maximum dose 10mg) i.v.
then if necessary 2-5 mg/h via perfusion (maximum dose 10mg/h); antidote: flumazenil (Anexate®)

TIA

Pathological/anatomical TIA definition : transient focal neurological deficit without DWI lesion on MRI
Time-based TIA definition: transient focal neurological deficit max. 24h duration
Definition Minor-Stroke: NIHSS Score < 4, symptoms stable or regressive

0-48h after symptom onset OR **recurrent./fluctuating symptoms**
→ **ED Neurology ASAP**

2-7 days
→ **ED Neurology urgently <12h) ***

> 7 days
→ **GP within 24h ***

Therapy: No medical therapy externally

Therapy: Start ASS

Work-up in ED: MRI, ECG, Stroke Lab

Ambulatory work-up: organized by GP

ABCD2 > 5 points ?

no

MRA: symptomatic stenosis? and/or

MRI: DWI-lesion or perfusion deficit?

yes

yes

no

Admission
(= Monitor at least 24h)

Ambulatory
Long-term rhythm monitoring ECG (3x7 days), TTE/TEE , (NVUS)

Ambulatory follow-up by fellow within 1 week
cMRI/MRA before (same day)
Long-term ECG (3x7 days)

Follow-up I telephone by ED-Fellow after 10-14 days (Recurrence? Medication?)

Follow-up II outpatient clinic after 3 months with cMRI + checking on work-up

Follow-up III outpatient clinic after 12 months: risk factor control

* In case of **warning symptoms** e.g. dissection (Horner, head/neck), vasculitis (cognitive deficits, behavioral abnormalities) or endocarditis (fever) **—> immediate referral**

ABCD2 Score

Risk factor	Points
Age ≥ 60 years	1
Systolic BP ≥ 140 or diastolic ≥ 90	1
Unilateral weakness with or without speech disturbance Speech disturbance without weakness	2 1
TIA duration ≥ 60 min TIA duration 10–59 min	2 1
Diabetes mellitus	1

6–7 points: high 2-day risk (8%)
4–5 points: intermediate 2-d risk (4%)
0–3 points: low 2-day risk (1%)

DD TIA DD Migraine with Aura
Motor symptoms -> primarily ischemic
Purely negative visual/sensory symptoms -> rather ischemic;
Positive sensory or visual symptoms -> DD ischemic, DD aura;
A migraine aura almost always has visual

Diagnostic work-up

Frequent causes (ASCOD, TOAST)		Other (rare) causes
≈20%	**Small vessel disease** (mostly single perforator occlusion; <15mm CT, <20mm MRI), no AF, no ipsilateral stenosis	Anti-Phospholipid Syndrome, Factor V Leiden
≈25%	**Cardioembolic**	Iatrogenic (e.g. periinterventional)
esp.	Atrial fibrillation / flutter	Vasculitis
	(Sub)acute myocardial infarction	Tumor-associated and other coagulation disorders (esp. DIC)
	Endocarditis	Drugs, Medications
≈20%	**Large artery disease**	Other arrhythmia (e.g. sick sinus), valvular vitium
esp.	Arterio-arterial embolism (ICA, VA Stenosis), ICAD	Chronic infection (esp. HIV, Hep B/C, syphilis)
	Aortoembolic (also from Aorta descendens possible)	R-L-Shunt pulmonary
	Non-arteriosclerotic Vasculopathy (e.g. FMD, Carotid Web)	Fabry disease, other genetic mutations
<5%	**Dissection (cervical vessels**, less frequent Aorta**)**, especially among young stroke patients	Sickle cell anemia/other hemolytic crises
≈5%	**PFO/ASD –associated**, esp. among young patients	Polyglobulia/thrombocytosis

Etiological DD according to results

DD according to medical history and physical examination

? Valsalva or immobilisation (PFO/ASA)
? Positive familial history with onset < 40 years (Fabry disease, coagulopathy)
? < 50 years, previous art/ven thrombosis, abortion (anti-phospholipid syndrome), Fabry disease
? Throat/neck/eye pain, trauma, Horner, Tinnitus (dissection ICA/VA)
? Headache (vasculitis), thunderclap headache (reversible vasoconstriction syndrome)
? Heart murmurs, skin or retinal lesions (endocarditis, valvular calcification)
? Angina pectoris (acute or in the past)
? Acute chest/back pain (aortic dissection!, coronary syndrome)
? Peripheral vascular examination incl. BP-difference left-right (aortic dissection)
? Skin lesions (septic emboli, Fabry: angiokeratoma, Sneddon: livedo racemosa)
? Vision disturbance + hearing disturbance (Susac's syndrome => corpus callosum affected?)
? Signs of systemic rheumatic disease
? B symptoms, age >75, D-Dimer >1000µg/L, female sex, multiterritorial ESUS (tumor —> screening)
? Acute or chronic infection

DD according to laboratory results

- Signs of infection: Infection-associated coagulopathy? Malignancy? Endocarditis? Systemic disease?
- Thrombocytopenia/Thrombocytosis, Leucocytopathology: haematological disease?
- Anaemia: Malignancy? Sickle cell anaemia?
- D-Dimer
  - < 500: more likely arterio-arterial, aorto-embolic, microvascular
  - 500–3000: associated with atrial fibrillation
  - > 3000: Malignancy? Coagulopathy? -> screen for malignancy and consider thrombophilia screening

DD according to MRI

> 2 vessel territories affected: cardio-embolic, aorto-embolic, coagulopathy (D-Dimer? Fibrinogen?), paradoxical embolism, vasculitis
- 1 vessel territory with multipe ischaemia: arterio-arterial (Plaque-MRI?)

Diagnostic work-up

- **MRI incl. MRA (for a reliable evaluation of the distribution pattern of acute/chronic infarction and determination of the etiology, especially in view of a CEAI)**; if not possible, CT incl. CTA
- **Neurovascular ultrasound** in the case of relevant stenosis, arterio-arterial embolization or R/L-shunt (PFO)
- **12-lead ECG**
- **Long-term ECG** (see scheme below)
- **Cardioaortic Imaging** (see scheme below)
- **OSAS Screening (Respiratory Polygraphy)** in the first night or second night
  - AHI ≥ 30/h: send for PAP after discharge
  - AHI 10-29.9/h: reevaluate PAP after 3 months
  - AHI ≤ 10/h: only send for PAP if Epworth SS ≥ 10 or NoAS ≥8
- **Routine laboratory testing**: Na, K, CRP, ESR, glucose, HbA1c, creatine, urea, hs-Troponin T, CK, CK-MB, AST, ALT, GGT, TSH, pro-BNP, D-dimer, complete blood count, coagulation state, blood lipids
- **< 50 years and no other apparent etiology**: additionally lupus anticoagulant, anti-cardiolipin (IgG+M, not A!), anti-b2GPI (IgG+M, not A!) (if elevated after 3 months, repeat).

12-channel ECG and 72h continuous ECG monitoring for a minimum of 72 hours

AF diagnosis: manage according to guidelines

Risk Stratification for AF

Riskfactor	Comparatively low	Comparatively high
Patient characteristics		
Age, years	<60	≥75
Manifest heart failure, peripheral or coronary artery disease	Absent	Present
Echo-markers		
Left ventricular ejection fraction	Normal	<40%
Left atrial dilatation	Diameter <40 mm	>45mm LAVI >42 ml/m^2
Monitoring on the stroke unit	SVES <120/24h Atrial run <5 beats	SVES ≥500/24 hours Atrial runs >20 successive beats/24h
Blood Biomarkers		
MRproANP	<92 pmol/L	>200 pmol/L
NTproBNP	<200 pg/mL	>400 pg/mL

Low risk	Moderate risk	High risk
0 high risk factors > 2 low risk factors	All between low and high risk	≥2 high risk factors <4 low risk factors
No further monitoring	Rhythm monitoring for ≤30 days	Prolonged rhythm monitoring ≥30 days either by implantable cardiac device or repeat Holter ECGs

- **Monitoring only if anticoagulation or LAAO is an option**
- In addition to initiating anticoagulation, **all aspects of the holistic ABC care bundle should be optimized** after the diagnosis of atrial fibrillation (ESC Guidelines).
- In addition, **rhythm control measures should be considered and discussed** in patients with atrial fibrillation diagnosed within the last 12 months:
  - **Rhythmology consultation on stroke unit** (start antiarrhythmic drugs?)
  - **Referral to rhythmology after discharge** for evaluation of ablation 2-3 months after event
- If atrial fibrillation is detected in the cardiac monitor, the minimum duration is 2-6 minutes (after stroke/TIA) or 24 hours (primary prophylaxis) for justifying DOAC initiation

Cardioaortic Imaging

TTE: Standard imaging, especially in patients with a known etiology

TEE with the following criteria:
- Suspicion of endocarditis (urgent)
- <60 years: no other etiology (e.g. dissection, carotid web, etc.)
- 60-80 years: no other etiology, no cardiovascular comorbidities and low peri-interventional risk

Remark:
- If endocarditis is suspected and initial TEE non-diagnostic, repeat TEE after 3-5d and evaluate PET-CT
- Consider TEE in case of multiple or multi-temporal ischemia

If specific pathology(ies) suspected:
- TEE/TTE combined
- Cardioaortic MRI*
- Cardioaortic CT*

*In a timely manner on an outpatient basis or from rehabilitation if inpatient treatment is not possible.

Pathology	TTE	TEE	Cardioaortic CT*	Cardioaortic MRI*
LV Thrombus	++ (CE)	+ (CE)	++	+++
LA/LAA (Thrombus)	+	+++	+++	++
PFO / ASD also order nvUS TCD	+	+++	+	+
Valvular pathology - native - on bio/mech. valve	 ++ ++	 +++ ++	 +++ (Valve-CT) +++ (Valve-CT)	 + +
Intracardiac tumor or metastasis	+	++	++	+++
Aorta (Atheroma, Dissection)	-	++	+++	++
LV function, LV aneurysm	++	++	++	+++
Cardiomyopathy	++	+	++	+++

RoPE Score (Risk of paradoxical embolism):

The RoPE score was developed to identify patients with cryptogenic stroke and PFO in whom the PFO was likely the cause of their stroke.
A high RoPE score in a patient with a cryptogenic embolic ischemic stroke and PFO and no other convincing etiology strongly suggests, but does not prove, that the causality of the stroke is related to the PFO.
The RoPE score **should not** be used to decide which stroke patients should undergo echocardiography.
The RoPE score **should not** be used alone to decide which cryptogenic stroke patients with PFO should undergo PFO closure (see PASCAL classification below).

					Sum 0-3	0% attributable risk
No arterial hypertension	1	Age 18-29	5		Sum 4	38% attributable risk
No Diabetes mellitus	1	Age 30-39	4		Sum 5	34% attributable risk
No prior Stroke/TIA	1	Age 40-49	3		Sum 6	62% attributable risk
Non-Smoker	1	Age 50-59	2		Sum 7	72% attributable risk
Cortical infarct location	1	Age 60-69	1		Sum 8	84% attributable risk
		Age ≥ 70	0		Sum 9	88% attributable risk

Kent et al. Neurology 2013
Kent et al. Jama 2021

PASCAL Classification

Only correctly applicable between 18-60 years. In the case of cryptogenic stroke (at least 72h ECG without atrial fibrillation), closure is generally indicated in patients < 60 years of age. In addition to age and vascular risk factors (RoPE), the concomitant circumstances that may favor a paradoxical embolism (e.g. evidence of leg vein thrombosis, onset of neurological symptoms in connection with a Valsalva maneuver), as well as any psychological factors, should be taken into account. At the age of 60-80 years, individual decision on closure taking into account the RoPE and PASCAL score.

		RoPE <7	RoPE ≥ 7
High	Simultaneous pulmonary embolism or DVT + PFO with ASA or large shunt	Likely	Very likely
Medium	PFO with large shunt or atrial septal aneurysm	Possible	Likely
Low	Small PFO without atrial septal aneurysm	Unlikely	Possible

After PFO closure, continue platelet aggregation inhibitors in the long term if well tolerated.

(A)symptomatic artery stenosis

Criteria for the classification of symptomatic carotid artery stenosis: (Judgement always by a vascular neurologist)
- very likely: proof of a plaque rupture with apposition thrombus in CT/MR-angiography
- probable: internal carotid artery stenosis of at least 50% + typical stroke distribution pattern in MRI, with no other cause of the stroke (TEE/TTE and at least 24-hour ECG monitoring test)

In general: CEA/stenting usually within a few days after symptom onset
- for high-grade asymptomatic stenosis and potentially symptomatic medium/low-grade stenosis consider plaque imaging (ultrasound, plaque MRI) and consider information for revascularisation
- **always high-dose statin therapy, for antiplatelet aggregation therapy see below**
- Decision CEA or CAS should be taken in an interdisciplinary board

ICA stenosis extracranial	<u>in case of CEA, elective</u>: •normally pre- and postoperative aspirin 100 mg or clopidogrel 75 mg monotherapy (stroke occurrence under aspirin or clopidogrel: consider aspirin 100 mg + clopidogrel 75 mg perioperatively) •in case of additional atrial fibrillation, as long as OAC is possible (depending upon infarct size): begin aspirin 100 mg 1 d preoperatively, therapeutic heparinization until surgery. After surgery: 7 d aspirin 100 mg + prophylactic heparin, then stop aspirin/heparin and begin (D)OAC
	<u>in case of stenting, elective</u>: •preinterventional aspirin 100 mg + Ticagrelor 90mg or clopidogrel 75 mg (possibly loading dose); postinterventional DAPT for at least 6 months (depending on stent type, result after stenting, follow up results), then monotherapy •in case of additional atrial fibrillation, as long as anticoagulation is possible (depending upon infarct size): normally N(OAC) + aspirin 100 mg; start aspirin at least 1 day before intervention
	<u>In case of CAS (stenting) during acute intervention:</u> •Aspirin 250–500 mg i.v. during stenting, control imaging afterwards for exclusion of bleeding, then start Clopidogrel, 75 mg (preferably without loading or loading with only 150 mg) •In case of hemodynamic dependence on the stented vessel: early control imaging after 2-6 h to rule out bleeding, then clopidogrel OR ticagrelor (whenever possible with loading after weighing up the benefit/risk) •I f there is a tendency to reocclusion or thrombus formation in the angio: DAPT loading via gastric tube and temporary Integrilin perfusor OR Cangrelor i.v. (loading Ticagrelor, then stop Cangrelor)
	In case of apposition thrombus: Stenosis > 50%: CEA/CAS as early as possible, consider transient therapeutic heparinization (1st choice LMWH) + statin high dose (for example, atorvastatin 80 mg) Stenosis > 50%: therapeutic heparinization (1st choice LMWH) + statin high dose; control MRI after 2 and 7 days; CEA/CAS in case of new ischaemia or persistent thrombus; in case of decrease of thrombus, consider conservative treatment
Stenosis of vertebral artery origin	Stenting normally only in cases of failure of best medical treatment (including transient therapy with aspirin + clopidogrel) preinterventional aspirin 100 mg + clopidogrel 75 mg (possibly as loading dose) postinterventional aspirin 100 mg + clopidogrel 75 mg usually for 12 months with drug-eluting stents, otherwise 6 months; then monotherapy
Intracranial artery stenosis	Aspirin 100 mg + clopidogrel 75 mg for 3 months, then de-escalate to monotherapy + statin at a high dose (for example atorvastatin 80 mg) Stenting should be performed only in exceptional cases and after failure of medical therapy

Arguments for and against CEA/CAS

	CEA	CAS (Stenting)
Anticipated interventional risk	individually	individually
Technical access	individually	individually
Malcompliance	pro CEA	
Prothrombotic status	pro CEA	
Bleeding tendency, previous bleeding under antiplatelet therapy	pro CEA	
Appositional thrombus with floating parts	pro CEA	
Severe renal insufficiency	pro CEA	
Indication for (D)OAC with **low embolic risk** when paused	pro CEA	
Indication for (D)OAC with **high embolic risk** when paused		pro CAS
Contralateral recurrence paresis		absolute indication
Contralateral carotid occlusion		pro CAS
Re-stenosis after CEA/CAS		absolute indication
Post-radiation stenosis		absolute indication
Mechanical heart wave		pro CAS

Dissections

- According to current data the preventive effects of aspirin and OAC are probably comparable. Primarily consider anticoagulation in: a) dissection with cerebral ischemia, b) no vascular occlusion and c) early onset <7d after initial manifestation
- OAC is generally contraindicated in the case of intradural dissections or dissections extending intradurally (elevated risk for SAH)
- In the case of uncertain diagnosis with fat-suppressed T1 sequences in MRI: extend to regular diagnostic work-up after stroke
- Off-label use of DOAC can be considered in individual cases

- Duration of secondary prevention with aspirin/OAC: switch from OAC to aspirin after 3–6 months; Continuation of ASA 100mg/d as long-term prophylaxis as an individual case-by-case decision based on vascular status (continue in case of persistent vascular pathology) and other benefit/risk constellation

Hyperperfusion syndrome

-after revascularization of haemodynamically relevant stenosis there is a danger of hyperperfusion syndrome
- risk factors: high grade stenosis, bilateral stenosis, perioperative hypertension, diabetes, female sex, age > 75 years, reduced reserve capacity
- clinically: headache, seizures, neurological deficits; risk: intracerebral haemorrhage
- occurrence 12 h–7 d after revascularization
→ therefore BP should normally be kept at < 140/100 mmHg postoperatively/postinterventionally
- in case of pronounced oedema poss. additional dexamathasone

Cerebral vasculitides

1 History

- B-Symptoms, recent infections
- Headache *thunderclap, temporal/occipital pain*
- Visual, hearing impairment, eye-pain sicca symptoms
- Oral/genital aphthae, sinusitis/epistaxis, asthma/cough
- Reynaud, arthralgia, skin changes
- Previous illnesses – *lymphoma/leukaemia*
- Immunosuppression *Diabetes, HIV, immunodeficiency*
- Medicaments *e.g. checkpoint inhibitors*
- Drugs *especially cocaine and amphetamines*
- Foreign travel/contact with animals/unpasteurized milk
- Family History

2 Status

- General internal status
- Auscultation over all large vessels
- Palpitation of temporal arteries
- Blood pressure at all extremities
- Skin: *livedo, nailfold bleeding, distal emboli, angio keratoma*
- Joints: *redness, swelling, pressure sensitivity, hyperelasticity*
- Eyes: *visual acuity, ocular fundus*
- ENT: *hearing test, Weber-/Rinne*

3 Blood

- BSR, CRP, differential blood count, LDH, CK, liver, kidney, ferritin, calcium, TSH, immune fixation + free light chains in serum, IgG/M/A
- Coagulation status including fibrinogen, D-dimer, lupus anticoagulant
- RF IgM, CCP, ANA, ANCA, SS-A, SS-B, dsDNA, cardiolipin-/beta-2-glycoprotein-IgM/IgG, C3/C4
- Urine drug screening
- Infectious serology: HIV, hepatitis B, C, syphilis, VZV, quantiferon test (before starting steroids, otherwise ELISpot)
- If there is fever or increased CRP: 3x2 blood cultures (endocarditis scheme)

4 CSF

- Standard including IEF
- Cytology
- If necessary, flow cytometry with CD4+/CD8+ quotient and haemat. Immune cell phenotyping
- BioFire, CXCL13, liquor-/serum index for borreliosis, VZV, HSV (consider eubacterial/panfungal PCR)
- Preserve 3 spare tubes (in case of suspected tuberculosis one tube with 10 ml)

Urine

- Urine status, protein/albumin/creatinine quotient
- in case of hematuria (WARNING bladder catheter) if necessary, urine sediment by nephrologist

5 Additional examinations

- MRI with dark blood- and T1 space sequences, perfusion
  → if inconclusive: cerebral angiography
- nvUS intra– and extracranial vessels
- >45 y or ANCA+ : including temporal arteries; large vessel involvement → arm arteries
- TEE
- CT thorax (abdomen/pelvis if B-symptoms)
- Consult ophthalmology: *If necessary fluorescence angiography , OCT angiography, vitreous puncture*
- If necessary, consult rheumatology
- If necessary, consult infectiology eubacterial/panfungal PCR, next generation sequencing
- Whole body PET in case of unclear large vessel affection /suspicion of sarcoidosis, lymphoma, small vessel vasculitis

6 Biopsy CNS

(diagnosis confirmed in 10–30%, alternative diagnosis in 30–50%)

- Early pause of antiplatelet agents
- target region: contrast enhanced non- eloquent areas; otherwise frontal lobe in non-ischemic area
- sample: meninges + cortex + white matter
- Analysis incl. bacteriology for detecting acid-fast rods, PCR mycobacteria, bacteria, fungi, in case of suspicion, also virus PCR

Biopsy other body regions

Evaluation before CNS biopsy *(eye, temporal arteries, nasal mucosa, lymph nodes, skin, muscle, nerve, kidney, lung, liver, bone marrow)*

Note: Small vessel vasculitis can only be detected with biopsy (MRA and DSA negative)

Radiologically suggestive: multiple ischaemias (WARNING DD emboli, coagulopathy, intravascular lymphoma, MELAS, etc.).
Clinically suggestive: clinical findings clearly exceeding the detected ischemia.
WARNING DWI lesion without perfusion deficit → lymphoma?

DD cerebral vasculitides

Primary cerebral vasculitis (PACNS)

(no pathognomonic clinical or paraclinical signs)

- **Clinic** headache (60%), cognitive deficits (50%), seizures (15%), rarely B-Symptoms
- **Blood** Elevated inflammation parameters (< 25%), otherwise normal
- **CSF** Pleocytosis (50%), protein elevation (70%), intrathecal IgG
- **Radiology** ischemic lesions, hemorrhagic lesions(10%), contrast-enhancing lesions (30%), meningeal contrast enhancement (20%), arterial stenosis in MRA (55%) resp. DSA (75%)

Systemic vasculitis/inflammatory disease

- **Takayasu's arteritis:** < 50 years. Carotidodynia, brachial claudication, visual disturbance (retinopathy) → rheumatism (US of the large vessels), MRA thorax/abdomen or PET-CT (before steroid administration)
- **Giant cell arteritis:** > 50 years. B-symptoms, AION/ZAV, temp./occipital headache, intermittent claudication, arthralgia → rheumatism (US temporal artery and large vessels), MRA thorax/abdomen or PET-CT, biopsy temporal artery (before steroids)
- **Polyarteriitis nodosa:** HBV/HCV, B-symptoms, neuropathy/myalgia/CK ↑, arthralgia, palp. purpura/livedo, abdominal sulfamethoxazole, NI (no glomerulonephritis), microaneurysms → ANCA neg., abdom. angiography (aneurysms)
- **Kawasaki syndrome:** children, adolescents, fever, conjunctivitis/uveitis, mucous/skin changes, lymphadenopathy → clinical criteria
- **Granulomatosis with polyangiitis:** hypertrophic pachymeningitis, pituitary gland, cranial nerves/neuropathy/ mononeuritis multiplex, sinusitis/otitis media, pneumopathy, kidneys (RPGN) → ENT (biopsy NNH), lung (Lufu), kidney (urine sediment)
- **Microscopic polyangiitis:** neuropathy/mononeuritis multiplex, livedo/palp. purpura, kidneys (GN), pneumopathy → nephro. (urine sediment)
- **Eosinophilic granulomatosis with polyanglitis:** mononeuritis multiplex, AION, sinusitis/otitis media, asthma, skin (subcutaneous nodules/ulceration/petechiae), kidneys (GN), eosinophilia → lab. (IgE), ENT (biopsy), lung (BAL, biopsy), kidney (urine sediment)
- **Cryoglobulinaemia**: haematological disorder (monoclonal Ig, MGUS, CLL, myeloma), chronic infection (HIV, HCV, HBV), autoimmune disease (SLE, Sjögren, RA); neuropathy, nephropathy, purpura → lab. (cryoglobulin)
- **IgA-vasculitis (Henoch-Schonlein purpura)** recurrent infection, purpura, arthralgia, abdominal pain, kidneys (GN) → IgA (elevated 50–70%), kidneys (urine sediment), biopsy skin/kidney if necessary
- **Goodpasture syndrome (anti-GBM disease)** kidneys (GN), alveolitis → lab. (Anti-GBM antibodies), kidneys (urine sediment), if necessary skin/kidneybiopsy
- **Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis):** uveitis, urticaria, arthralgia, pneumopathy, abd. pain, kidneys (GN), → lab. (C1q/C3/C4), nephro. (urine sediment)
- **Behçet's disease**: brainstem, thalamus/basal ganglia affected, optic neuritis, CSF pleocytosis, thrombosis, oral/genital ulcers, (pan-)uveitis, skin lesion, arthritis → laboratory (HLA B51, Il-6)**,** rheumatology (pathergy test)
- **Cogan's syndrome:** Eye redness/pain (interstitial keratitis), hearing impairment/vestibular symptoms, aortitis, recent infection/vaccination → ophtha, ENT (audiometry), neurootology
- **Rheumatoid arthritis:** (hypertrophy) meningitis, (compression) neuropathy, stiffness/polyarthritis, subcutaneous (+ cerebral) rheumatoid nodules, skin (palpable purpura, ulcer), → lab. (RF/CCP), rheumatology (ultrasound, puncture)
- **Sjögren's syndrome:** Neuro/ganglionopathy, HN, meningitis, myelitis, MS mimic, sicca symptoms, arthralgia/mylagia, skin (palpable purpura), kidneys (TIN) → lab. (cryoglobulin), rheumatology (Schirmer-/Saxontest, ultrasound parotid, biopsy)
- **Sarcoidosis: Cranial nerves**, Pachyleptomeninges, pituitary gland, med. lymphadenopathy, eosinophilia, CSF Glu ↓Lac↑, → ACE, Vit. D, PTH, Ca+, CSF (sIL-2R, lysozyme, CD4+/CD8+-index), CT thorax, pneumo. (BAL with CD4+/CD8+-Index), PET-CT
- **IgG4-associated disease:** pachymeningitis, orbita, pituitary, neuropathy, periaortitis/arteritis, pancreas, salivary/gland → lab. (IgG4; 30% normal), biopsy of affected organ
- **Deficit of adenosine deaminase-2 (DADA2):** adolescence, similar to c-PAN, skin, immunodeficiency (IgM↓), anaemia/

DD Cerebral vasculitides

Infectious diseases

- **Mycoplasma pneumoniae:** pneumonia, maculopapillary erythema, high erythrocyte sedimentation rate, haemolytic anaemia → *M. pneumoniae* PCR from TBS/CSF and serology, cold agglutinins
- **Bartonella henselae (cat scratch disease):** cats, fever, lymphadenopathy, neuroretinitis, → Bartonella henselae serology (low specificity) and PCR (low sensitivity)
- **Tropheryma whipplei** farmers, GI symptoms, arthralgia, lymphadenopathy/B symptoms, myorhythmias/ supranuclear gaze palsy → T. whipplei PSA staining and PCR CSF (PCR duodenum if necessary)
- **Rickettsial fever (Rocky Mountain spotted fever):** N-/M-America, fever, headache, petechial rash, anaemia/ thrombocythemia/DIC → → serology
- **Leptospira:** contact with rats/mice/farm animals, field work/farmers, fever, kidney/liver involvement → serology
- **Brucella (Mediterranean fever)** raw milk/livestock, meningo-encephalitis, cranial nerve involvement, fever -> serology/SAT in serum and CSF
- **Fungi:** Immunosuppression, aneurysms ICA, CAW), perforator strokes → galactomannan/1,3-beta-D-glucan in serum, BAL; culture from CSF; broad-spectrum PCR for fungi (panfungal PCR) if necessary (Unispital Zürich or Basel)

Other

- **Aβ-related angiitis (ABRA)/CAA-related inflammation (CAA-ri):** Rapidly progressive dementia, marked leukoencephalopathy with enhancement, microbleeds/superficial siderosis → amyloid staining in biopsy

Vasculitis Mimics

with vascular changes in imaging

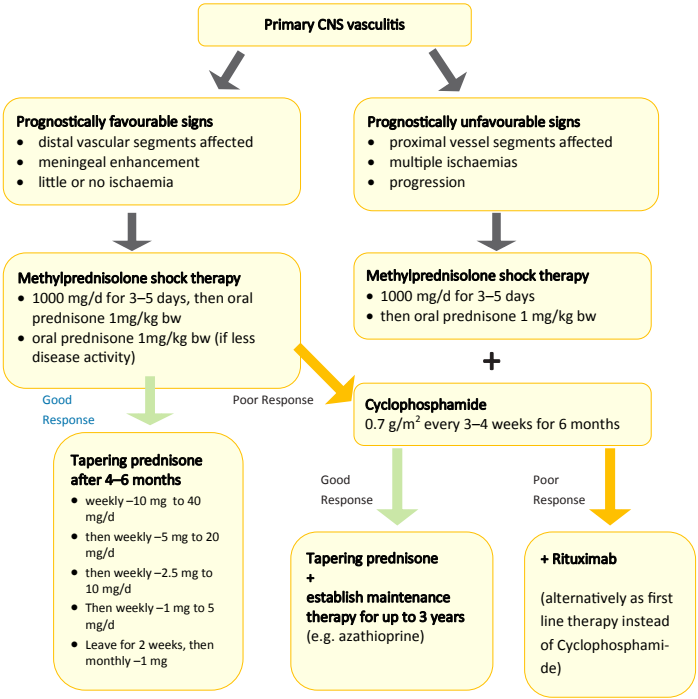
- **Atherosclerosis:** large/medium vessels, vas. RF, CHD/peripheral arterial occlusive disease, normal CSF (NPV 80–95%), Asian origin, WARNING: also contrast agent-enhancement in MRI
- **RCVS**: see own chapter
- **Vasospasm:** e.g. drug-associated, SAH-associated
- **Intravascular lymphoma (granulomatous cerebral vasculitis):** DWI dysfunction without perfusion deficit, lymphadenopathy, B-symptoms, history → (intravascular) lymphoma → flow cytometry in serum and CSF (often unremarkable!), EBV serology and PCR, MRI spinal axis incl. cauda equina
- **Radiogenic Vasculopathy**
- **Fibromuscular dysplasia, Marfan-/Ehlers-Danlos Syndrome**
- **Divry van Bogaert-Syndrome, Sneddon's Syndrome** Livedo racemosa
- **Moya-Moya disease**

without vascular change in imaging

- **Endocarditis:** fever, CRP-elevation, stigmata, microbleeds → BK 3x2 incl. HACEK group; if no pathogen Coxiella brunetti and Bartonella henselae; if aseptic (SLE?)
- **Multiple sclerosis/NMOSD/ADEM**
- **Posterior reversible encephalopathy syndrome (PRES)**
- **Lymphoma/glioma**
- **Susac syndrome:** Encephalopathy/CSMZ, sensorineural hearing loss, visual impairment/arterial branch occlusion, corpus callosum/periventricular lesions, leptomeningitis → ophtha. (fluorescence angio, OCT-A), ENT (audiometry)
- **Erdheim Chester disease**
- **Fabry disease**
- **CADASIL:** Migraine with atypical aura, CVI/TIAs, Leukoencephalopathy (temporopolar, capsula externa)/lacunae before age 40 years → CADASIL → NOTCH3-gene
- **RVCL (autosomal dominant retinal vasculopathy with cerebral leukodystrophy):** Retinopathy CVI/TIA, leukoencephalopathy, migraine, renal insufficiency →TREX 1-gene
- **HERNS (hereditary endotheliopathy with retinopathy, nephropathy, and stroke)**
- **COL4A01-mutation**

Primary CNS Vasculitis – Treatment

NOTE if clinically stable and biopsy negative, consider waiting without therapy and scheduling short-term follow-up



Cyclosphosphamide scheme

Strict verification of the indication

- confirmed CNS vasculitis or highest degree of suspicion despite negative biopsy (PACNS, severe inflammatory cerebral amyloid angiopathy ABRA / CAA-ri)
- CNS / PNS involvement in the context of systemic vasculitis, if without specific therapy

Pre-treatment work-up

- Absolute contraindication: allergy, pregnancy / lactation, severe bone marrow depression, acute infection, severe urinary obstruction; relative: treated HIV, chronic Hep B, latent TBC, previous immunosuppressive therapy, etc.
- Declaration of consent from the patient / relatives
- Risk of infertility: conservation of egg cells (not immediately possible) / sperm, consider GnRH agonist in cooperation with gynecology? Contraception guaranteed up to 6 months after the end of CYC (M and F)
- Clarification of vaccination status / latent infections: HIV, Hep B / C, VZV; HPV in patients with SLE <30Y; possibly TB (quantiferon test), syphilis, malaria, strongyloides, schistosomiasis, etc. for longer stays / origin from risk area / risk profile
- Vaccinations:
  - Renewal of regular vaccinations; usually pneumococcal vaccination (Prevenar13 once before the start of immunosuppression), if necessary Hep B according to the rapid scheme (d1, d7, d21 or 3rd vaccination after the end of CYC / before further immunosuppression, especially rituximab)
  - Recommendation for influenza vaccination for patients and close family members once a year
  - Live vaccines (MMR, VZV, yellow fever, oral typhoid): only up to 4 weeks before immunosuppression (and from 6 months afterwards)!
  - Vaccination of those close to the patient, if the patient cannot be vaccinated (especially MMR, VZV, pneumococcus, influenza)
- Prophylaxis Pneumocystis jiroveccii pneumonia with Trimethoprim f. 3x / week (if intolerance Dapsone or Atovaquone); if necessary, therapy for latent Hep B, TB, Strongyloides etc. in consultation with Infectious Diseases
- Laboratory: blood count with differential, CRP, transaminases, creatinine, urine status, pregnancy test if necessary, IgG subclasses
- Chest X-ray (TB)
- ECG (QTc for concomitant medication ondansetron)
- with suspected urination disorder residual urine, due to bladder toxicity from CYC!
- Important: interaction test (especially allopurinol, phenytoin, insulin / antidiabetic drugs, etc.)
- definition of parameters for follow-up assessment (clinical scores including neuropsychology, CSF, MRI / vasculitis sequences, DSA)

Dose / administration

DGN-Scheme for PACNS / ABRA (= Mayo Clinic / Austin scheme)

- Dose: CYC 750 mg/m^2 body surface; maximal dose per infusion: 1200 mg
- Time interval: every 4 weeks for a duration of 6 months
- no official scheme for dose adjustment to age and renal function

Cyclops scheme (ANCA-associated vasculitis, if therapy with RTX is not preferred)

- Dose: CYC 15 mg/kg body weight; maximal dose per infusion: 1200 mg
- Administration pulse 1-3 every 2 weeks, then every 3 weeks
- Dose adjustment for age> 60Y and creatinine> 300 µmol / l (Appendix)
- Dose adjustment of further doses depending on the leukocyte nadir:
  - Leukocyte nadir 1-2G / l: dose reduction by 40%
  - Leukocyte nadir 2-3G / l: dose reduction by 20%

Controls / further pulse therapies

Controls: Laboratory: Day 10-14: blood count with differential («Leukocyte nadir»), CRP, transaminases, creatinine

For every sequential pulse:

- Anamnesis: infection / cystitic complaints / hematuria; Laboratory: blood count with differential, CRP, creatinine, urine status, pregnancy test?
- Indication for interruption of therapy with cyclophosphamide:
  - Hematology: leukopenia <3000 / µl, granulopenia <2000 / µl, thrombopenia <100,000 / µl; aplastic anemia (distinguished from inflammatory and bleeding anemia)
  - Urology: non-glomerular hematuria / cystitis
- Documentation of the cumulative CYC dose in the diagnosis (increase in carcinogenicity, risk of hemorrhagic cystitis; maximum cumulative dose 20g)

Re-evaluation

- Usually after 6 months aim for remission-maintaining therapy with alternative immunosuppression (e.g. azathioprine, methotrexate, rituximab); Avoid cyclophosphamide therapy > 12 months or cumulative dose of 25g.

Reversible Cerebral Vasoconstriction Syndrome

Symptoms

- typically thunderclap headache (in about 65%, sometimes with nuchal onset and then spreading to biparietal), lasting minutes to hours, rarely days; often persistence of a milder headache thereafter
- often accompanied by nausea, photophobia, phonophobia
- depending on severity, neurological deficits, epileptic seizures

Typical triggers

- Sex, pressure, coughing, sneezing, urinating, bathing/showering, swimming, laughing, cannabis, cocaine, excess alcohol

CSF

- Cell count increase and protein increase possible → follow-up after 2 weeks

MRA/CTA/DSA

- typically: diffuse vasoconstriction: although it can still increase over a period of weeks (almost complete) reversibility occurs within 12 weeks.

Diagnostic criteria

- acute and severe headache, often thunderclap headache with/without focal deficits or epileptic seizures
- monophasic course without new symptoms after >4 weeks
- segmental vasoconstriction in CTA/MRA/DSA
- no aneurysmal SAH
- CSF normal or cell count <15 or protein <100 mg/dl
- complete or almost complete normalization of vasoconstriction within 12 weeks

$RCVS_2$ score ≥ 5: PPV 98% NPV 67% sensitivity 94% specificity 86%

Use only in patients aged 18-55 years with new onset intracranial arteriopathy to differentiate RCVS from other causes

	Yes	No
Repeated or singular thunderclap headache	5	0
ICA intracranially affected	-2	0
Vasoconstrictive trigger present	3	0
Female sex	1	0
Subarachnoid haemorrhage	1	0

Complications

- Convexity SAH (non-aneurysmal)
- ICH
- Ischemias, especially watershed infarcts
- Reversible encephalopathy syndrome
- Brain edema

Therapy

- No established treatment; consider: nimodipine, verapamil, magnesium sulfate

Cerebral venous and sinus thrombosis

- etiological work-up: infection, coagulation disorder
- **LMWH in therapeutic dosage**: e.g. enoxaparin (1mg/kg bw, 2x/d) (a non-randomized study even showed superiority in respect to efficacy and hemorrhagic complications; especially in patients with congestion hemorrhage)
- **alternatively therapeutic heparinization** (aPTT 1.5-2.5x baseline aPTT)
  particularly in patients with risk of craniectomy; **switch to OAC in the course of time**
- alternatively Dabigatran can be considered

CAVE: anticoagulation is a relative contraindication in Behçet's disease

- continue therapeutic heparinization/LMWH also after occurrence of congestion hemorrhages
- IVT or mechanical recanalization in exceptional cases or in studies (e.g. TO-ACT)
- in case of large hemorrhagic infarctions and impending lateral herniation: decompressive craniectomy as early as possible without removal of hematoma or infarcted tissue

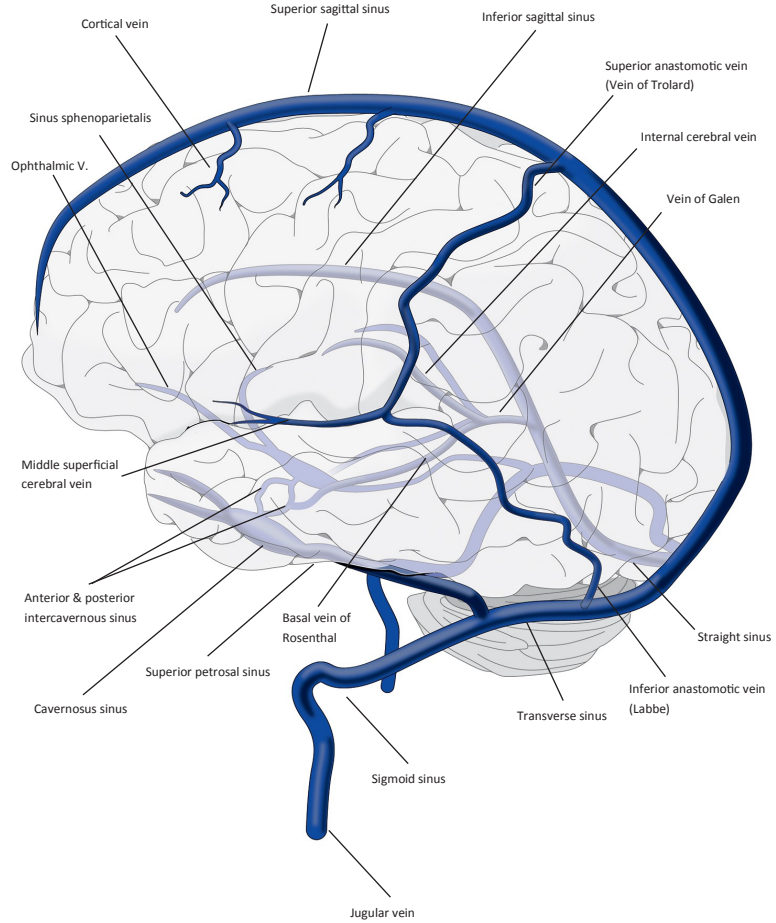
- **Smoking cessation! Discontinuation of estrogen-containing contraceptives**
- **Duration of OAC 6 months** (except in case of progressive thrombosis at follow-up MRI or known thrombophilia)
- Usually examination for coagulation disorders after stopping OAC

Therap. heparinization unfractionated heparin

- **complete baseline coagulation status before start of therapeutic heparinization**
- if baseline aPTT is abnormal (normal: 26-37sec) or in case of extensive thrombosis, consult a hematologist and control anti-factor-Xa-activity (aim 0.3-0.6 U/ml)
- usual aPTT aim: 1.5-2.5x baseline aPTT
- strictly check thrombocytes every 2 days during the course of therapy (HIT? => 4Ts score)

The following dosage scheme is for patients at the Inselspital with low bleeding risk. Depending on infarct size, the dosage should be reduced individually.

Therapy start		Bolus 60-70 U/kg (max. 5000U) i.v. continuously 12-15 U/kg/h (max. 1000 U/h)	Re-evaluation after 6h
Dose adaption depending on aPTT and Anti-Xa			
aPTT	**Anti-Xa**		
< 35 sec	< 0.2 U/ml	Bolus 40 U/kg Increase infusion rate by 3 U/kg/h	Re-evaluation after 6h
36-45 sec	0.2-0.29 U/ml	No bolus, increaase infusion rate by 1.5 U/kg/h	Re-evaluation after 6h
46-70 sec	0.3-0.7 U/ml	No change	Re-evaluation after 6h, then 1x/day
71-90 sec	0.71-1.0 U/ml	Reduce infusion rate by 1.5 U/kg/h	Re-evaluation after 6h
> 90 sec	> 1.0 U/ml	Pause infusion for 1 h then reduce by 2-3U/kg/h (if aPTT >200sec pause infusion for 2h)	Re-evaluation after 6h


Cortical vein
Superior sagittal sinus
Inferior sagittal sinus
Superior anastomotic vein
(Vein of Trolard)
Sinus sphenoparietalis
Internal cerebral vein
Ophthalmic V.
Vein of Galen
Middle superficial
cerebral vein
Anterior & posterior
intercavernous sinus
Basal vein of
Rosenthal
Straight sinus
Superior petrosal sinus
Inferior anastomotic vein
(Labbe)
Cavernosus sinus
Transverse sinus
Sigmoid sinus
Jugular vein

Secondary prevention

Etiology	First stroke	Re-Stroke → always repeat or escalate examinations for etiology
no reason determined (specially no cardiac embolism source, no symptomatic stenosis)	ASS 100mg or Clopidogrel 75mg or ASS+Dipyridamole Ticagrelor (Brilique®) in case of intolerance to the other agents	Change to Clopidogrel 75mg or ASS+Dipyridamole Ticagrelor (Brilique®) in case of intolerance to the other agents
	Initial therapy: in case of high-risk TIA (ABCD2>3 points) or minor stroke within 24h after symptom onset and NIHSS < 6, small infarct): 4 weeks ASS 100mg + Clopidogrel 75mg (loading 600mg) when hemorrhagic transformation is excluded and individual bleeding risk is not elevated	
	If additionally CHD, peripheral arterial occlusive disease or asymptomatic carotid artery stenosis: rivaroxaban (Xarelto®) 2x2.5mg + ASA 100mg/d instead of aspirin monotherapy, initiate after 3-4 weeks	
valvular AF (Def: AF with rheumatic mitral stenosis)	OAC INR 2-3	1. optimize dosage if neccessary 2. consider OAC INR 2.5-3.5 3. consider OAC + ASS 100mg
symptomatic extracranial carotid stenosis	>50% degree of stenosis: CEA/CAS < 50% with radiologically proven plaque rupture: individual + statin at high dose	< 50% stenosis with radiologically proven plaque rupture: consider CEA/CAS
symptomatic extracranial vertebral artery stenosis	ASS 100mg + 4 weeks Clopidogrel 75mg + statin at high dose Contralateral hypoplasia: consider stenting	Consider stenting if already under best medical treatment, otherwise longer-term DAPT
symptomatic intracranial stenosis	ASS 100mg + Clopidogrel 75mg for 3 months, then monotherapy + statin at high dose	ASS 100mg + Clopidogrel 75mg (duration individually) + statin at high dose + consider stenting if stroke under best medical treatment, argument pro stent: hemodynamic infarcts
Non-valvular AF	**DOAC 1st choice;** Occurrence under sufficient or insufficient OAC: - Clarify compliance and correct intake (take RIV with meals); switch VKA to DOAC - In case of AF diagnosis in the last year, rhythmological consultation and referral to rhythmology for evaluation of rhythm control - Search for competing, non-cardioembolic causes (e.g. carotid stenosis) - No additional ASA in case of occurrence under DOAC except in the short term for symptomatic arteriosclerotic stenoses! - Evaluate LAAO if no other cause (ELAPSE trial)	

Instructions for the initiation of antiplatelet aggregation therapy after ischemic stroke

- in case of conservative treatment: immediately
- after mechanical EVT: usually immediately with loading (250-500mg ASS or 300-600mg Clopidogrel)
- after IVT, Bridging, Urokinase i.a.: after exclusion of bleeding in 24h control imaging
- in case of imminent space-occupying brain edema neurosurgeons should be involved immediately. If a potential craniectomy is considered, no administration of antiplatelets (see separate guidelines).

Instructions for the earliest initiation of (D)OAC after ischemic stroke

cave: assumes exclusion of parenchymal hemorrhage (type 2) & endocarditis, cave sensitivity MRI >> CT
TIA/small to medium-sized infarcts (see right): Onset <48h, possibly later with basal ganglia involvement
Large infarcts (see next page): Start d6, if necessary follow-up CT to rule out bleeding
- No bridging therapy with platelet aggregation inhibitors
- When changing therapy, consider "transient dual therapy" due to delayed loss of effect of previous medication (depending on T1/2)
- Highly embolic source of embolism (e.g. mechanical heart valve): immediate start of (possibly sub-)therapeutic heparinization if necessary, except in the case of very large infarction/bleeding
- In case of relevant hemorrhage (PH1, PH2) in the follow-up imaging, usually start after 10-14d

Myocardial infarction (sub)acute

- consider DOAC application for 3 months also without thrombus finding, esp. with embolic infarct distribution
- stenting in patients with (D)OAC indication → (D)OAC + clopidogrel (consider DOAC low dose in large infarctions), triple therapy in acute stroke only in exceptional cases (esp. in-stent-thrombosis, stent main stem)
  If AF is indication for (D)OAC: consider atrial appendage closure, afterwards only dual antiplatelet therapy
STEMI: Coro immediately; NSTEMI: Coro as soon as clopidogrel + ASS or (D)OAC + clopidogrel is possible (depending on indication); Coro immediately in case of severe arrhythmia, hemodynamic instability, persistent pain

Detection of AF or atrial thrombus in patients taking aspirin + clopidogrel due to coronary stent

DOAC long-term therapy + usually 1 year clopidogrel; during dual therapy consider (transient) DOAC low dose depending on infarct size

Intracardial thrombus

Ventricular: (D)OAC for 3 months, then control TEE and consider change to antiplatelet therapy
Atrial appendage thrombus: DOAC therapy life long also without proven AF

Symptomatic stenosis

see page 18

Coronary heart disease or peripheral arterial occlusive disease + high risk for ischemic events

Consider Rivaroxaban 2x2.5mg + ASS 100mg/d

Severe heart failure with severe hypokinesia/akinesia

No DOAC except in case of intra cardial thrombus (bleeding outweighs benefit). DOAC can be considered for ESUS with restricted EF or regional wall motion disorders.

Infectious Endocarditis

No antiplatelet therapy/heparin/(D)OAC; if valvular replacement is indicated, early operation seems to be beneficial

Pulmonary embolism

DOAC, start depends on infarct size; duration: 6 months in case of unequivocal provocative factors (surgery, immobilization >48h, plaster cast on leg), otherwise long-term therapy;
PFO occlusion in case of long-term DOAC therapy not indicated, otherwise PFO closure also with PASCAL „unlikely“

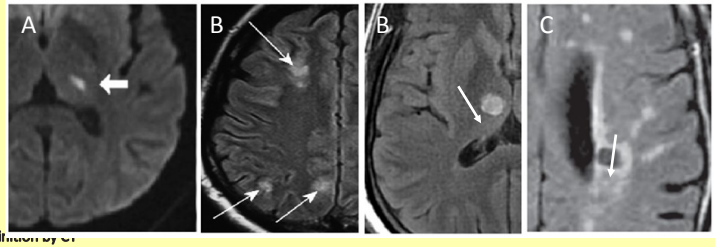
Paraneoplastic Coagulopathy

LMWH therapeutic dosage (2x/d, not 1x/d) or Edoxaban or Rivaroxaban or Apixaban

Covert cerebrovascular disease / brain infarction

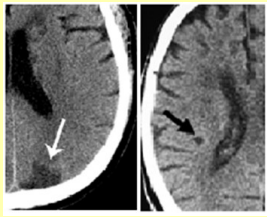
- most frequent incidental finding in CT/MRI (no TIA or stroke suspicious episodes in medical history)
- prevelence dependent on cardiovascular risk profile and age (~30% in people at age 70)
- increased stroke risk and severity, risk for dementia, depression and subclinical deficits

Definition by MRI
- acute or subacute ischemia (see A, p.e. acute diffusion lesion with signal decrease in ADC and without symptoms and without other explanation
- chronic ischemia:
  - T2/FLAIR hyperintense lesion, T1 hypointense lesion non-lacunar (see B)
    - ◊ cerebellar or supratentorial cortical, or
    - ◊ supratentorial subcortical >3mm with location in deep gray matter and without other explanation
  - lacunar lesion (see C): ≥3mm, not corresponding to enlarged perivasculuar space



Definition by CT
- cortical defect zone or lacunar lesion

Incidental SVD/leukoencephalopathy:
incidentally discovered cerebrovascular SVD significantly above the age norm should also lead to cardiovascular work-up and counselling with the aim of optimally controlling the cardiovascular risk factors.



Diagnostics
- screen for vascular risk factors and obtain a comprehensive history of previous cardioaortic interventions
- complete vessel imaging if not already done with initial imaging
- pulse palpation, 12-channel ECG, at least 72h ECG monitoring
- TTE/TEE

Therapy
- optimal risk factor control
- ASS with consideration of risk/benefit profile, other indication for antithrombotic treatment ?
- treatment of blood pressure is the same as in secondary prevention guidelines
- consider treatment of carotid artery stenosis > 60% of the affected vessel after consideration of risk/benefit profile, in case of
  - acute ischemia, or
  - multiple chronic ischemia in the corresponding vessel territory

Direct oral anticoagulants (DOAC)

- indicated in strokes with evidence of non-valvular AF
- in cerebral venous thrombosis and dissection: phenprocoumon/acenocoumarol or dabigatran
- not recommended in anti-phospholipid-antibody syndrome or valvular AF (valvular: rheumatic mitral stenosis)
- in case of known elevated GIT bleeding risk: preferable lower doses of DOAC especially in patients > 75 years

	Factor II-inhibitor	**Factor X-inhibitors**		
	Dabigatran (Pradaxa®)	**Apixaban (Eliquis®)**	**Rivaroxaban (Xarelto®)**	**Edoxaban (Lixiana®)**
General information	CI: Child-Pugh A-C	CI: Child-Pugh C	CI: Child-Pugh B+C	CI: Child-Pugh C
Dose if CrCl ≥ 50 ml/min	2 x 150mg (≥ 80 years: 2x110mg)	2 x 5mg (2 x 2.5mg if two of the following criteria are fulfilled: ≥80 years, ≤60kg, creatinine ≥ 133 µmol/l)	1 x 20mg	1 x 60mg (1 x 30mg if bw < 60kg)
Dose if CrCl 30-49 ml/min	2 x 110mg		1 x 15mg	1 x 30mg
Dose if CrCl 15-29 ml/min	contraindicated		1 x 15mg, control of plasma coagulation recommended	1 x 30mg
Dose if CrCl <15 ml/min	contraindicated	not recommended	contraindicated	not recommended
Inductors (effect diminished) (bold print: contraindication)	**Rifampicin**, St John's wort, carbamazepine	Rifampicin (edoxaban: dosage reduction not necessary), phenytoin, carbamazepine, phenobarbital, St John's wort		
Inhibitors (effect enhanced) (bold print: contraindication)	Verapamil, **ketoconazole**, **itraconazole, voriconazole**, **HIV-protease inhibitors, quinidine, dronedarone, cyclosporine, tacrolimus,** amiodarone	Verapamil, ketoconazole, itraconazole, voriconazole, posaconazole HIV-protease inhibitors		
$T_{1/2}$	12-17h	9-14h	5-9h	10-14h
Set off time before surgery (in agreement with surgeon)	24h up to 72h in case of large operations 4d with CrCl < 50ml/min	24h 48h in case of high bleeding risk, renal failure, elderly patients	24h 48h in case of high bleeding risk, renal failure, elderly patients	24h before 48h in case of high bleeding risk, renal failure, elderly patients

Risk factors

Responsible for 9/10 Strokes	Responsible for 4/5 Strokes	**Hypertension** (>140/90 mmHg)
		Lack of physical activity (< 150min/week moderate or <75 min intensive exercise)
		Overweight (BMI >25, abdominal girth >m:94cm/f:88 cm)
		Unhealthy diet
		Dyslipidemia
		Smoking (incl. pipe, cigars)
		Psychosocial stress
		Alcohol abuse (> 30 drinks/month; f>15g/d, m>30g/d)
		Diabetes mellitus (fasting blood sugar ≥7mmol/l, HbA1c ≥ 6.5%); impaired fasting glucose: 5.6-6.9mmol/l
		Family history (m <55 years, f<65 years)
		Pre-stroke/TIA
		Sleep related breathing disorders
		Chronic renal failure
		Migraine with aura (at least 2 auras in a lifetime)
		Pregnancy
		Atrial tachycardia
		Increased variability in blood pressure
		Cardiac wall motion abnormalities
		Contraception
		Hormone replacement therapy
		Acute infection (esp. influenza)
		Depression

Risk stratification

Risk	Criteria	SCORE2 risk chart
Very high risk	• Previous vascular event: cerebral stroke, myocardial infarction, symptomatic peripheral arterial occlusive disease • Detection of atherosclerotic plaques, silent ischemia • Previous revascularization of an artery • Diabetic patients with end-organ damage (e.g., microalbuminuria) or ≥three major risk factors or disease duration >20 years • Severe renal insufficiency (GFR<30 ml/min./m^2) • Familial dyslipidemia with a risk factor	>10%/10 years
High risk	• 1 poorly controlled risk factor (e.g., LDL cholesterol >4 mmol/L, triclycerides >8 mmol/L, or BP ≥180/110 mmHg) • Familial dyslipidemia without poorly controlled risk factor • Diabetic patients ≥10 years of disease duration, without end-organ damage and without additional risk factors • Moderate renal insufficiency (GFR 30–59 ml/min./m^2	5–10%/10 years
Moderate risk	• Young diabetics (if type 1 diabetes <35 years, if type 2 diabetes <50 years) with a duration of disease <10 years, without other risk factors	1–5%/10 years
Low risk	No criteria met	<1%/10 years

Arterial hypertension

Stepwise drug treatment: Target value after ischemic stroke <130/80 mmHg

1. Monotherapy in: >80 yrs. And/or frail patients, low vascular risk, AH grade 1, high normal blood pressure and high/very high risk
2. Otherwise dual combination therapy, 1st choice ACE inhibitor/sartan+calcium channel blocker or ACE inhibitor/sartan+diuretic; in case of beta-blocker indication (angina pectoris, post myocardial infarction, heart failure, rhythm control): combination of beta-blocker + other antihypertensive (ACE inhibitor, sartan, calcium antagonist, diuretic)
3. Triple combination therapy (sartan + diuretic + calcium antagonist): if max. dose of dual combination therapy is insufficiently effective
4. Spironolactone in the absence of contraindications (including GFR <45 mL/min., potassium >4.5 mmol/L) and insufficiently effective triple combination therapy
5. Alternative/supplementary classes of hypertensives (e.g., alpha-1 blocker) in case of insufficient efficacy of the above-mentioned combinations of antihypertensives, or intolerance

Notes

- Blood pressure variability significantly increases stroke risk → calcium antagonists
- Caution is needed in the case of vascular occlusion and/or high-grade stenoses (if necessary, higher target values/slower decrease)
- All antihypertensives can be combined in any way, except sartans and ACE inhibitors
- GFR <30ml/min.: thiazide diuretics are not effective

Secondary arterial hypertension

Look for in the case of resistance to therapy (especially in patient <75 years, normal weight, healthy lifestyle, absence of diabetes mellitus and/or organ damage due to vascular risk factors)

- Causes: sleep-associated respiratory failure, primary hyperaldosteronism, chronic renal failure, pheochromocytoma, fibromuscular dysplasia, coarctation of the aorta, Cushing's syndrome, Hyperparathyroidism, medications (oral contraceptives, sympathomimetic mucosal decongestant therapy, NSAIDs, cyclosporine, erythropoietin, chronic steroid therapy, chemotherapeutic agents), drugs (cocaine, amphetamines, anabolic steroids), other substances (licorice)

	Systolic	Diastolic	Recommendations
Optimal	<120	<80	-
Normal	120–129	80–84	-
High-normal	130–139	85–89	< 65 years, low/moderate risk: primarily non-drug therapy < 65 years, high/very high risk: drug + non-drug therapy ≥ 65 years: primarily non-drug therapy
AH grade 1	140–159	90–99	<80 years, low/moderate risk: Combined non-drug (focus) and drug therapy < 80 years high/very high risk: intensive drug and non-drug measures ≥ 80 years: primarily non-drug measures
AH grade 2	160–179	100–109	Combined non-drug and drug therapy (>80 years especially with good AZ)
AH grade 3	≥ 180	≥ 110	Combined non-drug and drug therapy (>80 years especially with good AZ)
Isolated systolic AH	> 140	and < 90	Non-drug therapy + regular check-ups

Dyslipidemia

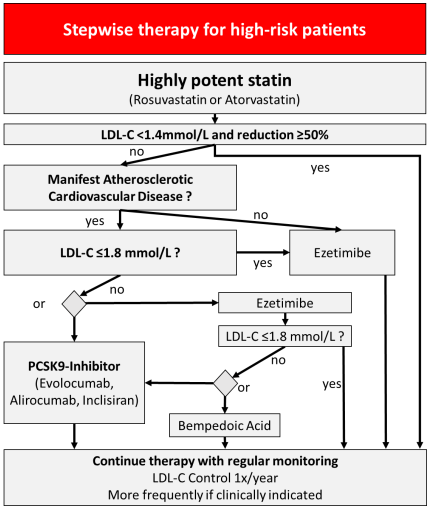
CAVE Important note on individualized therapy

The treatment of dyslipidemia and the application of the scheme below requires a correct pre-selection of patients. Patients without arteriosclerosis and with dissection, confirmed paradoxical embolization, iatrogenic strokes, etc. do NOT require mandatory statin therapy. In these cases, the indication should be based on the criteria for primary prevention (not listed here).

General

- For every 1 mmol/L increase in total cholesterol, relative risk of ischaemic cerebral infarction increases by 25%
- In cerebral infarction associated with atheromatosis, achievement of a target LDL cholesterol <1.8 mmol/L shows a better prognosis than a target of 2.3–2.8 mmol/L
- For symptomatic/multiple stenoses/significant atheromatosis of the aorta: usually a high dosage (e.g. atorvastatin 80 mg), target LDL value: < 1.4 mmol/L
- *Rosuvastatin, Pitavastatin, Atorvastatin **Evolocumab, Alirocumab, Inclisiran

See AGLA Pocketguide Prävention der Atherosklerose 2023



Vascular risk:	Low	Moderate	High or arteriosclerosis detected	Very high or symptomatic stenosis
LDL	**Target <3mmol/L**	Target <2.6mmol/l	Reduction of baseline value by >50% Target <1.8 mmol/L	**Reduction of baseline value by >50%.** **Target <1.4 mmol/L**
Non-HDL cholesterol (TG-HDL)		Target <3.4mmol/L	Target <2.6mmol/L	Target <2.2mmol/L
TG	Target <1.7 mmol/L			

Diabetes mellitus

General

- Recommended target value of HbA1c <7%
- Avoid hypoglycaemia, as it increases vascular risk
- Target value of blood pressure in patients with diabetes: <65 yr <130/80 mmHg, >65 yr <140/80 mmHg
- in case of high/very high risk (see below): aspirin 100 mg/day possibly already part of primary prophylaxis

Risk stratification in patients with diabetes

Very high risk: Diabetes mellitus + vascular clinical event or organ damage that has already occurred, or >3 other vascular risk factors, or type 1 diabetes mellitus with a duration of >20 years
High risk: Duration of disease >10 years without organ damage but with at least one additional vascular risk factor
Moderate risk: Young patient with diabetes mellitus type 1, and <50 yr for patient with diabetes mellitus type 2, with short duration of disease (<10 years) and no other vascular risk factors

Non-medical: weight reduction, Mediterranean diet, physical activity, smoking cessation

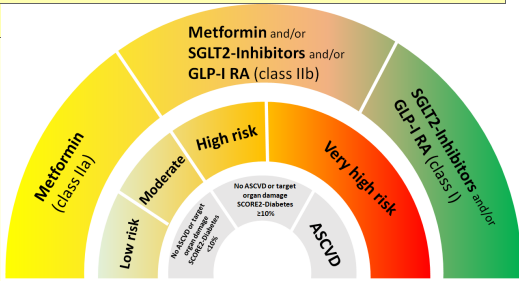
Medications

Metformin additionally for (very) high cv risk if required for glucose control

LDL targets for diabetes
- Very high risk: <1.4mmol/L
- high risk: <1.8mmol/L
- moderate risk: <2.6mmol/L

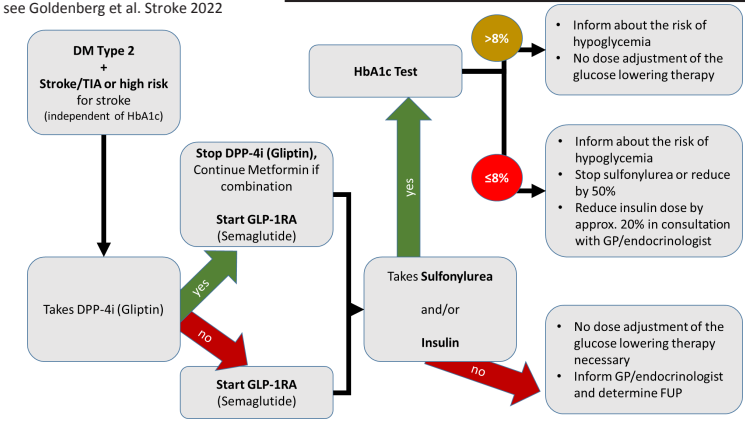
Finerenone Kerendia®
for impaired renal function
to delay progression.

GLP1-RA for overweight patients even if no other indication (DM2)



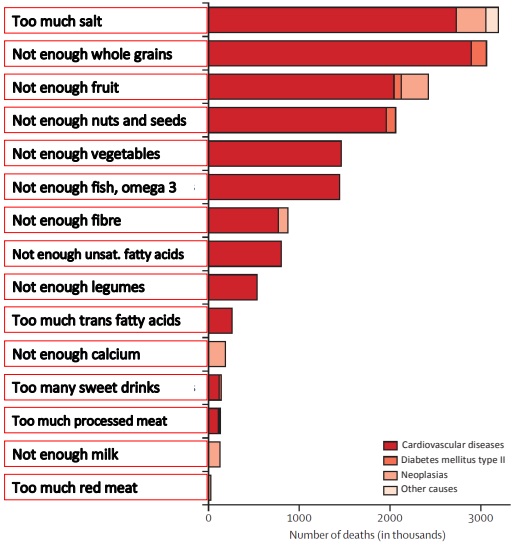
Risk stratification for DM2 according to presence of atherosclerotic cardiovascular disease (ASCVD), target organ damage and 10-year risk; see Marx et al. EHJ 2023

see Goldenberg et al. Stroke 2022



Diet

- **Recommendation**: consumption of fresh fruits, vegetables (the more the better, i.e. ≥3 servings/day). ≥5 servings: risk reduction 26% (RR 0.74; 95% CI 0.69–0.79; p <0.0001). 3–5 servings: risk reduction 11% (RR, 0.89; 95% CI 0.83–0.97; p = 0.005).
- Beneficial effect of **Mediterranean diet** (consumption of legumes, whole grains, low-fat dairy products, fish, unsaturated fatty acids e.g. olive oil): risk reduction 44%
- Beneficial effect of **DASH diet** (low-fat diet rich in minerals, vitamins and whole grains): risk reduction 25%
- **Salt consumption** <5 g/day; reduction by 1 teaspoon/day: risk reduction 30%
- Consumption of **coffee** has probably a beneficial effect (U-shaped curve for association with risk of stroke, max. 3–4 cups/day associated with 17% risk reduction)
- Consumption of **tea** (green and black) has probably a beneficial effect (risk reduction of 13% with intake of 3 cups/day)
- Consumption of dark **chocolate** has probably a beneficial effect
- Max. **alcohol** consumption <14 units/week for men and <8 units for women (1 unit=250 ml beer or 125 ml wine); avoid binge drinking.
- Avoid drinks with refined sweeteners
- Unfavourable effect of saturated fatty acids
- Questionable or very small unfavourable effect of red meat



Adapted according to GBD 2017 Diet Collaborators. Lancet

Body weight

- Target BMI <20–25kg/m^2
- Target abdominal circumference: men: < 94 cm, women: < 80 cm
- Stroke mortality increases by 40% per 5 kg/m^2 increase in BMI

Smoking

- Smoking cessation: medical counselling, self-help interventions, group behavioural therapy, telephone counselling, medications (e.g., varenicline, alternatively bupropion, clonidine) are effective
- For addresses of advisory centres see www.stop-tabak.ch

Ambulatory support programme

- Consider enrolling patients into ambulatory support programmes for secondary prevention

Chronic coronary heart disease and heart failure

Chronic coronary heart disease:
- ASA 100mg/d + rivaroxaban 2.5mg 2x/d if no increased risk of bleeding
- GLP1-RA in CHD and type 2 diabetes
- SGLT2 inhibitors in LVEF <41% even without DM2
- no long-term beta-blocker therapy

Heart failure (reduced EF): sacubitril/valsartan (Entresto), beta-blockers (carvedilol), spironolactone, SGLT2I
Heart failure (normal EF): diuretics (if volume overload), SGLT2I for LVEF <41% even without DM2, spironolactone

Physical inactivity

Physical activity has a beneficial effect on vascular risk factors, has antidepressant effects and promotes smoking cessation

Recommendation: at least 20–60 min. exercise on 3–5/days per week of at least moderate intensity (e.g. walking, jogging, swimming, cycling)
(specific recommendation for high blood pressure: 60–90 min./week, weight reduction: 225–420 min./week, diabetes: 150 min./week)
- 8% of all deaths are related to physical inactivity
- 28% reduction in relative risk of stroke, myocardial infarction and vascular fatality with physical activity (compared to 22% with ASA, 21% with statins, and 21% with antihypertensives)
- Stroke risk reduced by 30% with >40min of moderate/high intensity activity 3–4x/week

Sleep apnoea syndrome

- Screening with respiratory polygraphy
- Treatment with CPAP/APAP/ASV indicated with
  1. AHI ≥ 30/h: send for PAP after discharge
  2. AHI 10-29.9/h: reevaluate PAP after 3 months
  3. AHI ≤ 10/h: only send for PAP if Epworth SS ≥ 10 or NoAS ≥8

Non-traumatic intracerebral haemorrhage (ICH)

Emergency department

Neuro-IMC/ Stroke Unit

depending on OP indication and capacity

Treat fever quickly, Strictly control glucose

ICH consultation

Interdisciplinary Management (neurology, neurosurgery)

- Evaluation of therapy limitations at an early stage
- Positioning: upper body elevation usually at least 30°, otherwise free mobilization
- Discontinuation: antiplatelet agents, (D)OACs and heparins

A B C D Care

A

Reverse **A**nticoagulation	Begin <15 minutes after diagnosis on CT/MRI See next page for the scheme

B

Lower **B**lood pressure if >160/90mmHg	Begin <15 minutes after diagnosis on CT/MRI

Blood pressure target ≤ 140/90mmHg AS SOON AS POSSIBLE

Important: a) Avoid fluctuations of >20% → early perfusor
b) Avoid reduction of >60mmHg in the first hours

- Medication:
  1. Choice: Uradipil (Ebrantil®) 5–10 mg i.v. bolus-wise, 5–40 mg/h via perfusor
  2. Choice: Labetalol (Trandate®) 20–80 mg i.v. bolus-wise, 1–2 mg/min via perfusor, Clevidipin (Cleviprex) 2-16 mg/h (only short term, see page 11)
  3. Choice: Clonidine (Catapresan®) 25–500 mg i.v. bolus-wise

  Avoid: i.v. nitrate derivatives (possible negative effect).

C

Contact neurosurgery	Rapid evaluation by neurosurgeon regarding indication for surgery

- Individual decision on haematoma evacuation in non-basal ganglia haemorrhage with GCS 9-13 (ENRICH).
- No indication for surgery in case of basal ganglia hemorrhage
- Ventricular drainage in the case of cerebrospinal fluid circulation disorder

D

Diagnostics	See work-up algorithm

- Blood pressure measurement on an outpatient basis <130/80 mmHg; instruct patients in self-measurement and documentation (bring findings to consultation), get 24h-RR
- Evaluation/restart of antithrombotics: consultation (see scheme)

3-month check-up	12-month check-up	Annual follow-ups
MRI if not performed in acute phase	Incl. MRI (indication "ICH/ microangiopathy")	• only for selected patients • under OAC according to ICH • high cerebrovascular risk • Individual indications for imaging

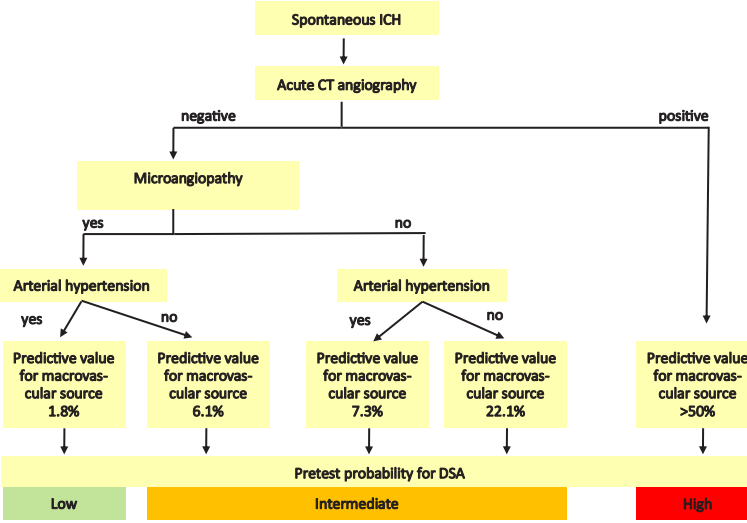
Anticoagulation/antiplatelet-associated ICH

Always: stop antiplatelet therapy/(D)OAC/heparins		
Anticoagulant	**Reversal regimen**	**Note**
Alteplase	See also page 14 **→ Fibrinogen (Haemocomplettan P)** or **Prothrombin complex concentrate** (involve haematology) **→ Tranexamic acid** **(Tranexam OrPha) i.v. 1000 mg over 10 min** **→ blood pressure target ≤ 140/90 mmHg**	**See page 14**
Phenprocoumon and INR >1.3	Prothrombin complex concentrate: 30 IU/kg bw -> check INR (point-of-care) after 15 minutes and re-dose if necessary. + vitamin K: if INR ≥ 1.5 → 10 mg i.v., then dosage depending on INR; onset of drug effect approx. 4-6h	Repeat prothrombin complex concentrate in case of insufficient INR decrease after 15min. Then INR at least 1x/d (and if necessary repeat vitamin K)
Heparin UFH	Protamine sulfate: If Heparin was stopped ≤1h or anti-Xa acitivity ≥ 0.35: 1000 E i.v. (1ml) per 1000 E heparin given during the last 3 hours (max. 5000E); If Heparin was stopped 1–3h before or anti-Xa acitivity 0.15-0.35: 500 E i.v. (0.5ml) per 1000 E heparin given during the last 3 hours (max. 5000E)	Involve haematology; beware of contraindications!
Heparin LMWH	**Andexanet alfa (Ondexxya™):** see below Alternatively Protamine sulfate: Last therapeutic dosage given ≤8h or anti-Xa acitivity ≥ 0.5: 5000 E protamine sulfate Last therapeutic dosage given 8-12h or anti-Xa acitivity 0.3-0.5: 2500 E protamine sulfate	Involve haematology; beware of contraindications!
Xa-Inhibitors Apixaban/ Edoxaban/ Rivaroxaban/	**Andexanet alfa (Ondexxya™):** depending on intake/DOAC dose - low dose: 400mg bolus (30mg/min), continuous infusion 4mg/min over 120 min (480 mg) = 5 vials - high dose: 800mg bolus (30mg/min), continuous infusion 8mg/min over 120 min (960 mg) = 9 vials Prothromplex® (equivalent VKA) as an alternative option	measure anti-Xa of Apixaban/ Rivaroxaban/Edoxaban on admission **cave**: increased risk of ischemic stroke and myocardial infarction with Andexanet, but better effect on hematoma expansion compared to PCC
IIa-Inhibitor Dabigatran	Idarucizumab (2x2.5 g) as specific antidote available	Obtain thrombin time and anti-IIa activity / drug levels on admission
Antiplatelet	No specific treatment	thrombocyte infusion potentially harmful
Thrombocytopenia	Severe thrombocytopenia(<70.000/ml)/severe platelet dysfunction: **consider TC**	
Hemophilia or factor deficiency	Substitution of the coagulation factor after consultation with hematology	

Note: No efficacy in studies: steroids, tranexamic acid, activated Factor VIIa.

Diagnostic algorithm for ICH

1) **Primary imaging in ED with CT or MRI** always with **angiography** – suspicion of macrovascular bleeding cause (AVM, aneurysm, bleeding in SVT, etc.)?
2) **Indication for invasive Angio** (IADSA): interdisciplinary decision neuroradiology, neurosurgery, neurology, structured decision pathway is helpful (see below)
3) **SVD – Small vessel disease**: signs of microangiopathy in CT/MRI (leucencephalopathy, microbleeds)
4) **Follow-up imaging after 24h for evaluation of hematoma expansion** (prognostic marker and quality control)



Wilson et al, European Stroke Journal 2017

Re-initiation of anticoagulatory medication after ICH

- **Heparin for prevention of thrombosis:** LMWH (e.g. Enoxaparin) after follow up imaging after 24h or pneumatic compression stockings
- **Antiplatelet monotherapy** ASS/Clopidogrel: depending on individual risk after follow up imaging earliest 7d after ICH
- **Phenprocoumon for mechanical heart valve**: earliest 7d after ICH in case of high embolic risk, otherwise 14d
- (**D)OAC for atrial fibrillation:** individual decision, consider atrial appendage closure

Microbleeds

- differential diagnosis of incidental „microbleeds“ findings in SWI: prior extracorporeal bypass (ECC), ECMO, thrombus, metastasis, microangiopathy, vasculitis, cerebral amyloid angiopathy
- most frequent origin: microangiopathy
- consider cerebral amyloid angiopathy (see below)

Microbleeds & Antiplatelet therapy/(D)OAC
- Effect of secondary prophylaxis with antiplatelet therapy and (D)OAC outweighs bleeding risk
- Bleeding risk and risk for ischemia rises with number of microbleeds, but risk for ischemia remains higher

Cerebral amyloid angiopathy (CAA)

- Progressive dementia
- Frequently one or multiple small ischemic strokes or microbleeds in follow up images
- Frequently concomitant white matter hyperintensities

MRI: modified Boston criteria 1.5 for age >55 y

Possible CAA
- Singular bleeding lobar, cortical or cortical-subcortical localisation (cerebellar allowed)
- or focal or disseminated superficial siderosis
- exclusion of other causes of ICB

Probable CAA
- multiple bleedings lobar, cortical or cortical-subcortical localisation (cerebellar allowed)
- or singular, cortical-subcortical bleeding and focal or disseminated superficial siderosis
- exclusion of other causes of ICB

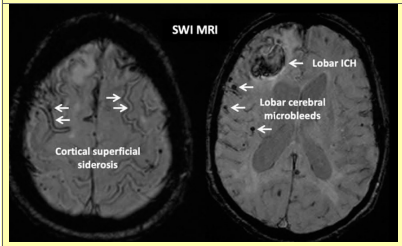
Definitive CAA
- Autoptic proven

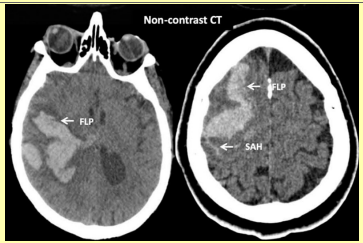
Cave: use Boston criteria only if patient has one of the following:
- cognitive decline
- cerebral hemorrhage
- "spells"

NOT as screening for all MRIs in asymptomatic patients

Boston criteria 2.0: are more sensitive, but less specific (possible overdiagnosis)

CT: Edinburgh criteria
Finger-like projections (FLP): elongated extension from the hematoma (longer than wide)
Subarachnoid hemorrhage (SAH): extension of the bleeding in subarachnoid space





Hostettler, Seiffge & Werring, Expert Rev Neuroth 2019

Amyloid angiopathy & Antiplatelet therapy/(D)OAC
- with probable CAA: stop antiplatelet therapy/(D)OAC ONLY IF no other explanation for CMBs and CAA clinically symptomatic, see above
- consider atrial appendage closure in case of atrial fibrillation
- in case of mehanical waves individual decision (reports of low embolic risk without OAC in some types of valves)

CAA-related Inflammation (CAA-ri)

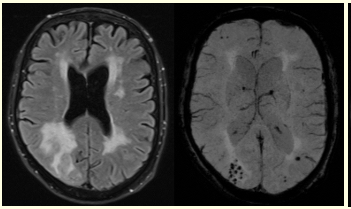
Diagnostic criteria

Possible CAA-ri (if all 5 criteria are met)

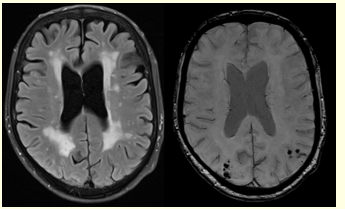
1. Age ≥ 40 years
2. Presence of at least one clinical symptom not directly associated with ICH, consisting of headache, impaired consciousness, behavioural abnormalities, focal neurological symptoms, epileptic seizures
3. MRI showing evidence of hyperintensities in the medullary canal extending to the surrounding subcortical medullary canal
4. Presence of at least one of the following corticosubcortical haemorrhages: cerebral macrohaemorrhage, cerebral microhaemorrhage, cortical superficial siderosis
5. Exclusion of neoplasia, infection, or other genesis.

Likely CAA-ri

1. Age ≥ 40 years
2. Presence of at least one clinical symptom not directly associated with ICH, consisting of headache, impaired consciousness, behavioural abnormalities, focal neurological symptoms, epileptic seizures
3. MRI demonstrating unifocal or multifocal hyperintensities in the medullary (corticosubcortical or deep medullary) bed that are asymmetric and extend to the surrounding subcortical medullary bed (and the asymmetry is not a result of old ICH)
4. Presence of at least one of the following corticosubcortical haemorrhages: cerebral macrohaemorrhage, cerebral microhaemorrhage, cortical superficial siderosis
5. Exclusion of neoplasia, infection, or other genesis



Right occipital asymmetric FLAIR hyperintensity + microbleeds

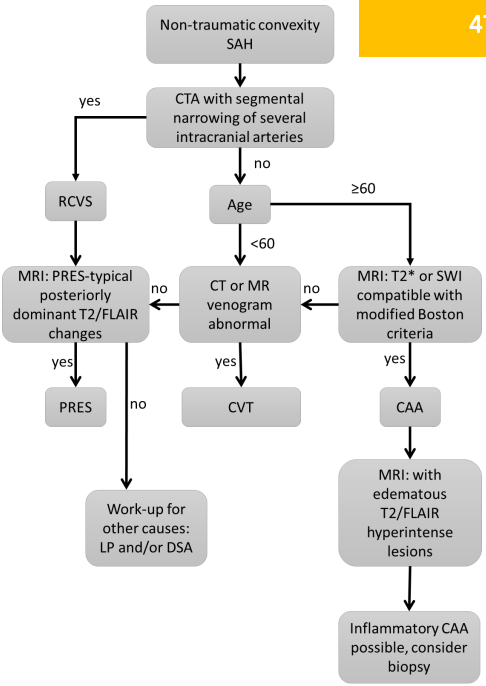


2 months after steroid therapy

Therapy

1. Steroid therapy
   - High-dose therapy with solumedrol 1g/d for 3d, followed by
   - Steroid maintenance therapy prednisolone 1mg/kg bw (under gastric and osteoporosis protection).
2. Additional immunosuppression, insufficient evidence as to which is preferable
   - Cyclophosphamide
   - Mycophenolate mofetil
   - Rituximab
3. Early control with ICH consultant after 4–6 weeks incl. MRI

Algorithm Convexity SAH



	RCVS	PRES	CVST	CAA
Age	<60	<60	<60	≥60
Headache	frequent	frequent	frequent	Rare
Confusion / consciousness alteration	rather rare	frequent	rather rare	rather rare
Seizures	rather rare	frequent	~ 1/3	rather rare
Transient Episodes with focal neurological deficits	rather rare	Unusual	rather rare	frequent
Nausea / Vomiting	rather rare	rather rare	rather rare	Unusual
Visual symptoms	frequent	frequent	rather rare	Unusual
Diagnostic testing				
CT/A/V & MRI/A/V	Caliber irregu-larities	Typical changes	Detection of venous throm-bosis and infarction/ bleeding	Modified Boston Criteria
EEG	usually normal	Frequently altered	usually normal	usually normal
CSF (in addition to Xanthoch-romia)	Frequently normal	Protein increase, pleocytosis occurs	Normal except for congestive infarction or hemorrhage	frequently normal

Monogenic neurovascular diseases

Syndrome/ Abbreviation	Gen, Inheritance	Symptoms	Imaging
CADASIL	NOTCH3, aut.-dom.	Migraine, cognitive problems, depression, epileptic seizures, recurrent stroke ischemic > hemorrhagic	Hyperintensity, emphasized anterior temporal lobe and caps. ext., lacunar infarcts
CARASIL	HTRA1, aut.-rec.	Spasticity, cognitive problems, alopecia, back pain, spondylosis, recurrent stroke ischemic > hemorrhagic	WMH
Fabry	GLA X-chrom.	Episodes of pain in hands and feet, angiokeratomas, corneal opacity, involvement of kidneys, heart	
RVCL / HERNS	TREX1 aut.-dom.	Loss of vision, cognitive problems, stroke-like episodes, liver and kidney dysfunction, retinal microangiopathy	Dominantly ischemic SVD
MELAS	Mitochondrial	Strokelike episodes, migraine, muscle weakness, epil. Seizures, short stature, hearing loss, episodic vomiting, diabetes, cardiomyopathy, retinitis	DWI-impaired, but NOT ADC-attenuated, territory-spanning lesions, atrophy, basal ganglia calcification
Ehlers-Danlos IV	COL3A1, aut.-dom.	Hypermobility of joints, thin skin and tendency to bruises, intestinal and uterine ruptures, subluxations and pain, muscle cramps	Cerebral aneurysms and/or spontaneous arterial dissections
COL4A– and COL4A2 associated angiopathy	COL4A1, COL4A2 aut.-dom.	Brain hemorrhages, epileptic seizures, migraine, ophthalmologic anomalies, kidney, heart, muscle involvement, possibly cognitive symptoms	Hemorrhagic SVD, aneurysms, extensive WMH, porencephaly
DADA2	ADA2 aut.-rec.	Polyarteritis nodosa, small vessel vasculitis, recurrent fever, livedo racemosa childhood, hepatosplenomegaly, hematologic abnormalities, immune dysregulation,	Lacunae and hematoma. SVD, spinal infarcts, intracranial aneurysms, inflammatory perivascular tissue in the basal and
Fam. Moya-Moya	ACTA2, MTCP1, RNF213, GUCY1A3	Headache, hypoperfusion, telangiectasia, cognitive impairment, epilept. seizures	(bilateral) stenosis ICA-T/M1, collaterals ("cloud")
Fam. Hemiplegic migraine	CACNA1A, ATP1A2, SCNA1 aut.-dom.	Migraine with aura and motor paresis/ hemiplegia	Primarily ischemic SVD
Sickle cell disease	HBB aut.-rec.	Anemia, pain attacks, infections, lung/ kidney/spleen manifestations, African descent	Moyamoya-like
Marfan	FBN1 aut.-dom.	Lens dislocation, cataract, myopia, arthritis, large habitus, pectus excavatum, dural ectasia	Aortic aneurysm/dissection, Carotid artery dissection

General Remarks:

- Genetic testing only if clinical or imaging findings are suggestive and the patient wishes it (declaration of consent with signature)
- M. Fabry by blood drop test (stroke unit)
- Cost approval by health insurance fund required in advance, blood sample can already be taken
- If clinical or imaging findings are compatible with several syndromes, direct panel testing.
- If clinical/imaging findings are highly suggestive of a syndrome, single gene sequencing first
- Further phenotypes and manifestations are described here (SVD) and here (also non-SVD)

Non-binding recommendations according to DGN/DSG position paper, period given in months, for further recommendations (SAB, AVM, cavernomas, vasculitis see link).
Recommendations for period only if somatically and neurocognitively able to drive!

	Private driving	Other categories
TIA, low risk profile	1	3
TIA, high risk profile	3	6
TIA, ICAD	6	No
Ischemic stroke, low risk e.g. after CAS/CEA, cryptogenic stroke, AF with DOAC, SVD	1	3
Ischemic stroke, high risk, e.g. best medical management of symptomatic stenosis, AF without anticoagulation, dissections, high vascular risk profile	3	6
ICH due to deep perforator arteriolopathy, BP well controlled	1	3
ICH due to CAA or symptomatic ICH with more than 5 asymptomatic microbleeds or superficial siderosis	No	No

Life after Stroke - Checklist

Complaints	Fatigue/sleepiness, sleep disorders, headache, pain, emotional disorders, depression, anxiety, memory/concentration disorders, dizziness, unsteady gait, paralysis, visual disorders, swallowing disorders, incontinence, sexuality -> Which of the above are particularly disabling? Treatment suggestion?
Spasticity	Documentation with modified Ashworth scale **Focal**: Botox; **generalized**: Baclofen, tizanidine, tolperisone, clonazepam
Social life	Friends, independence (bathing/showering, eating, mobility, stairs, getting dressed), hobbies, driving a car -> why social withdrawal? Optimization of mobility, tiredness/mood?
Work	Workload, Insurance, adapted activity? -> Need advice, social services, consultation with company? Rehab consultation
Prevention	Stop or reduce smoking, (target) weight, physical activity, healthy diet (fruit/vegetables, little salt, little red meat, whole grains) Blood pressure values, general practitioner checks, sleep hygiene -> Stop smoking consultation, nutritional advice, handing out prevention booklet
Medication	Compliance, adherence, correct dose, side effects? Which ones? -> Counseling, medication dosage, reminder, alternative preparations
Therapies	Physiotherapy, Ergotherapy, Speech therapy, Neuropsychological therapy–Unmet need? —> ambulatory therapy, interval rehab as an option

Central Retinal Artery Occlusion (CRAO)

GP / first contact

If suspicion of CRAO/BRAO, immediate referral to a hospital with the possibility of intravenous thrombolysis (notify ophthalmology and neurology in advance)

Ophthalmology — „time is retina“

Acute, painless monocular loss of visual acuity <12h - patient has **top priority**, emergency and time pressure - involve attending immediately!

Symptom onset - determination of symptom onset (time, with wake-up/unclear time window "last normal"), monocular/binocular? Previous amaurosis fugax?

Visual acuity - usually ≤ 0.05 or hand movement (cave: rarely spontaneously reperfused occlusion with improvement)

Finger perimetry (DD hemi/branch occlusion), motility restrictions
RAPD - Relative afferent pupillary deficit in the affected eye?

Tensio measurement

Funduscopy (in miosis): Embolus? Cherry red spot of the macula? Cilioretinal vessel? Bleeding? Anterior segment of the eye.

Clinical suspicion of **giant cell arteritis? (**temporal arteritis):
Chewing/combing/head pain? B-symptoms? Rheumatologic underlying disease?

In case of **loss of vision <12h** Stroke emergency work-up (MR/CT angiography, stroke laboratory incl. ESR, and start of secondary prophylaxis), always notify attending neurologist, coordinate management with ophtha

Transport - For transfer and handover of the patient to the emergency neurologist within the 4.5 h time window, the patient should, if possible, be taken directly to the ED accompanied by the ophthalmologist (fastest transport option).

ED Neurology

Acute, painless monocular loss of vision <12h - patient has top priority, **emergency and time pressure**!

If a patient presents directly to the ED **within the 4.5 h time window** WITHOUT a prior ophthalmological examination, contact the duty ophthalmologist at _____ immediately and organize an ophthalmological examination as quickly as possible (exclusion of critical differential diagnoses such as retinal detachment, vitreous hemorrhage), examination as above

Normal stroke workflow (NIHSS, MRI/CT Priority 1 if <4.5h)
Patients with CRAO or retinal branch occlusion are admitted, diagnosed and treated like patients with ischemic stroke, even if symptoms >4.5h.

Evaluation of i.v. thrombolysis if symptom onset <4.5 h (individual decision depending on loss of visual acuity / time window / patient preference and only after cMRI/cCT to exclude (sub)acute, hem.-transformed infarcts) Exclusion of further contraindications see page Contraindications to i.v. thrombolysis.

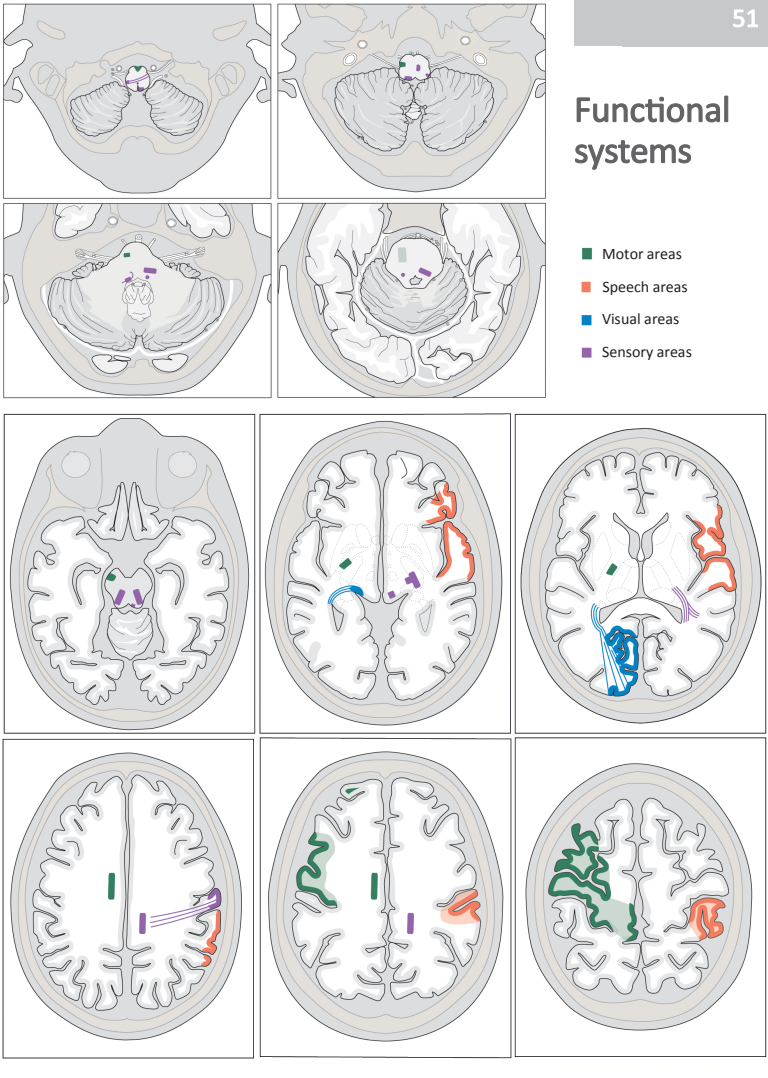
In **case of suspected giant cell arteritis** (chewing pain, painful on palpation, hardened, possibly pulseless superficial temporal artery, pain when combing hair, B symptoms) no intravenous thrombolysis, if ESR high and possibly elevated CRP, immediate administration of 1g methylprednisolone i.v.; Admission and then: consultation rheumatology, ultrasound of temporal arteries, MRI with dark blood sequences, if necessary biopsy of temporal artery.

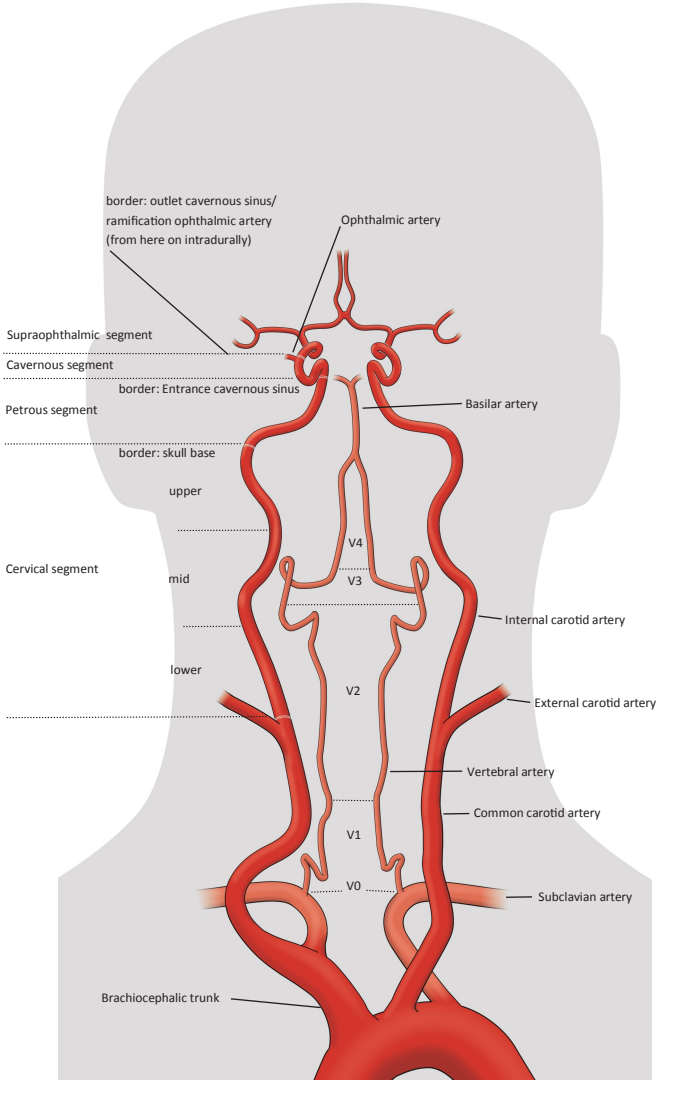
Etiology: embolism (cardiac, carotid artery), thrombosis, giant cell arteritis, collagenoses (polyarthritis nodosa, SLE), coagulation tendency (polycythemia, antiphospholipid-AB, oral contraceptives), sickle cell anemia, TPHA
Differential diagnosis: occlusion of the ophthalmic artery, AION, certain lipid storage diseases (e.g. Tay-Sachs)
Organize: OCT (swelling/washing of inner retinal layers), fluorescein angiography if necessary

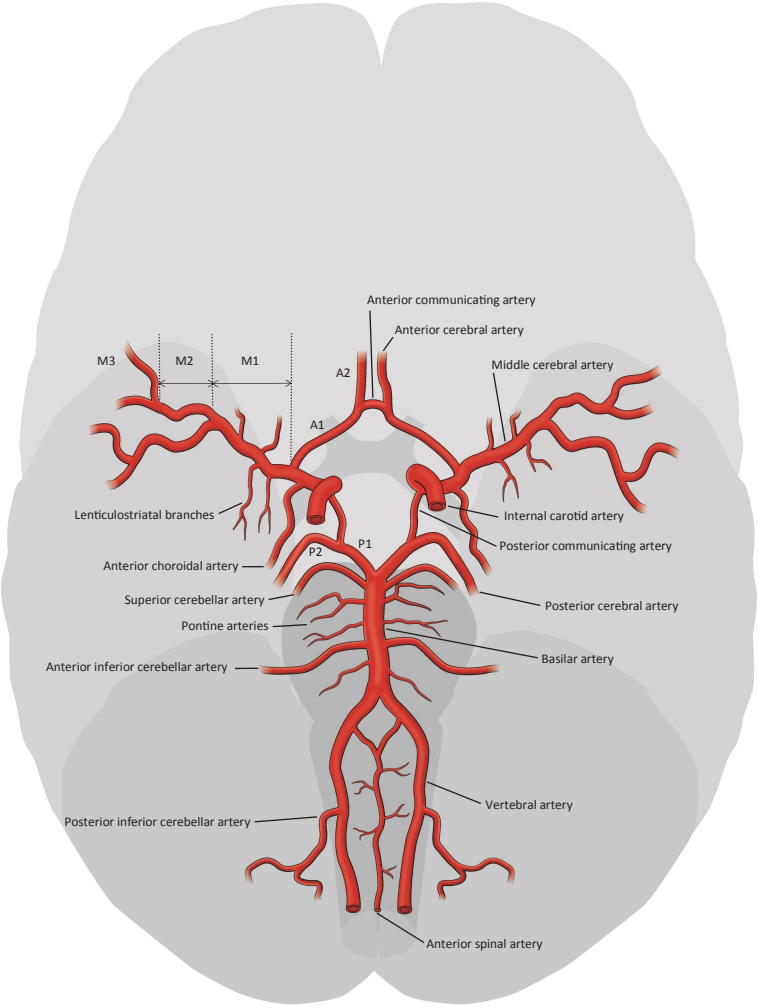
Always **admit to stroke unit** if intravenous thrombolysis, cerebral ischemia or carotid stenosis
Always interdisciplinary consultation: admission (ABCD2 score analogous to TIA pathway) Stroke Unit or Ophtha; usually start ASA.
-> Follow-up at Ophtha (pressure measurement, documentation of fundus, OCT, visual acuity) or private ophthalmologist if available (during/at the end of hospitalization, otherwise during the first month).

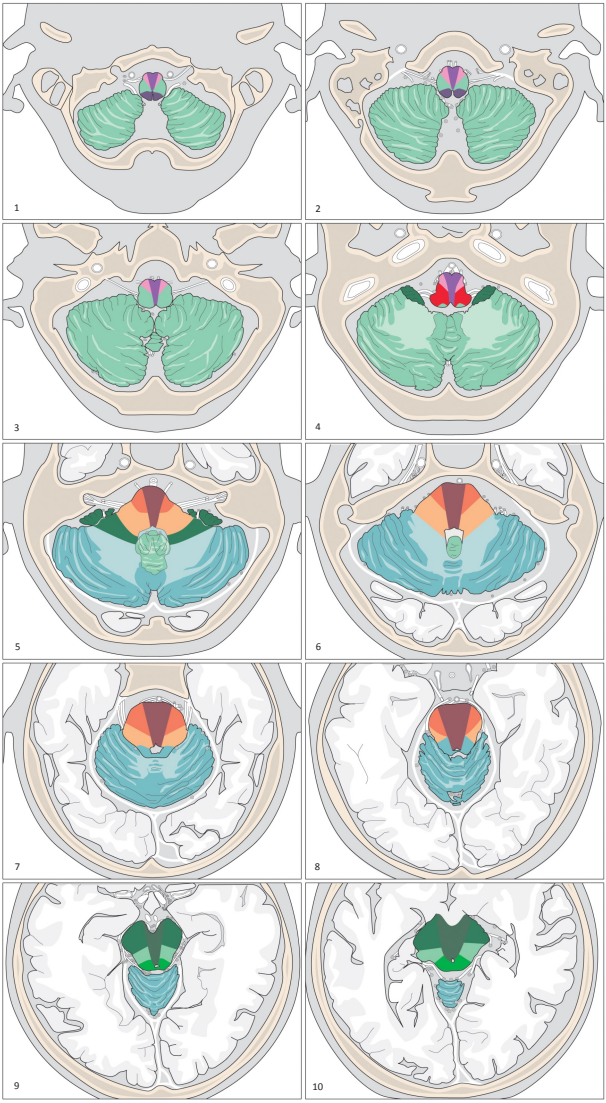
Credit and thanks to Prof. Sven Poli

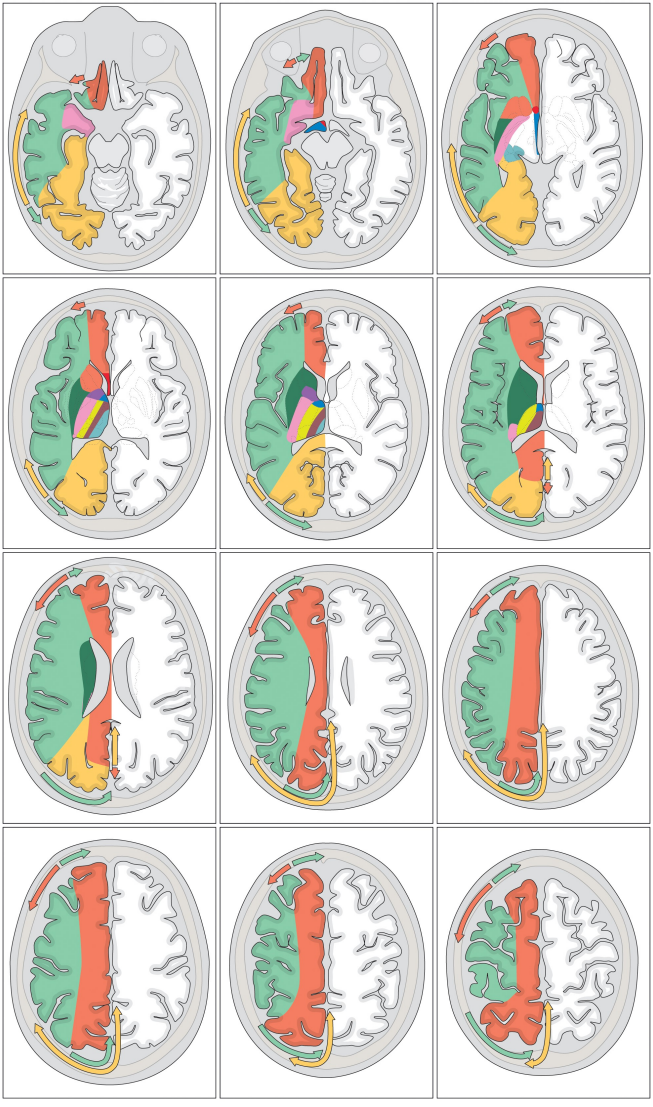
Functional systems

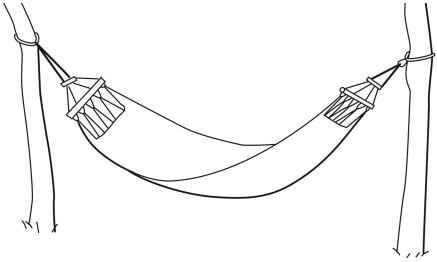


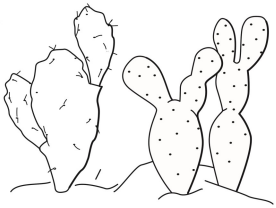

border: outlet cavernous sinus/
ramification ophthalmic artery
(from here on intradurally)
Ophthalmic artery
Supraophthalmic segment
Cavernous segment
border: Entrance cavernous sinus
Petrous segment
Basilar artery
border: skull base
upper
V4
Cervical segment
mid
V3
Internal carotid artery
lower
V2
External carotid artery
Vertebral artery
Common carotid artery
V1
V0
Subclavian artery
Brachiocephalic trunk

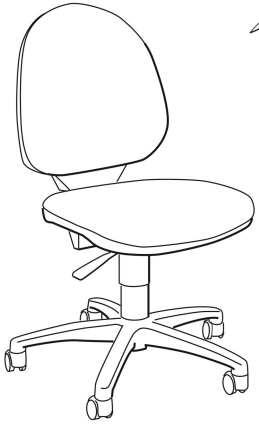

Anterior communicating artery
Anterior cerebral artery
M3
M2
M1
A2
Middle cerebral artery
A1
Lenticulostriatal branches
Internal carotid artery
Posterior communicating artery
P2
P1
Anterior choroidal artery
Superior cerebellar artery
Posterior cerebral artery
Pontine arteries
Basilar artery
Anterior inferior cerebellar artery
Vertebral artery
Posterior inferior cerebellar artery
Anterior spinal artery

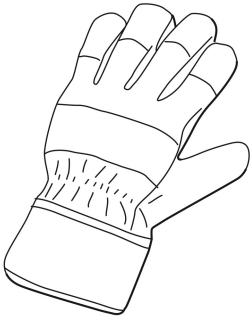

Medulla oblongata (Fig. 1-4)
Anterior spinal artery
Anterior spinal artery
Vertebral artery
Posterior inferior cerebellar a.
Posterior spinal artery
Vertebral artery
Anterior inferior cerebellar a.
Posterior inferior cerebellar a.
1
2
3
4
Pons (Fig. 5-8)
Medial pontine a. of basilar a.; branches of posterior cerebral artery
Lateral pontine a. of basilar a.
Lateral pontine a. of basilar a.
Anterior inferior cerebellar a.
(Fig. 8: Superior cerebellar a.)
Anterior inferior cerebellar a.
Posterior inferior cerebellar a.
Superior cerebellar a.
5
6
7
8
Mesencephalon (Fig. 9-10)
Central posteromedial a. of posterior cerebral artery
Collicular and choroidal posterior medial a. of posterior cerebral artery
Collicular and choroidal posterior medial a. of posterior cerebral a.
Collicular and choroidal posterior medial a. of posterior cerebral a., superior cerebellar a
Superior cerebellar artery
9
10


Anterior cerebral a.
Middle cerebral a.
Middle cerebral a., lenticulostriate branches
Posterior cerebral a.
Anterior choroidal a.
Posterior choroidal a. (from P2)
Anterior communicating artery
Posterior communicating artery
Thalamoperforating A. (from P1 or BA; if jointly main trunk: Percheron artery)
Thalamogeniculate a. (from P2)
Internal carotid a.









Close your eyes

He‘s a chip off the old block.

Harm set, harm get.

HUCKLEBERRY

BASEBALL PLAYER

Glasgow Coma Scale

Eye opening response	4 Spontaneously 3 To speech 2 To pain 1 No response
Best verbal response	5 Oriented to time, place, and person 4 Confused 3 Inappropriate words 2 Incomprehensible sounds 1 No response
Best motor response	6 Obeys commands 5 Moves to localized pain 4 Flexion withdrawal from pain 3 Abnormal flexion (decorticate) 2 Abnormal extension (decerebrate) 1 No response

CHA_2DS_2-VASc-Score (stroke risk with AF)

Risk factor	Points	(N) O A C I F >1 P O I N T	Sum	Risk/year taking Aspirin
Congestive heart failure	1		0	0%
Hypertension	1		2	2.2%
Age > 75	2		3	3.2%
Diabetes mellitus	1		4	4.8%
Stroke/TIA/thromboembolism	2		5	7.2%
Vascular disease (heart, peripheral)	1		6	9.2%
Age 65-74 years	1		7	11.2%
Woman	1		9	12.2%

Modified Rankin Scale (mRS)

0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs
3	Moderate disability, requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend own bodily needs
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

NIH Stroke Scale

Points	Category	Explanation
	Level of consciousness	0 Alert 1 Not alert, but arousable by minor stimulation 2 Not alert, requires repeated stimulation to attend. Or, obtunded and requires painful stimuli to make movements 3 Makes only reflexive posturing movements to repeated painful stimuli. Or, they are totally unresponsive
	Orientation anarthria, intubation=1, coma=2	Ask the current month and the patient's age. 0 Answered both questions correctly 1 Answered one correctly 2 Answered neither question correctly or aphasia
	Commands	Ask the patient to open/close the eyes and make a fist/relax the non-paretic hand. 0 Performed both correctly 1 Performed one correctly 2 Performed neither correctly
	Best gaze uncooperative=1, coma=2	0 Normal 1 Partial gaze palsy = Conjugate gaze deviation that can be overcome with voluntary or reflexive activity 2 Forced deviation
	Visual Fields not evaluable=0, neglect=1, coma=3, in case of aphasia, evaluate reaction	0 No visual loss 1 Partial hemianopia 2 Complete hemianopia 3 Bilateral hemianopia
	Facial palsy coma=3	0 Normal 1 Minor paralysis (flattened nasolabial fold or mild asymmetry while smiling) 2 Partial paralysis (total or near total paralysis of lower face) 3 Complete paralysis of upper and lower face
Left:	**Motor arm** coma=4	0 No drift, remains in position for 10 sec. after an initial dip 1 Jerks or drifts to an intermediate position without encountering support before the full 10 sec. 2 Some effort against gravity. Drifts down before 10 sec. 3 No effort against gravity and the arm falls 4 No voluntary movement
Right:		
Left:	**Motor leg** coma=4	0 No drift, remains in position for 5 sec. after an initial dip 1 Jerks or drifts to an intermediate position without encountering support before the full 5 sec. 2 Some effort against gravity. Drifts down before 5 sec. 3 No effort against gravity and the leg falls 4 No voluntary movement
Right:		

NIH Stroke Scale Part 2

Points	Category	Explanation
	Limb ataxia coma, aphasia, paralyzed=0	0 Absent 1 Present in one limb 2 Present in two limbs
	Sensory bilateral loss=2, coma=2 aphasia=rather 1	0 Normal 1 Mild to moderate sensory loss, patient feels asymmetry between the two sides but is still aware of being touched 2 Severe or total sensory loss, patient is not aware of being touched on the face, arm, and leg
	Best language Intubated patients should be asked to write, coma=3	0 No aphasia 1 Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension without significant limitation on ideas expressed or form of expression 2 Severe aphasia; all communication is fragmentary; great need for inference, questioning, and guessing by the examiner 3 Mute or global aphasia; globally aphasic patients have no usable speech or auditory comprehension
	Dysarthria coma=2	0 Normal 1 Mild to moderate dysarthria; patient can still be understood 2 Severe dysarthria; patients are either mute or speech is so slurred they cannot be understood out of proportion to any dysphasia that is present
	Extinction and inattention coma=2	0 Absence of neglect 1 Inattention to one modality only (visual, tactile, auditory, spatial, or personal inattention) 2 Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients only to one side of space

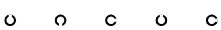
0.05

0.1

0.2

0.25

0.32



0.4

0.5

0.63

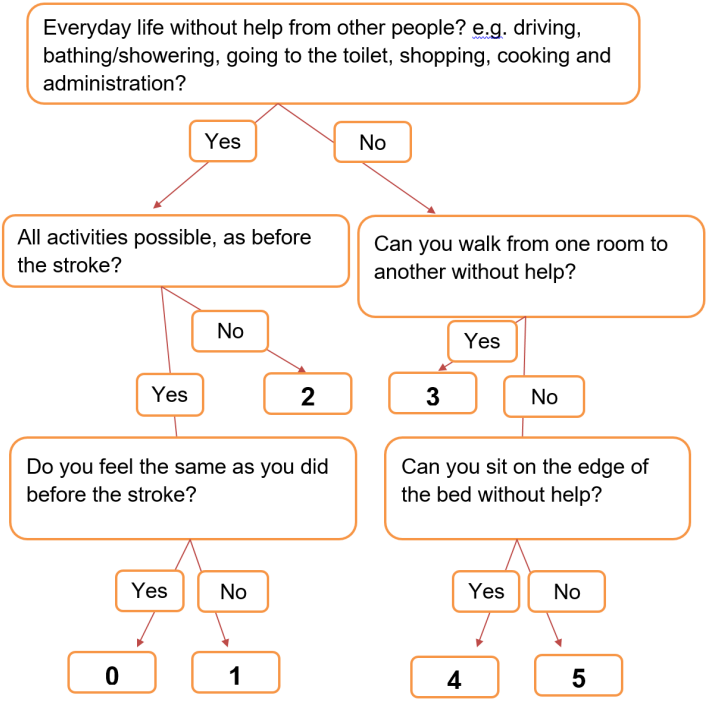
0.8

1.0

Distance: 40cm

Visus

Simplified modified Rankin Bruno et al. Stroke 2011



NIHSS (see page 60 for details)

Item	Rating		Item	Rating
LOC	0 Alert 1 not alert 2 Sopor 3 Coma		**RIGHT and LEFT Motor Legs** Amputation or stiffe-ning=0, Coma=4	0 no drift 1 drift (< 5sec) 2 active movement against gravity 3 no active movement against gravity 4 no movement at all
Orientation Anarthria, Intubation=1, Coma=2	Ask months and age 0 both correct 1 one correct 2 none correct		**Limb ataxia** with coma, aphasia, plegia=0	0 missing 1 one extremity 2 two extremities
Commands	Close eyes, squeeze hand 0 both correct 1 one correct 2 none correct		**Sensitivity** bilateral=2, Coma=2 if no reaction to pain, with aphasia rather 1	0 Normal 1 Light 2 Heavy to complete
Oculomotor Insufficient cooperation=1, Coma=2	0 normal 1 partial palsy 2 forced deviation		**Aphasia** Let intubated (wake) patients write, coma=3	0 Normal 1 light to moderate 2 Severe 3 Mute, global
Visual field Not assessable=0, Neglect=1, Coma=3, rate if aphasia blink to frighten-ing movement	0 no restriction 1 partial hemianopsia 2 complete hemianopsia 3 bilateral hemianopsia		**Dysarthria** Coma=2	0 normal 1 mild to moderate 2 Severe (anarthric or incomprehensible)
Facial palsy Grimaces at pain stimulus, coma=3	0 normal 1 low 2 partial 3 complete		**Neglect** Not assessable=0, coma=2	0 None 1 Extinction 2 Severe neglect >1 quality
RIGHT and LEFT motor function arms with amputation or joint fusion=0, coma=4	0 no drift 1 drift (< 10 sec) 2 active movement against gravity 3 no active movement against gravity 4 no movement at all			

GCS	
Eyes	1 No reaction; 2 to pain; 3 to speech; 4 spontaneously open
Verbal	1 no reaction; 2 uncomprehensible; 3 random speech; 4 disorientated, answers questions; 5 oriented and answers
Motor	1 no reaction; 2 extension; 3 flexion; 4 defense-Flexion; 5 localizes pain; 6 obey commands