Klasifikace subtypů ischemické CMP: TOAST, CCS a ASCO

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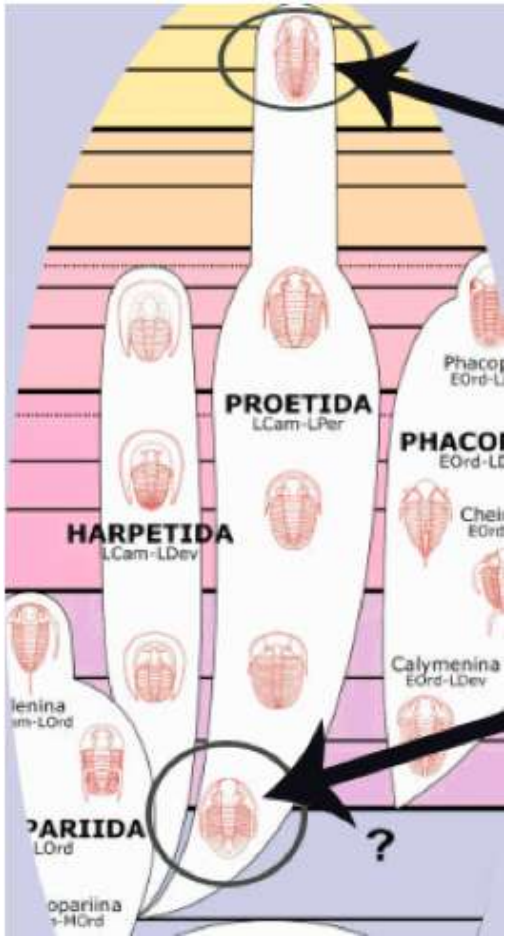
Proč klasifikovat?

- Metodika multicentrických studií – přesnost vzájemné domluvy (hrušky s hruškami)
- Epidemiologie a prognostika
- Správná volba sekundární prevence

Předpoklad:

- Minimální diagnostický panel s jasnými definicemi kategorií



Používané klasifikační systémy

- Stroke Data Bank (SDB, Harvard Stroke Registry, NINDS Stroke Data Bank) - **1978**
- Lausanne Stroke Registry and the Étude du profil Génétique de l'Infarctus Cérébral (GÉNIC) study – **1988**
- Oxfordshire Community Stroke Project (OCSP) – **1991**
- **TOAST** (Trial of ORG 10172 in Acute Stroke Treatment) – **1993**
- SSS-TOAST - **2005**
- **Causative Classification System (CCS)** - **2007**
- **ASCO** - **2009**

TOAST subtypy

TABLE 1. TOAST Classification of Subtypes of Acute Ischemic Stroke

Large-artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Possible or probable depending on results of ancillary studies.

Klasifikace dle TOAST

- 2 stupně:
- **pravděpodobný (probable) -** klinický nález a vyšetřovací metody svědčí pro daný subtyp a ostatní subtypy byly vyloučeny
- **možný (possible)** – klinický nález a vyšetřovací metodiky naznačují subtyp, ale vyšetření není kompletně ukončeno

TOAST – neurčená etiologie UND

- Zcela negativní nebo nekompletní vyšetření
- 2 a více možných příčin, kdy se lékař nedokáže definitivně rozhodnout
- Např.
  - FiS + 50% ipsilaterální ICA
  - Lakunární syndrom + 50% ipsilaterální ICA

Causative Classification System (CCS)

- Podle váhy důkazu 3 kategorie:
- Evidentní (evident) – jediný možný mechanismus etiologie
- Pravděpodobný (probable) – více možných etiologických faktorů zároveň s rizikem CMP >2%/rok
- Možný (possible) - <2% roční riziko CMP, jednorázový rizikový faktor/situace nebo evidentní faktor, který nebyl kompletně dovyšetřen

Table **Causative stroke subtypes according to the Causative Classification of Stroke System (CCS)[a]**

5 Subtype CCS	8 Subtype CCS	16 Subtype CCS
Supra-aortic large-artery atherosclerosis	Supra-aortic large-artery atherosclerosis	Supra-aortic large-artery atherosclerosis
		Evident, probable, possible
Cardioaortic embolism	Cardioaortic embolism	Cardioaortic embolism
		Evident, probable, possible
Small-artery occlusion	Small-artery occlusion	Small-artery occlusion
		Evident, probable, possible
Other uncommon causes	Other uncommon causes	Other uncommon causes
		Evident, probable, possible
Undetermined	Undetermined	Undetermined
	Unknown-cryptogenic embolism	Unknown-cryptogenic embolism
	Unknown-other cryptogenic	Unknown-other cryptogenic
	Unclassified	Unclassified
	Incomplete evaluation	Incomplete evaluation

CCS

ASCO - metodika

Stupeň kauzality

1. Rozhodně možná příčina indexové CMP
2. Kauzalita je nejasná
3. Nepravděpodobná příčina indexové CMP, ale rozhodně přítomen možný rizikový faktor

Úroveň diagnostického průkazu

A) Přímý průkaz standardní metodikou (gold standard)

B) Nepřímý důkaz méně senzitivní nebo specifickou metodikou

C) Slabý důkaz při nepřítomnosti specifické vyšetřovací metodiky

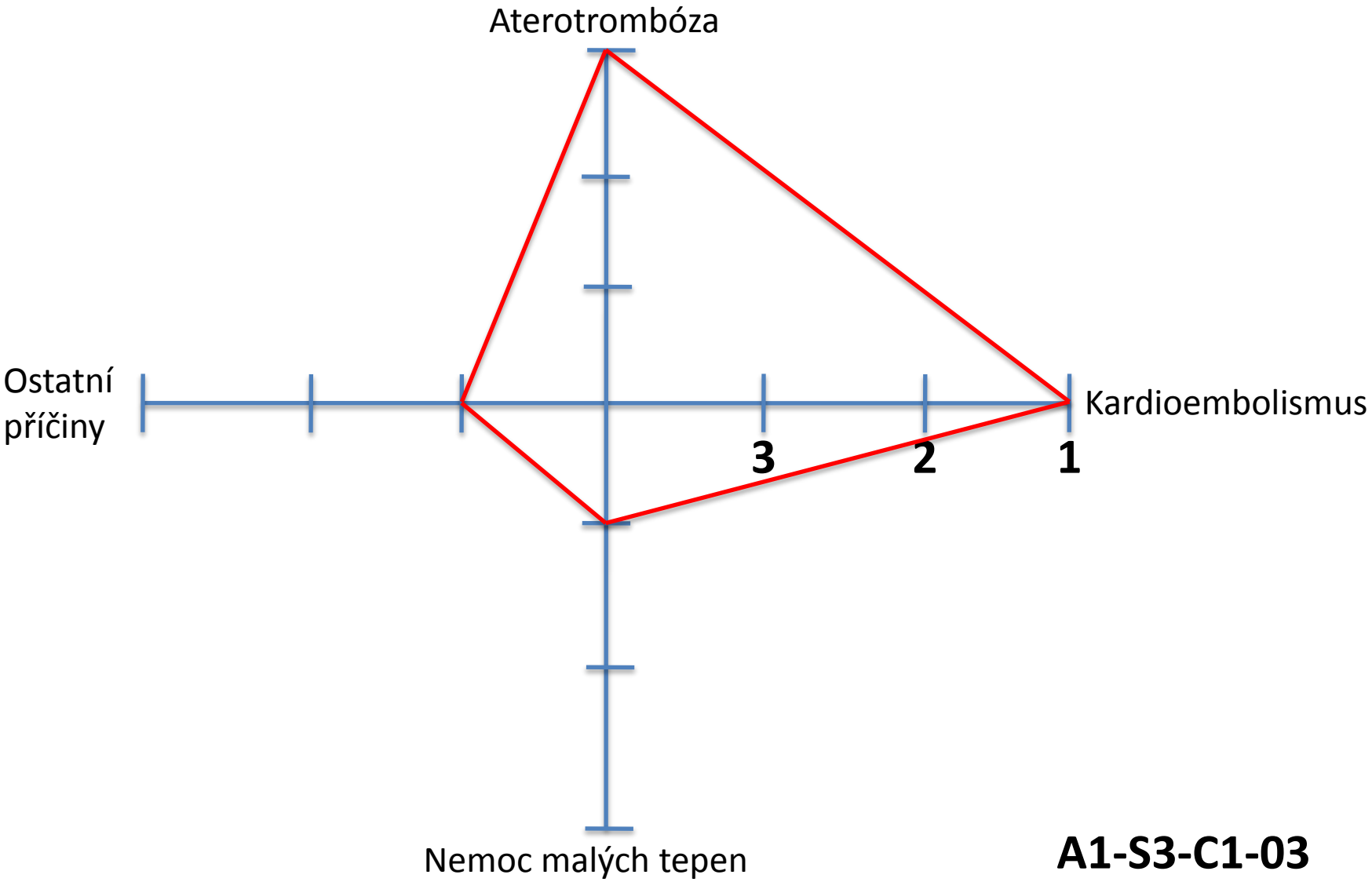
Hodnotíme 1, 2, 3 jak výše uvedeno, není-li rizikový faktor přítomen vůbec pak hodnotíme 0, při nedostatečném a nedokončeném vyšetřovacím programu hodnotéme 9.

Modelový pacient

- Ipsilateralní stenóza ICA 70% (A1)
- Leukoaraióza, microbleeds (S3)
- FiS (C1)
- Trombocyty 700,000/mm^3 (03)

= **A1-S3-C1-03**

ASCO - diagram



A1-S3-C1-03

ASCO – diagnostický panel – příklad kardioembolismus

Ruling out a cardiac source of embolism:
Minimum is negative ECG and auscultation by a cardiologist;
Maximum is negative ECG/telemetry/Holter ECG and negative TEE, negative cardiac CT/MRI, negative abdominal CT/MRI (search for old or simultaneous subdiaphragmatic visceral infarction).
Ruling out a PFO by best available technology:
Microbubble injections with Valsalva maneuver;
With assessment by either TCD of the MCA or TTE (TTE usually allows a better Valsalva maneuver than under TEE).
In case of a negative TTE/TEE, if one doubts the quality of the technique used to search for microbubbles crossing, a confirmation can be obtained by TCD technique: negative results in both techniques is the gold standard for ruling out PFO.

Cardiac disease

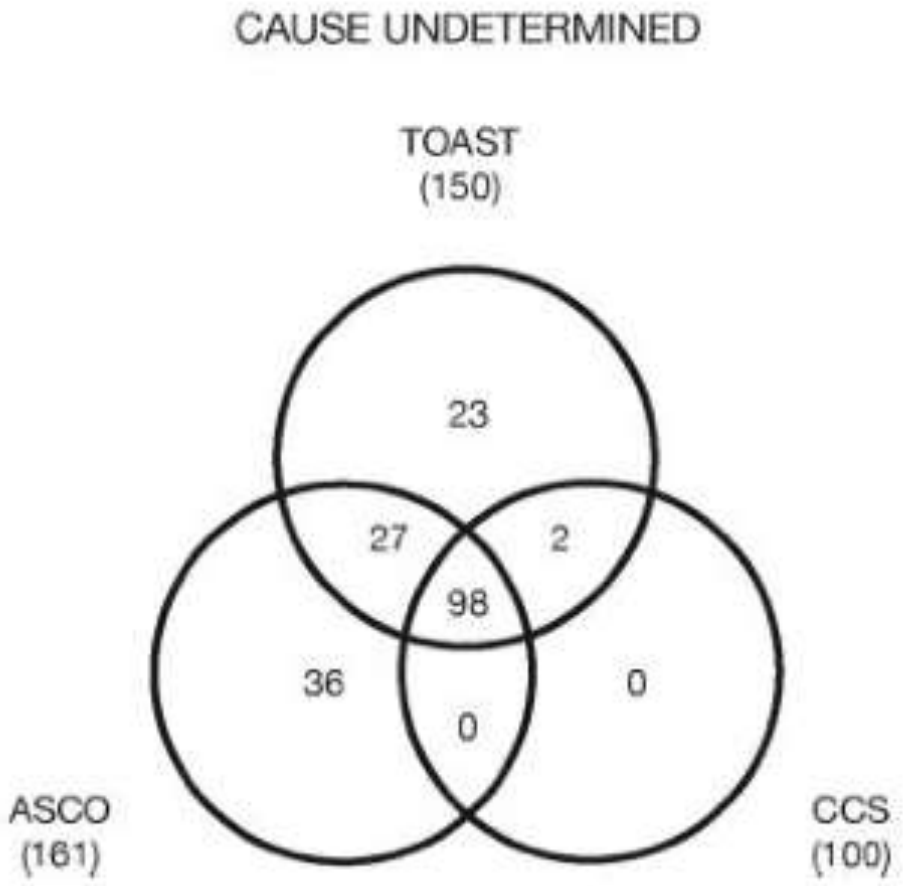
- TEE for: valvular disease, atrial and aortic thrombus, atrial tumor or endocarditis;
- TTE for: left ventricle mural thrombus or endomyocardial fibrosis;
- Cardiac ultra-fast CT or MRI for some cardiac pathologies (intracardiac thrombi, a tumor, endomyocardial fibrosis);
- Pathology (autopsy evidence, macro- and microscopic demonstration of a cardiac source of embolism);
- ECG documentation for atrial fibrillation;
- Combined ECG and biologic (troponin) documentation for myocardial infarction; or pathology (autopsy evidence, macro- and microscopic demonstration of MI).

Porovnání ASCO, CCS vs. TOAST

- Oproti TOAST – CCS:
  - méně pacientů s neurčenou etiologií (26.2% vs. 39.4%; *P*<0.000001)
  - větší množství kardioembolických (o 6.9%; *P*=0.004), LVD (o 44.1%; *P*=0.00006), SVD (o 27.3%; *P*=0.00006) a s jinou určenou příčinou=OC (o 91.7%; *P*=0.001)
- Oproti TOAST - ASCO (započetno grade 1):
  - méně SVD (o 29.1%; *P*=0.007)
  - více LVD/aterotrombotické (o 17.6%; *P*=0.03).
- Korelace mezi klasifikacemi od dobré (kappa 0.61 TOAST/ASCO grade 1 small artery category) po výbornou (kappa 0.95 TOAST/CCS a ASCO grade 1/CCS CE/AT)
- Využití ASCO grades 1-3 u pacientů s neurčenou etiologií podle TOAST: LVD(73.3%), CE (31.3%), SVD (64.7%), OC (12%)

Marnane et al. ***Stroke. 2010;41:1579-1586.***

Porovnání ASCO, CCS a TOAST



Marnane et al. ***Stroke. 2010;41:1579-1586.***

Klasifikace – originální publikace

- TOAST – Adams HP et al. Stroke 1993;24;35-41.
- ASCO – Amarenco P et al. Cerebrovasc Dis 2009;27:502–508.
- CCS – Ay H et al. *Stroke* 2007, 38:2979-2984.

Příloha – definice ASCO

Grades for atherothrombosis (A)		
1. Definitely a potential cause of the index stroke	Atherothrombotic stroke defined as:	
	(a)	Patients with any atherosclerotic stenosis 70–99% in an intra-/or extracranial artery supplying the ischemic field diagnosed by level A or B evidence; or
	(b)	Any atherosclerotic stenosis <70% in an intra-/or extracranial artery supplying the ischemic field with attached luminal thrombus diagnosed by level A or B evidence; or
	(c)	A mobile thrombus in the aortic arch; or
	(d)	Occlusion with imaging evidence of atherosclerosis in an intra-/or extracranial artery supplying the ischemic field.
2. Causality uncertain	(a)	Patients with any atherosclerotic stenosis 70–99% in an intra-/or extracranial artery supplying the ischemic field diagnosed by level C evidence; or
	(b)	Any atherosclerotic stenosis <70% in an intra-/or extracranial artery supplying the ischemic field with attached luminal thrombus diagnosed by level C evidence; or
	(c)	Aortic arch plaques >4 mm in thickness without a mobile component.
3. Unlikely a direct cause of index stroke (but disease is present)	(a)	Presence of carotid or vertebral artery plaque without stenosis; or
	(b)	Aortic arch plaque <4 mm; or
	(c)	Stenosis (any degree) in a brain artery, contralateral to the brain infarction or in the opposite circulation (either posterior or anterior circulation); or
	(d)	History of myocardial infarction or coronary revascularization or peripheral arterial disease.

Grades for small vessel disease (S)	
1. Definitely a potential cause of the index stroke	Association of: (a) Deep branch artery stroke: small, deep infarct with diameter <15 mm on MRI (or CT) in the territory corresponding to symptoms; and either (b) One or several old or silent lacunar infarcts in territories different from the index stroke; or (c) Leukoaraiosis on MRI (or CT), microbleeds on MRI (gradient echo imaging), dilatation of the perivascular spaces on MRI (or CT); or (d) Recent repeated similar TIAs – when they preceded the brain infarct by 1 month or less and attributable to the same territory as the subsequent BI (which increase the prediction for lacunar stroke from 57 to 80%, and are therefore supportive).
2. Causality uncertain	(a) Single, deep branch artery stroke; or (b) Clinical syndrome suggestive of deep branch artery stroke with no MRI/CT evidence of stroke (clinical syndrome suggestive of a deep branch artery stroke – classic lacunar syndromes: pure motor hemiparesis, pure sensory syndrome, ataxic hemiparesis, dysarthria clumsy-hand syndrome, and sensorimotor syndrome; or other 'nonlacunar' clinical syndromes. e.g. hemichorea, hemiballism, isolated dysarthria, etc.).
3. Unlikely a direct cause of index stroke (but disease is present)	Leukoaraiosis on MRI (or CT), and/or microbleeds on MRI (gradient echo imaging), and/or dilatation of perivascular spaces on MRI (or CT), and/or one or several lacunar infarcts (silent or old) in territories different from the index stroke.

Grades for cardioembolism (C)	
1. Definitely a potential cause of the index stroke	Cardioembolic stroke – demonstration of: (a) Mitral stenosis; (b) Prosthetic heart valve; (c) Myocardial infarction within the past 4 weeks; (d) Mural thrombus in left cavities; (e) Left ventricular aneurysm; (f) Any documented history or permanent or transient atrial fibrillation or flutter with or without spontaneous echo contrast or left atrial thrombus; (g) Sick sinus syndrome;
	(h) Dilated cardiomyopathy; (i) Ejection fraction <35%; (j) Endocarditis; (k) Intracardiac mass; (l) PFO plus in situ thrombosis; (m) PFO plus concomitant PE or DVT preceding the brain infarction.
2. Causality uncertain	(a) PFO and ASA; (b) PFO and concomitant DVT or PE (but not preceding the index stroke); (c) Spontaneous echo contrast; (d) Apical akinesia of the left ventricle and impaired ejection fraction (but >35%); (e) Only suggested by history of myocardial infarction or palpitation and multiple repeated brain infarcts on both sides or in both the anterior and posterior circulation; (f) Only suggested by abdominal CT/MRI or autopsy demonstration of the presence of systemic infarction (e.g. kidney, splenic, mesenteric) or lower limb embolism (in addition to the index stroke).
3. Unlikely a direct cause of index stroke	One of the following abnormalities: PFO, ASA, valvular strands, mitral annulus calcification, calcified aortic valve, nonapical akinesia of the left ventricle.

Grades for other causes (O)		
1. Definitely a potential cause of the index stroke (examples)	(a)	Arterial dissection by A or B evidence (table 3);
	(b)	Dolichoectasia with complicated aneurysm;
	(c)	Polycythemia vera, thrombocythemia >800,000/mm^3;
	(d)	Lupus erythematosus;
	(e)	Disseminated intravascular coagulation;
	(f)	Criteria for antiphospholipid antibody syndrome;
	(g)	Fabry's disease;
	(h)	Concomitant meningitis;
	(i)	Sickle cell disease;
	(j)	Ruptured cerebral aneurysm with or without demonstration of spasm in the territory of the brain infarct;
	(k)	Homozygote for hyperhomocystinuria.
2. Causality uncertain	(a)	Arterial dissection diagnosed by level C evidence (see table 3; only suggestive history or clinical syndrome, e.g. isolated acute painful Horner's syndrome, or only history of previous dissection);
	(b)	Fibromuscular dysplasia.
3. Unlikely a direct cause of index stroke (but disease is present)	(a)	Kinking or dolichoectasia without complicated aneurysm or plicature;
	(b)	Arteriovenous malformation or saccular aneurysm;
	(c)	Thrombocytosis >450,000 and <800,000/mm^3;
	(d)	Antiphospholipid antibodies <100 GPL units;
	(e)	Mild hyperhomocysteinemia heterozygote.