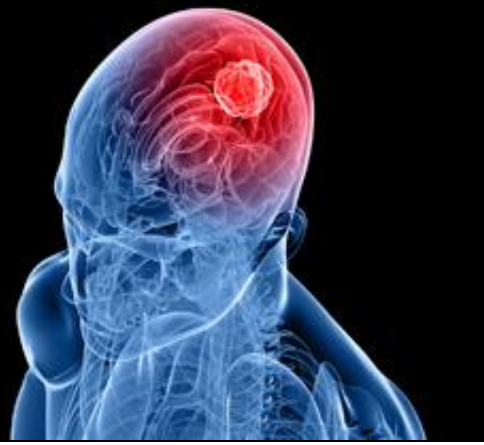
Prezentace je podpořena spol. Boehringer Ingelheim

Dabigatran v sekundární prevenci CMP



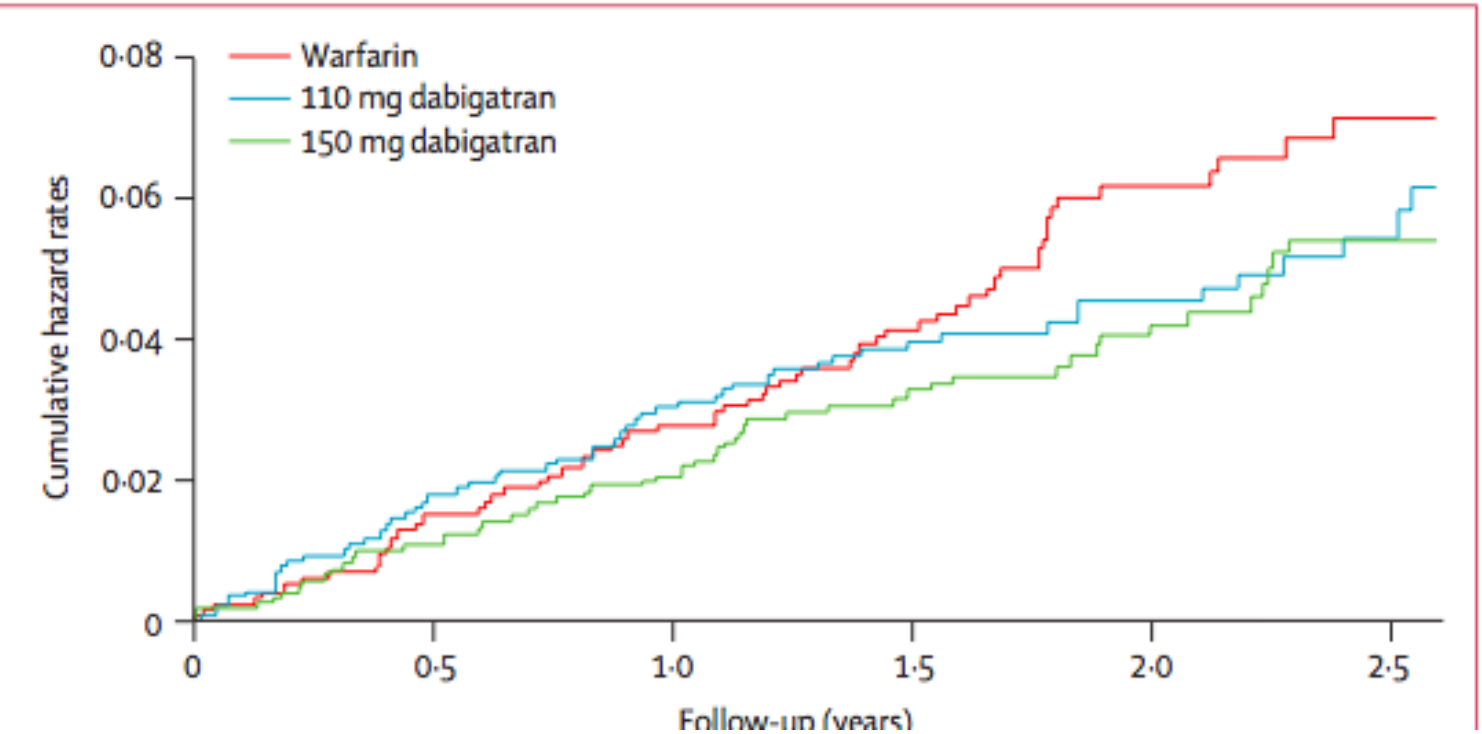
Aleš Tomek

2. LÉKAŘSKÁ FAKULTA
UNIVERZITY KARLOVY

NEUROLOGICKÁ KLINIKA
2. LF UK a FN Motol

FN MOTOL

RE-LY: Pacienti po iCMP – sekundární prevence

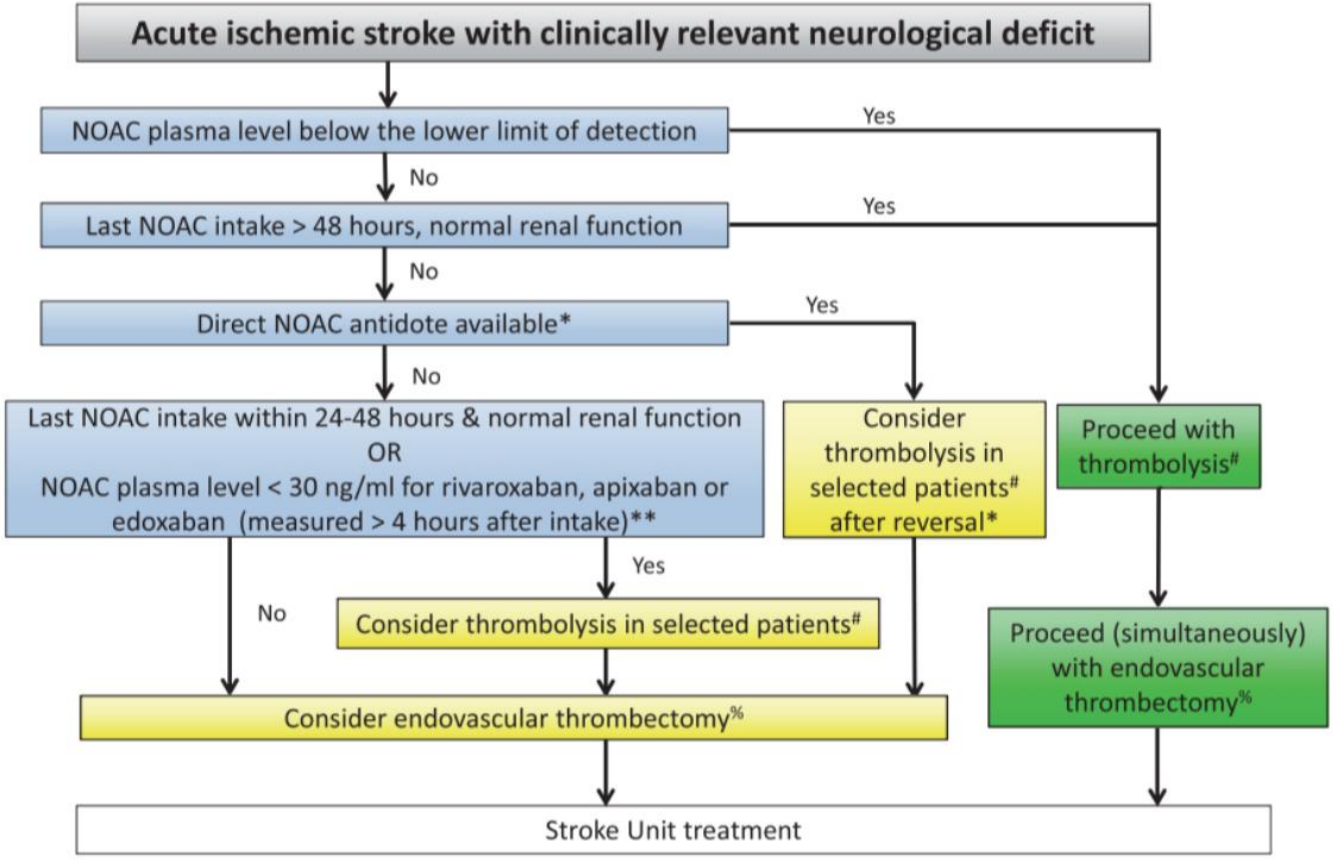


Ročně:
D 150 mg – 2,07%
D 110 mg – 2,32%
Warfarin – 2,78%

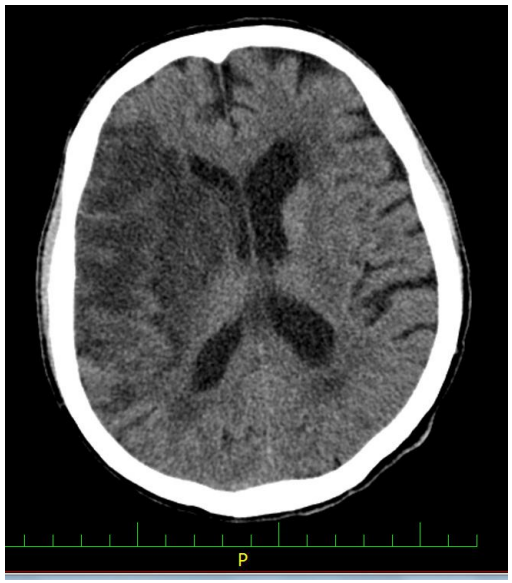
Vs. bez CMP:
D 150 mg – 0,87%
D 110 mg – 1,34%
Warfarin – 1,45%

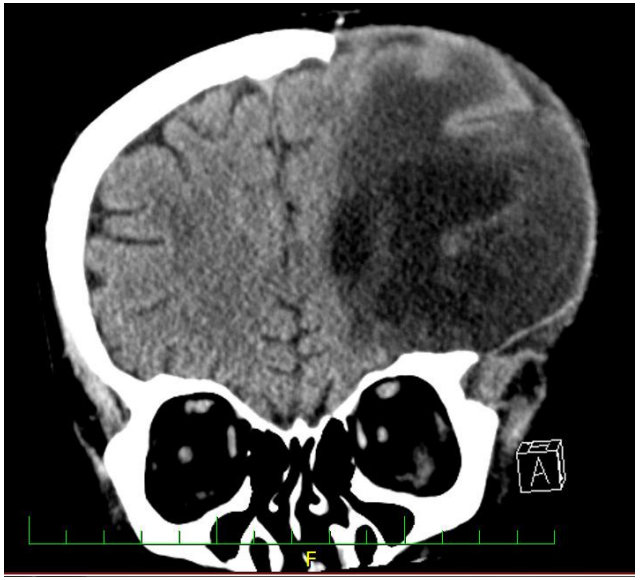
Diener HC et al. Lancet Neurol 2010;9:1157–63

Selhání – ischemická CMP



Steffel J et al. EHRA practical guide. Eur Heart Journal 2018. doi:10.1093/eurheartj/ehy136.





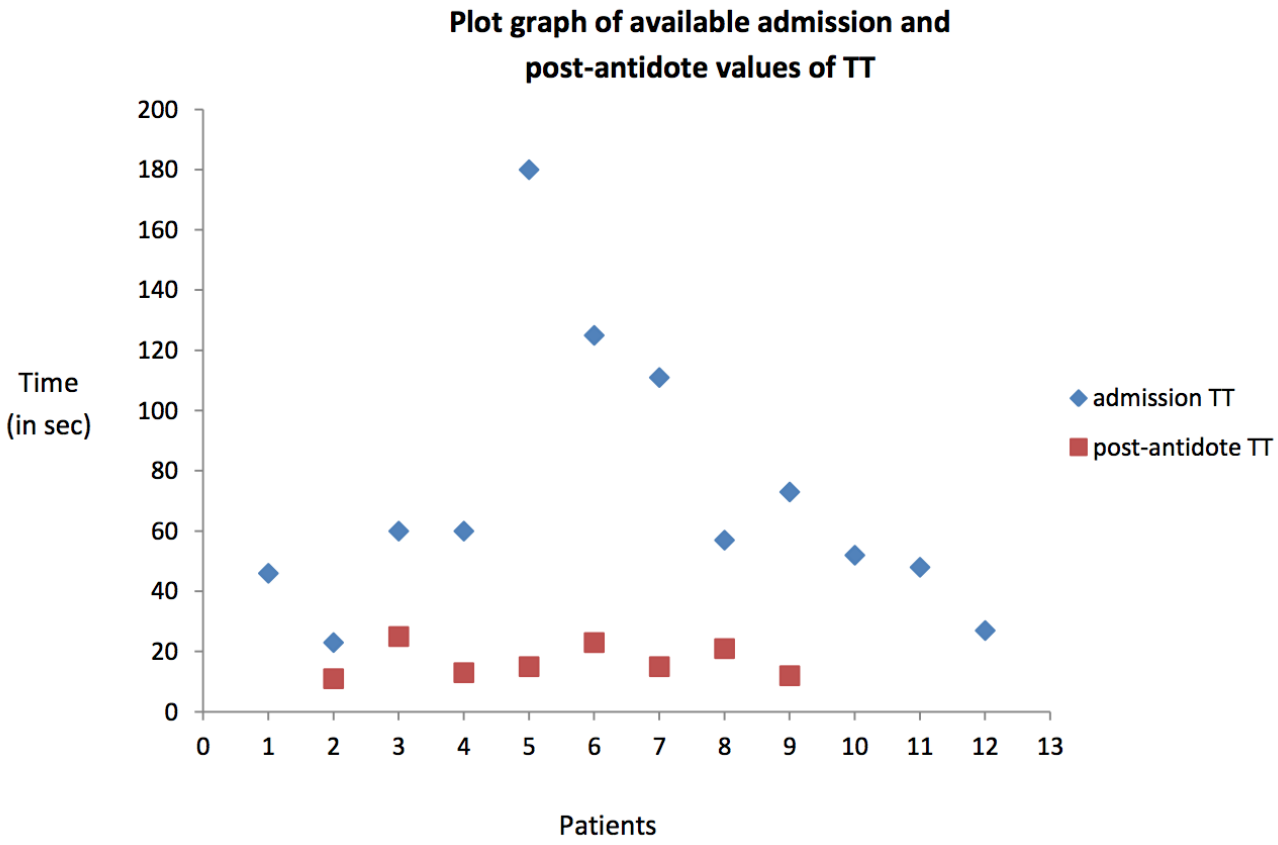
J Thromb Thrombolysis
DOI 10.1007/s11239-017-1476-2

Real-life experience with the specific reversal agent idarucizumab for the management of emergency situations in dabigatran-treated patients: a series of 11 cases

Milan R. Vosko[1] · Christof Bocksrucker[2] · Rafał Drwiła[3] · Petr Dulíček[4] · Tomas Hauer[5] · Johannes Mutzenbach[6] · Christoph J. Schlimp[7] · David Špinler[8,9] · Thomas Wolf[10] · Daša Zugwitz[11]

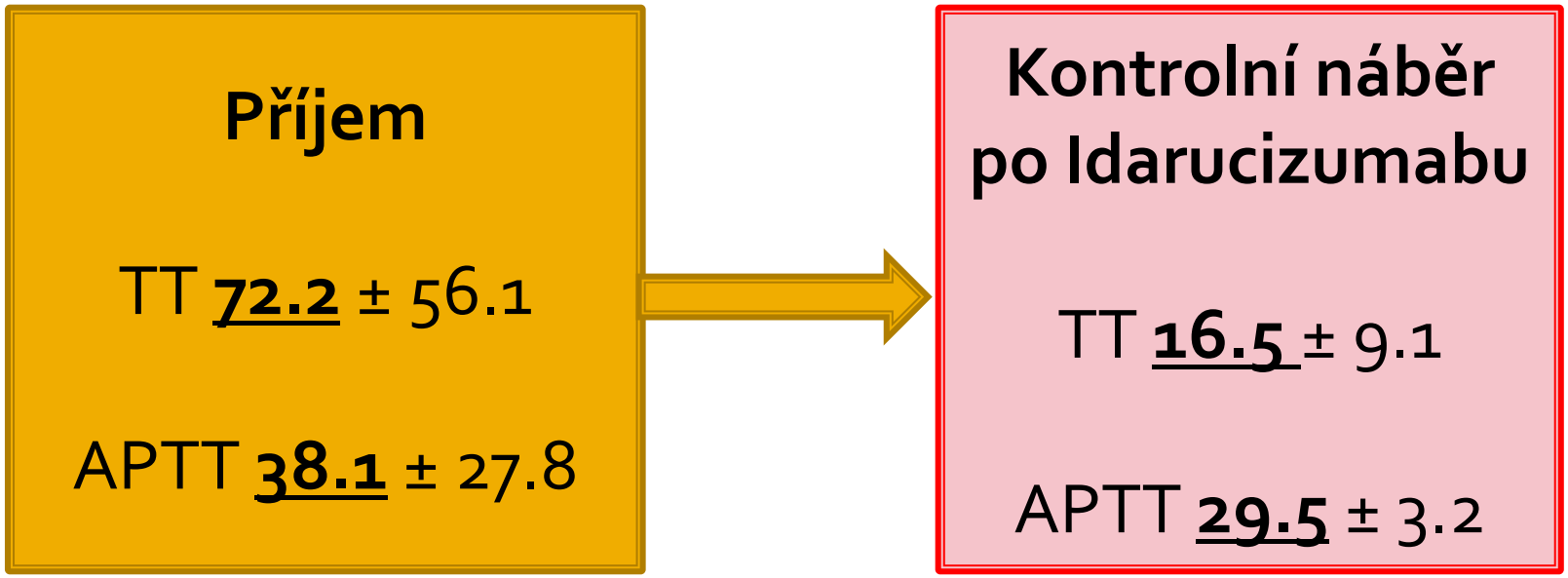
Normalizace TT u našich pacientů (n=13)

Graph B.



Šaňák, Jakubíček, Černík, Herzig, Kunáš, Mikulík, Ostrý, Reif, Rohan, Tomek, Veverka. JSCVD 2018 in print.

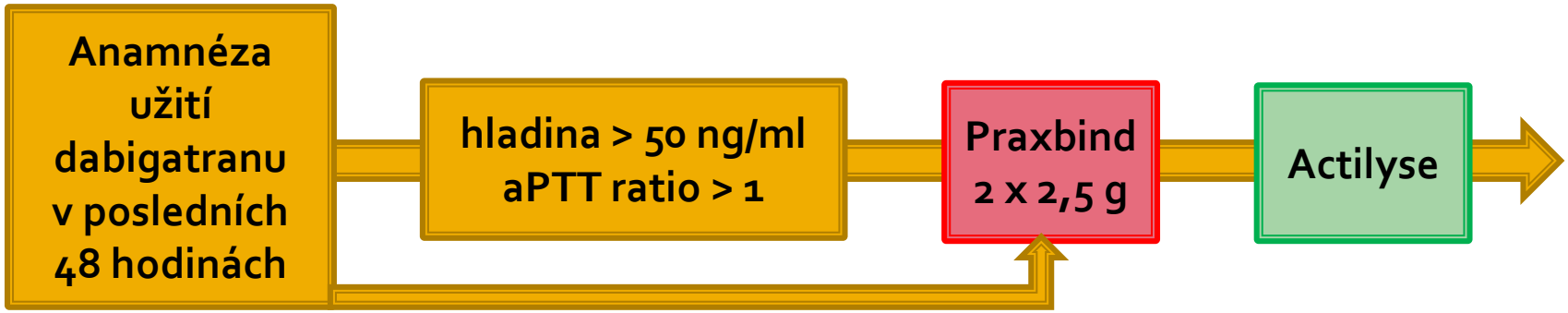
Vstupní parametry – IVT po podání Idarucizumabu



Medián podání IVT od zahájení Praxbind – 20 minut

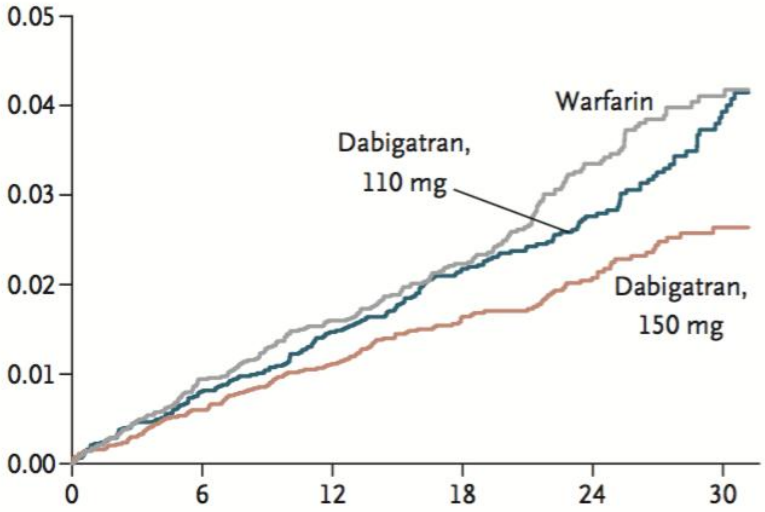
Šaňák, Jakubíček, Černík, Herzig, Kunáš, Mikulík, Ostrý, Reif, Rohan, Tomek, Veverka. JSCVD 2018 in print.

Nová doporučení pro trombolýzu na dabigatranu (CVS ČNS 2018)



V případě užívání dabigatranu a hodnotách aPTT a TT nad horní limit laboratoře nebo hodnotě dilutovaného trombinového času (Hemoclot) > 50 ng/l lze k okamžitému zrušení antikoagulačního účinku podat specifické antidotum Idarucizumab (Praxbind) v dávce 5 g (2 x 2,5 g/50 ml) intravenózně jako dvě po sobě následující infúze, každá v délce 5-10 minut nebo jako bolusová injekce. Po podání antidota je doporučeno odebrat kontrolní aPTT a TT a současně zahájit IVT. V případě výsledku kontrolních laboratorních hodnot aPTT a TT nad horní limit laboratoře je nutné okamžité ukončení IVT.

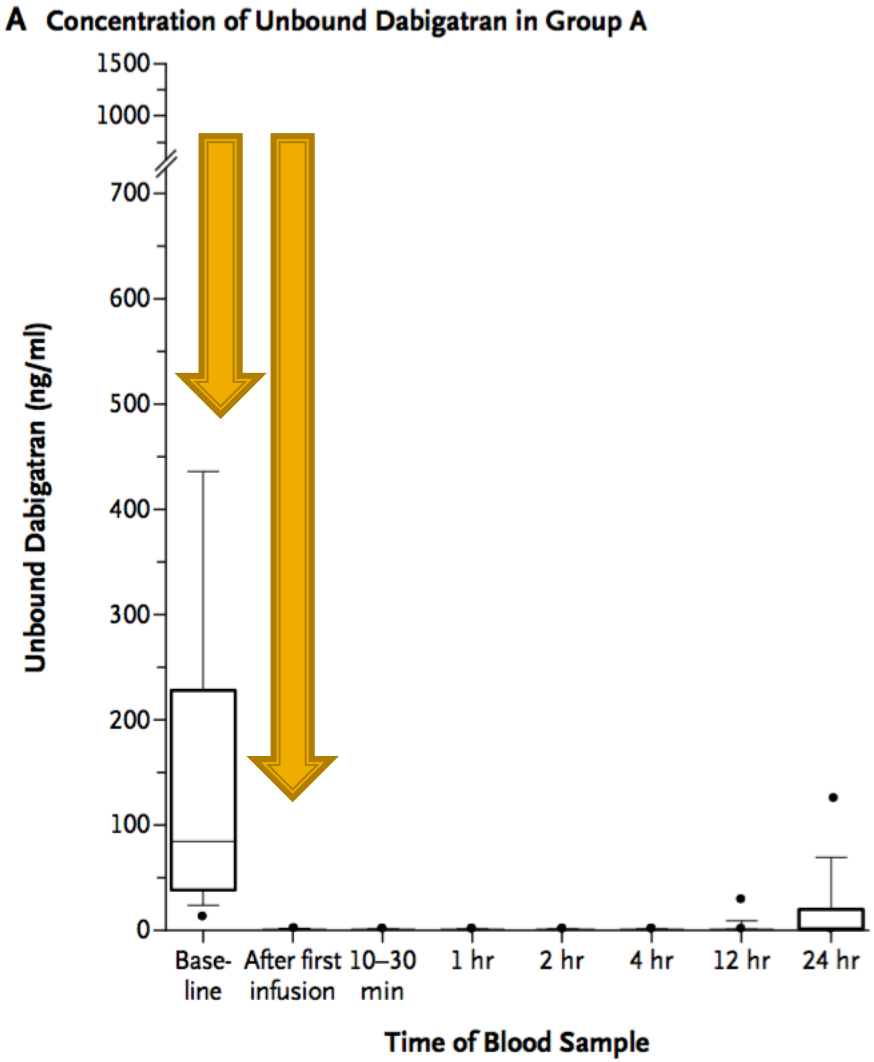
RE-LY – hemoragická CMP

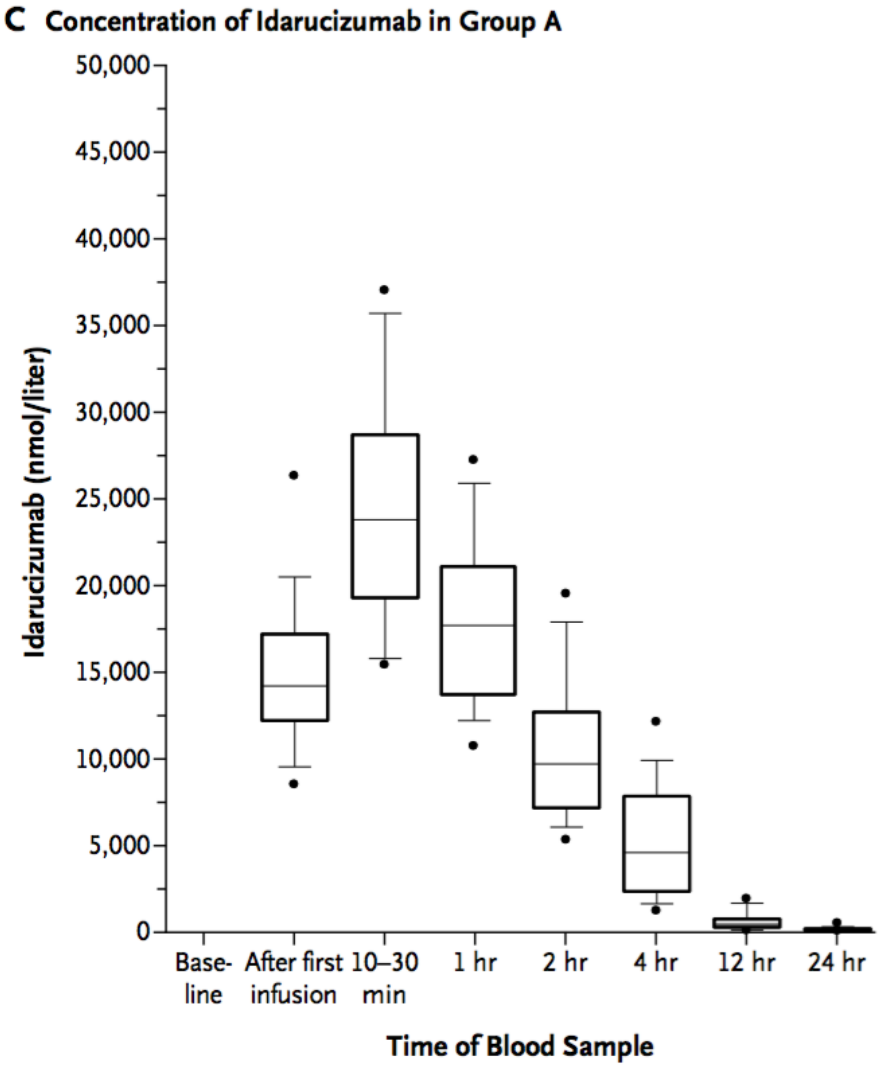


...omes, According to Treatment Group.

	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)	
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*
	182	1.53	134	1.11	199	1.69
Stroke	171	1.44	122	1.01	185	1.57
Hemorrhagic	14	0.12	12	0.10	45	0.38
Ischemic or unspecified	159	1.34	111	0.92	142	1.20
Nondisabling stroke	60	0.50	44	0.37	69	0.58
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00

Connolly SJ et al. N Engl J Med 2009;361:1139-51.

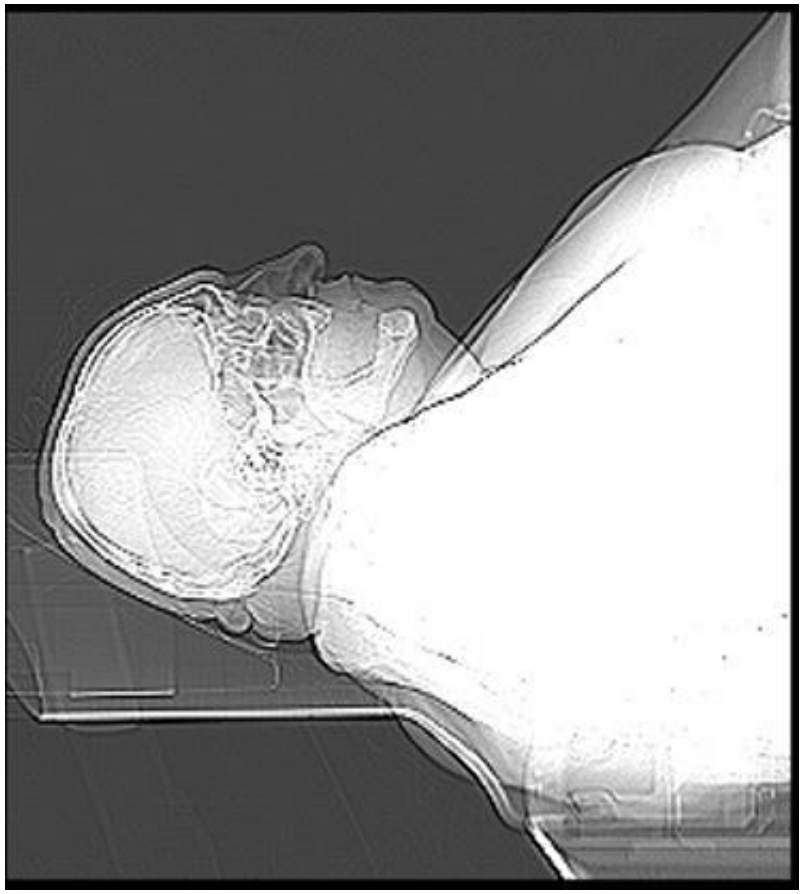




Pollack CV et al. NEJM 2015;373:511-20.

Pacient JS 1946

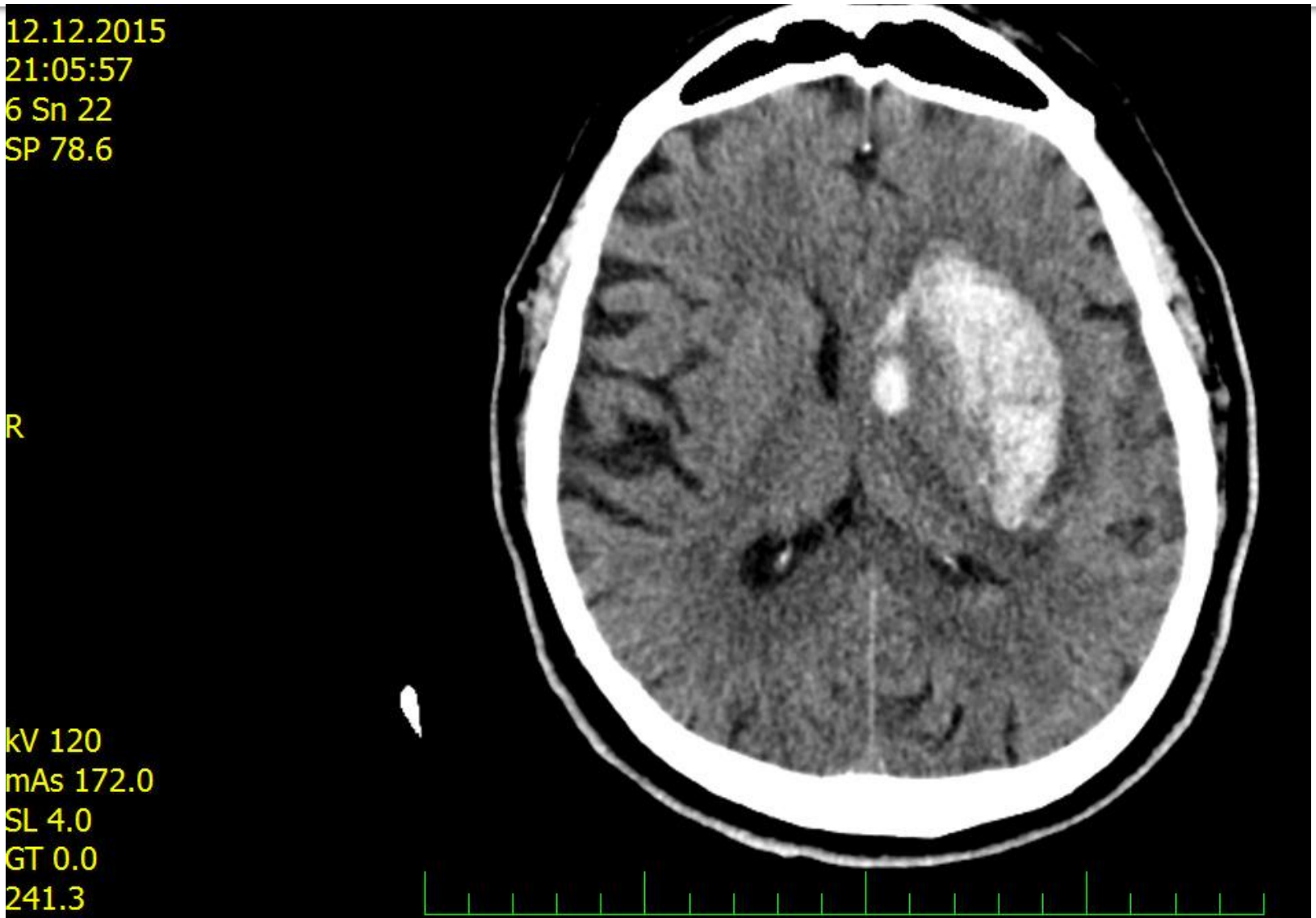
- Paroxysmální FS
- bez anamnézy IM, CMP
- FA: Pradaxa 150mg (3 roky)
- Morbidní obezita 150 kg/180 cm



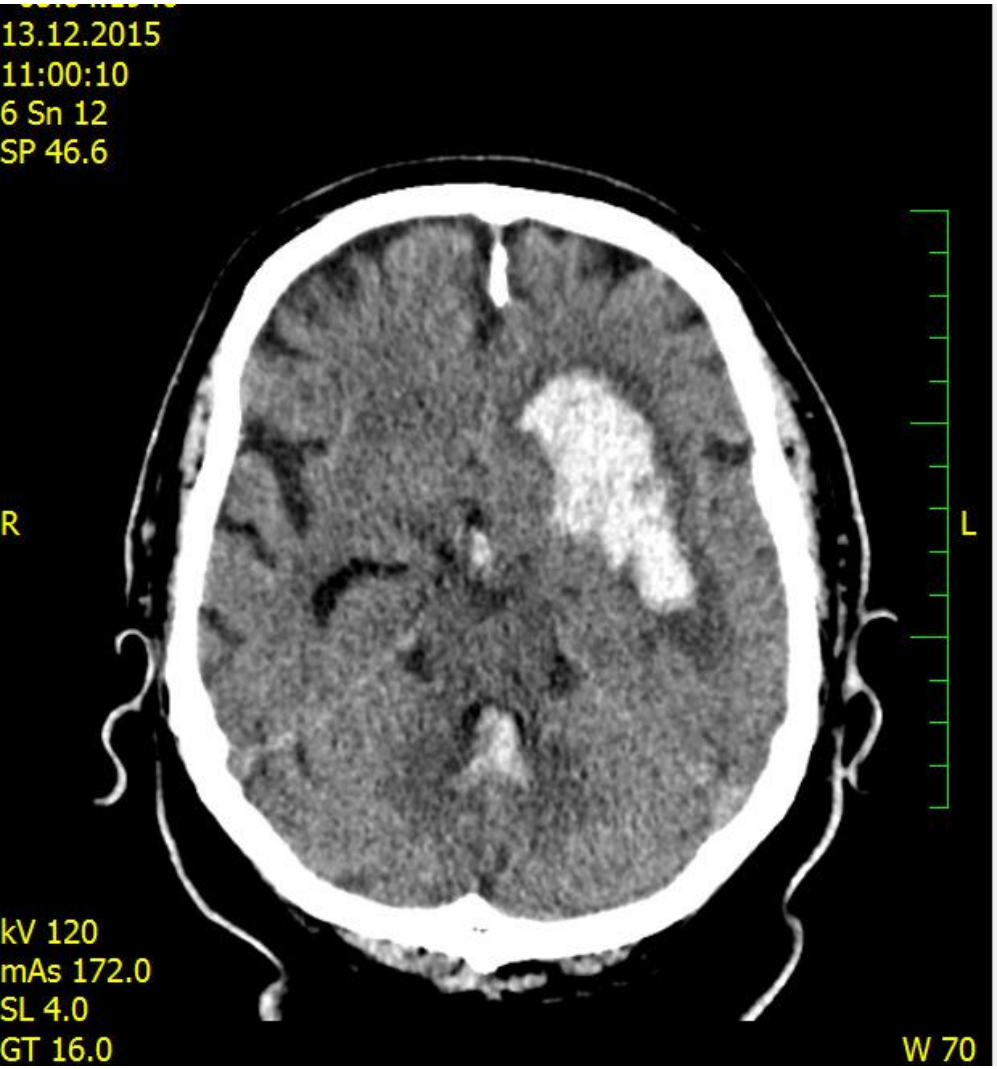
Průběh přijetí

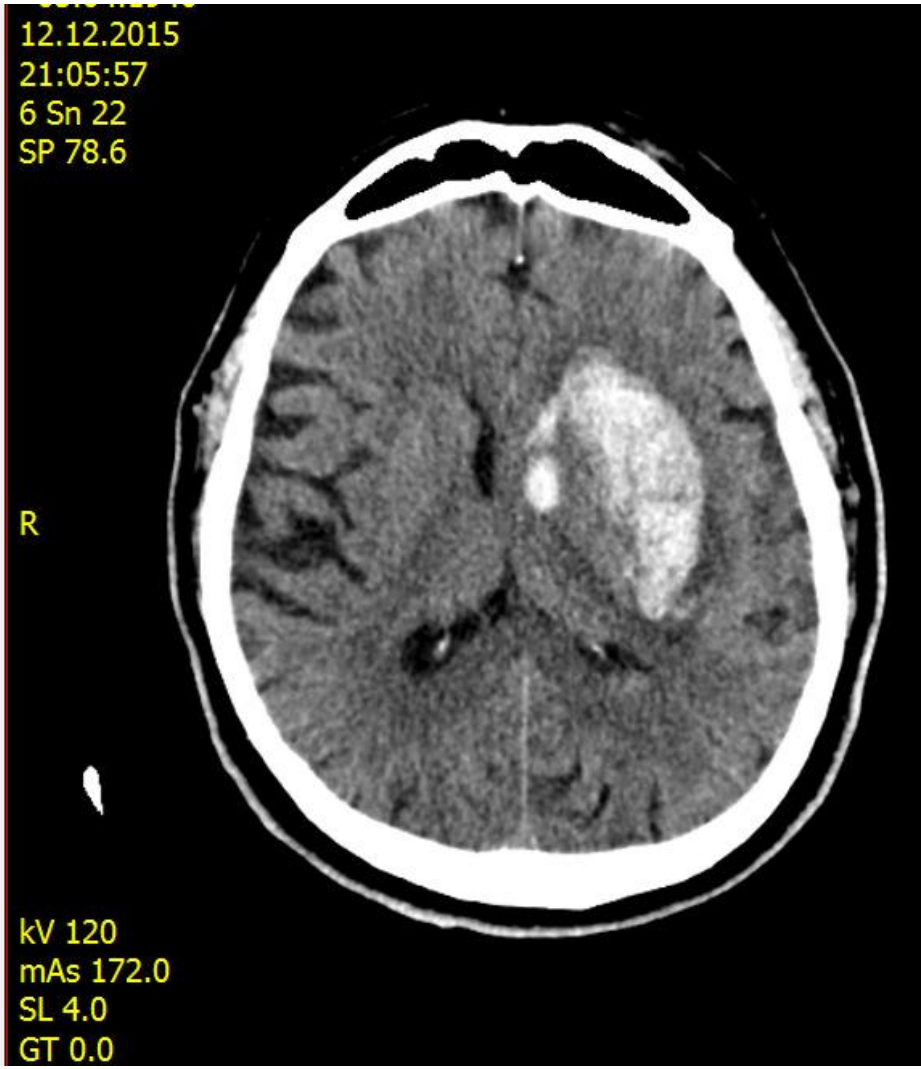
- 18:30 – užívá Pradaxa 150mg
- 19:45 – náhle se hroutí doma s dx. hemiparézou smíšenou fatickou poruchou
- 20:55 – Příjezd na OCPD
- 20:57 – odběry koagulace
- 21:04 – CT mozku s průkazem ICH
- 21:12 – příjezd na NeuroJIP
- 21:30 – podání Idarucizumabu – 1. dávka
- 22:00 – podání 2. dávky
- 22:10 – 23:00 – intubace + invaze

Vstupní CT 21:04, 12.12.

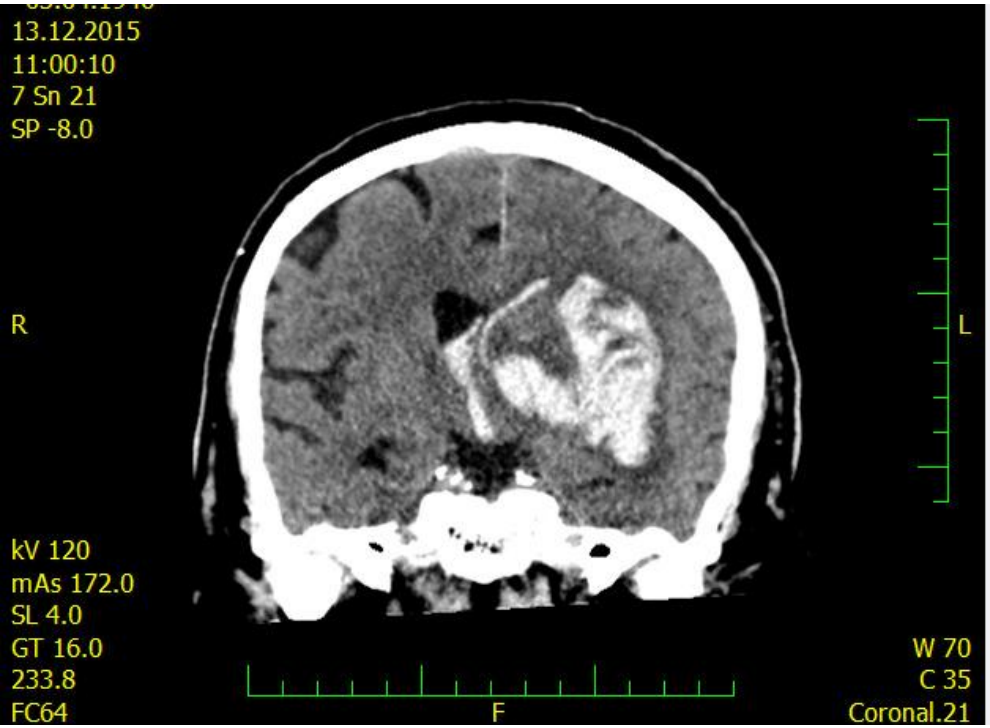


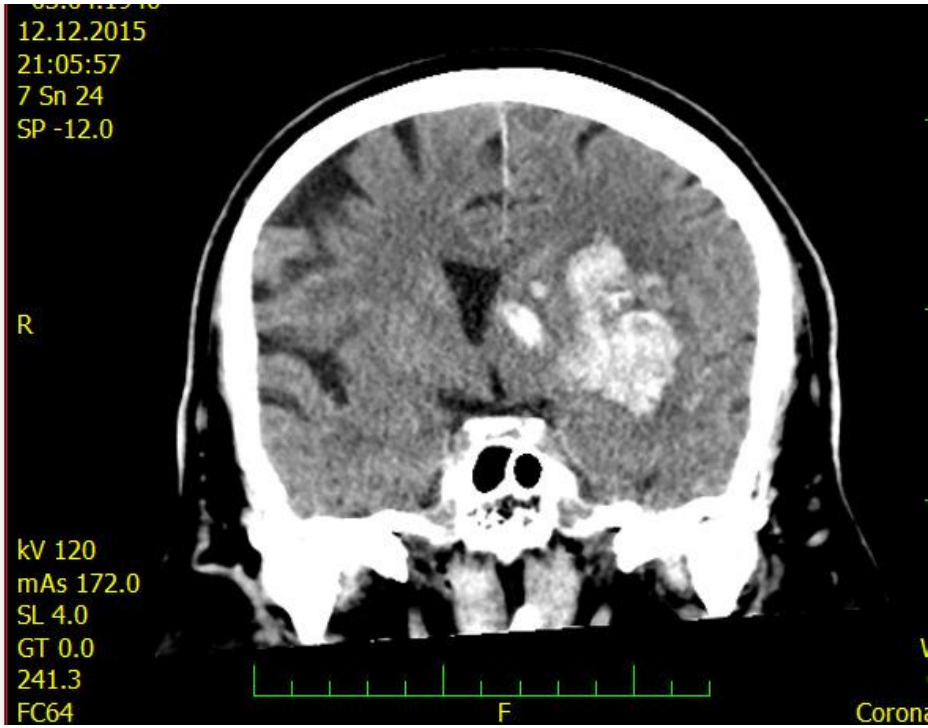
CT 1. a 2. (+14 hodin)



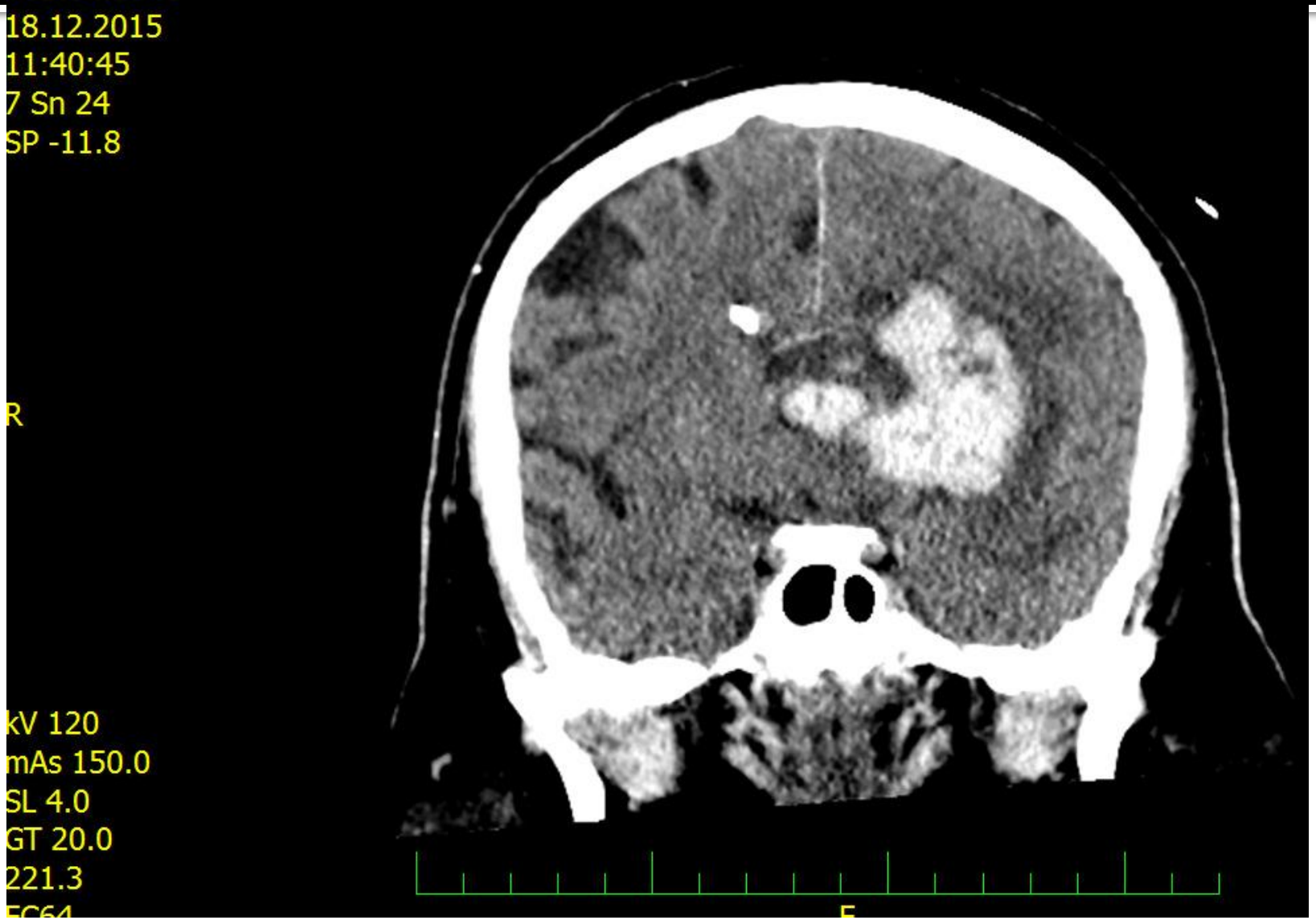


CT 1. a 2. (+14 hodin)

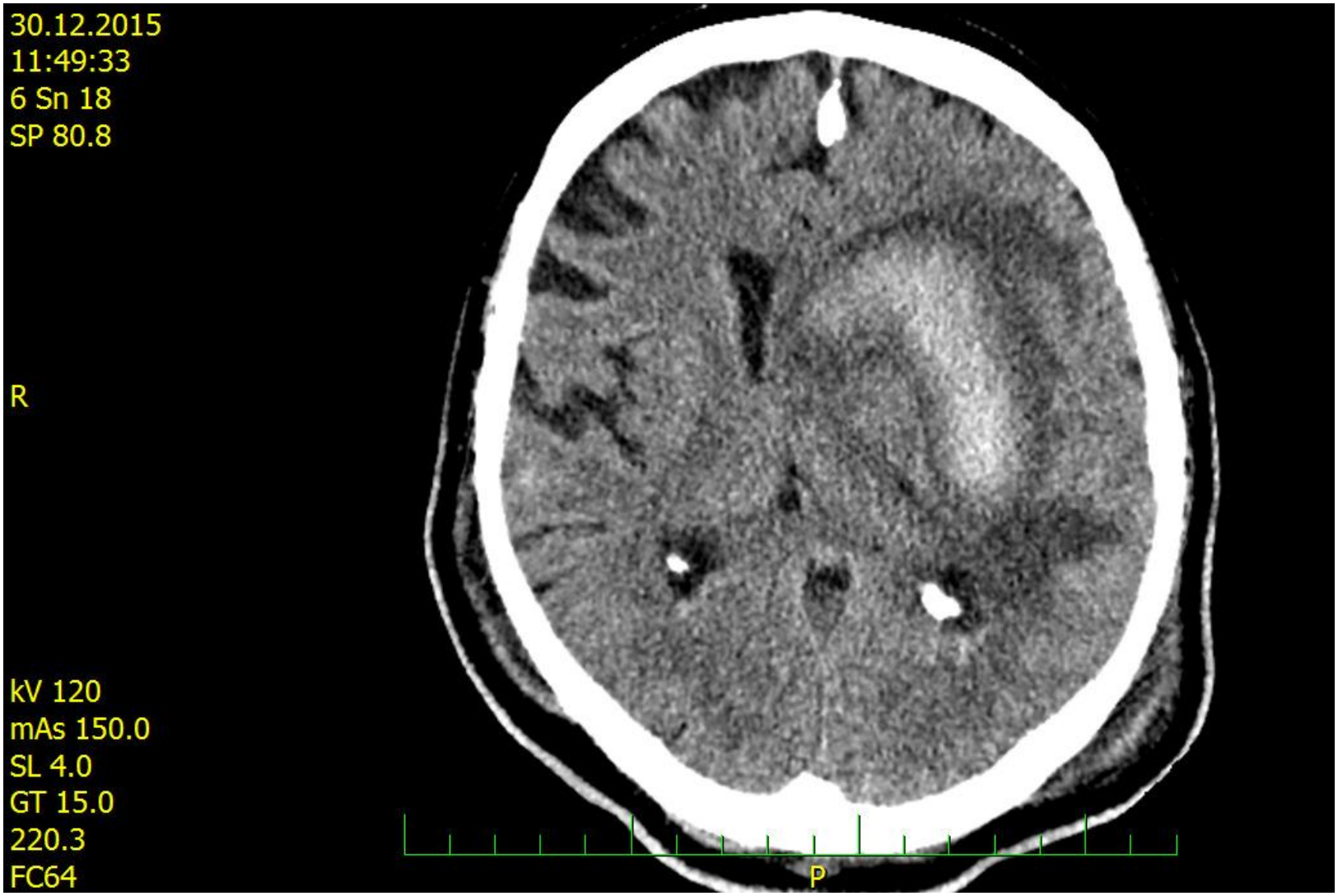




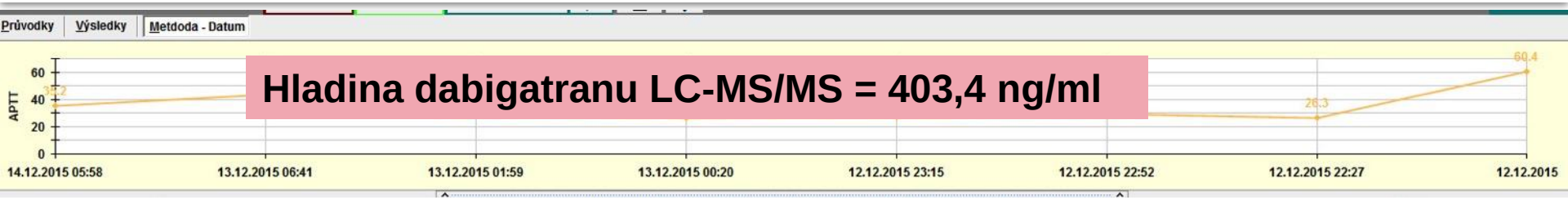
CT – 6. den (EVD od 2. dne)



CT po 16 dnech



Koagulační parametry

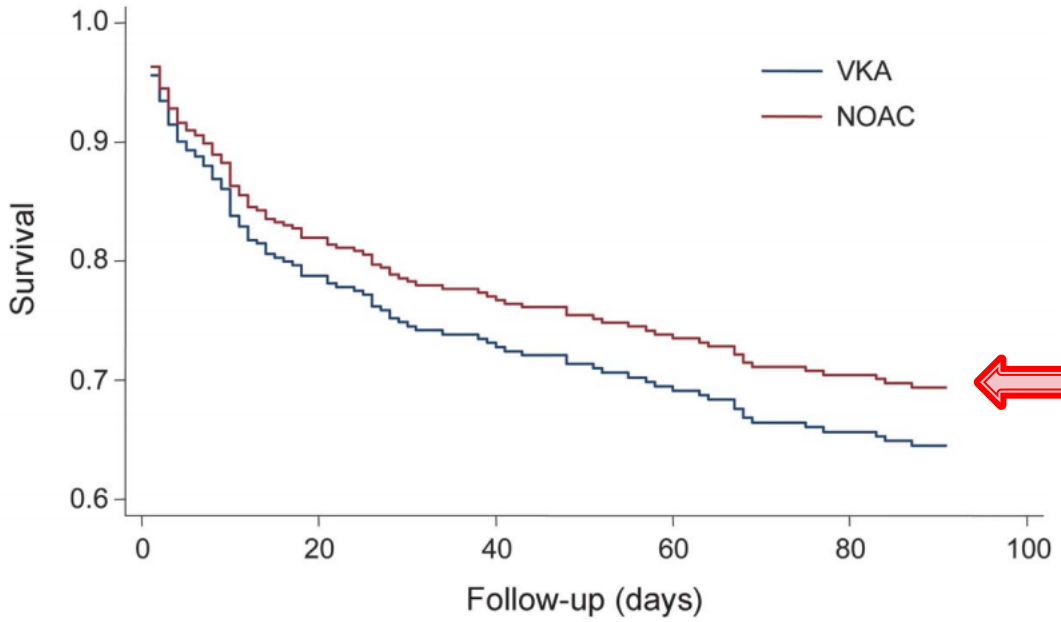


Hladina dabigatranu LC-MS/MS = 403,4 ng/ml

APTT	s	** 60.40	26.50
APTTN	s	29.10	29.10
RATIO	--	** 2.08	0.91
PT-Quick	s	12.00	10.60
PTN-Quick	s	10.80	10.80
INR	--	1.11	0.98
PT-RATIO	--	1.11	0.98
TT	s	<120.00	16.50
TTN	s	17.40	17.40
TT-RATIO		! >6.50	0.95
Fibr	g/l		
D Dim	ng/ml	<10	

Studie CROMIS-2 – porovnání ICH u pacientů léčených NOAC a warfarinem

Figure 2 Survival curve comparing non-vitamin K oral antagonist anticoagulant (NOAC)-associated intracerebral hemorrhage (ICH) and vitamin K antagonist anticoagulant (VKA)-associated ICH 90-day mortality



Number at risk

VKA	390	262	220	202	186	0
NOAC	90	64	55	51	48	0

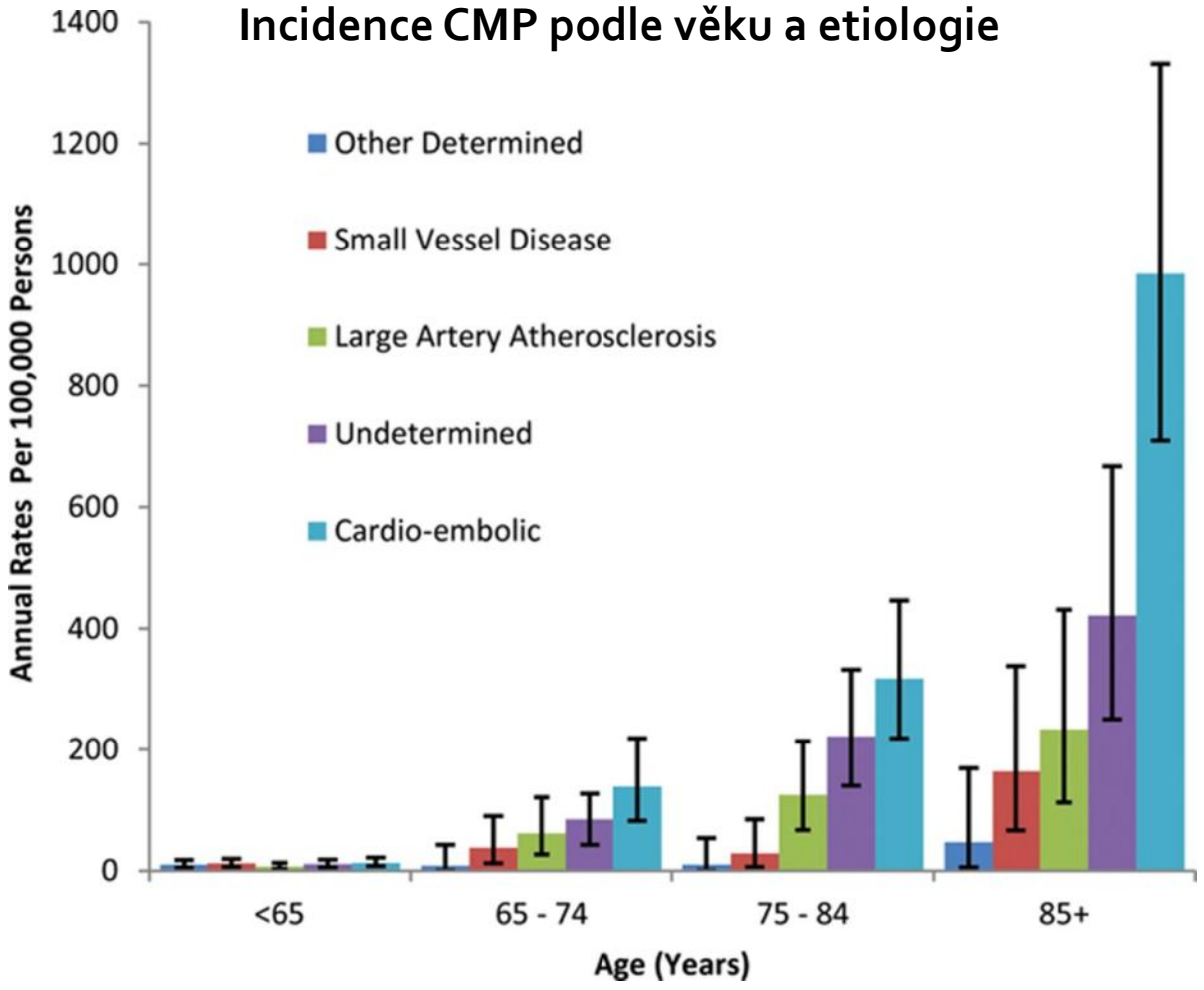
Adjusted for age; sex; baseline Glasgow Coma Scale score, ICH location, and log volume; intraventricular hemorrhage volume; and intracranial surgery.

baseline ICH volume, hematoma expansion, 90-day mortality, and functional outcome were similar following NOAC-ICH and VKA-ICH

Adjusted mortality
HR = 0.93 (0.52–1.64, p=0.79)

Wilson D et al. Neurology 2017;88:1693–1700

Proč používáme NOAC jen u prevence CMP při FS?



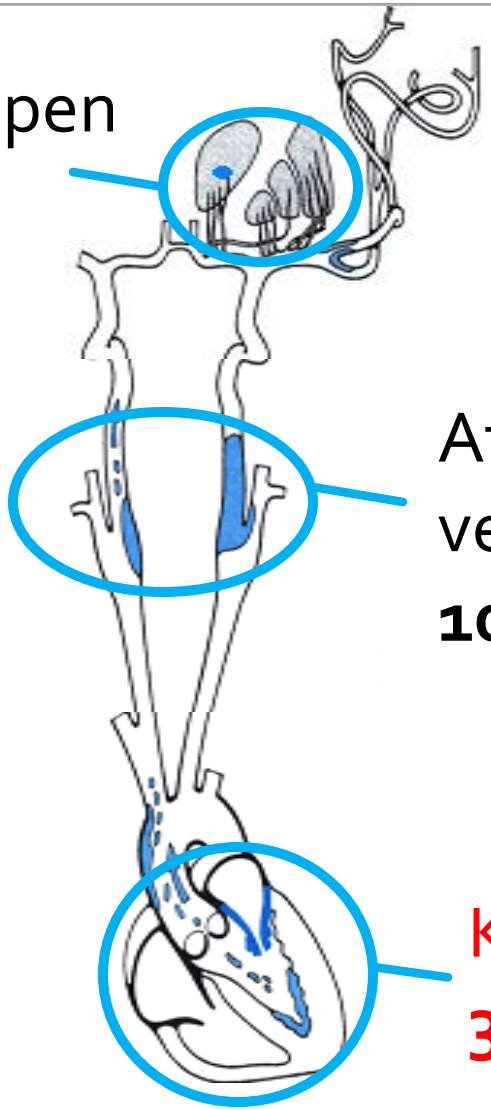
Leyden JM et al. Stroke. 2013;44:1226-1231.

Klasifikace TOAST

Nemoc malých tepen
20-25%

Kryptogenní
30 (20-40)%

Jiné: disekce, vaskulitidy, hyperkoagulace
2-5%



Atherosklerόza velkých tepen
10-15%

Kardioembolické
35%

M

TOAST – neurčená etiologie (1993)

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.

Kryptogenní

Adams HP et al. Stroke 1993;24;35-41.

Definice kryptogenního iktu

1877 – popis mechanizmu paradoxní embolizace- Julius Friedrich Cohnheim (1839-1884)

1978 – první použití „cryptogenic stroke" ve spojení s PFO

1988 – první literární citace termínu „cryptogenic stroke" opět ve spojení s PFO - Jay P. Mohr

Κρυπτος

CRYPTOGENIC STROKE

In this issue of the *Journal*, Lechat and colleagues[1] show that contrast echocardiography greatly increased the frequency with which patent foramen ovale was diagnosed in a series of young patients who had had strokes, especially in a subgroup with no known risk factors for stroke. These findings point up the value of noninvasive cardiac imaging in uncovering a risk factor in those whose stroke would otherwise be characterized as "cryptogenic." The diagnosis of cryptogenic stroke is more common, now that atherosclerotic stenosis or thrombosis of large arteries, formerly the accepted causes of a majority of strokes, have been shown to account for only a minority of them.[2]

Mohr JP. NEJM 1988;318:1197-8.

“Limitace” kryptogenního iktu

- Termín definován různě, různými autory, většinou používán ve spojitosti s PFO
- Samotný pojem je tedy kryptogenní
- Není definován jasný diagnostický panel
- Velmi záleží na rozsahu vyšetření, čím vice hledáme, tím méně je kryptogenních iktů

ESUS: Embolic Strokes of Undetermined Source

Non-lacunar brain infarcts without proximal arterial stenoses or cardioembolic sources with a clear indication for anticoagulation

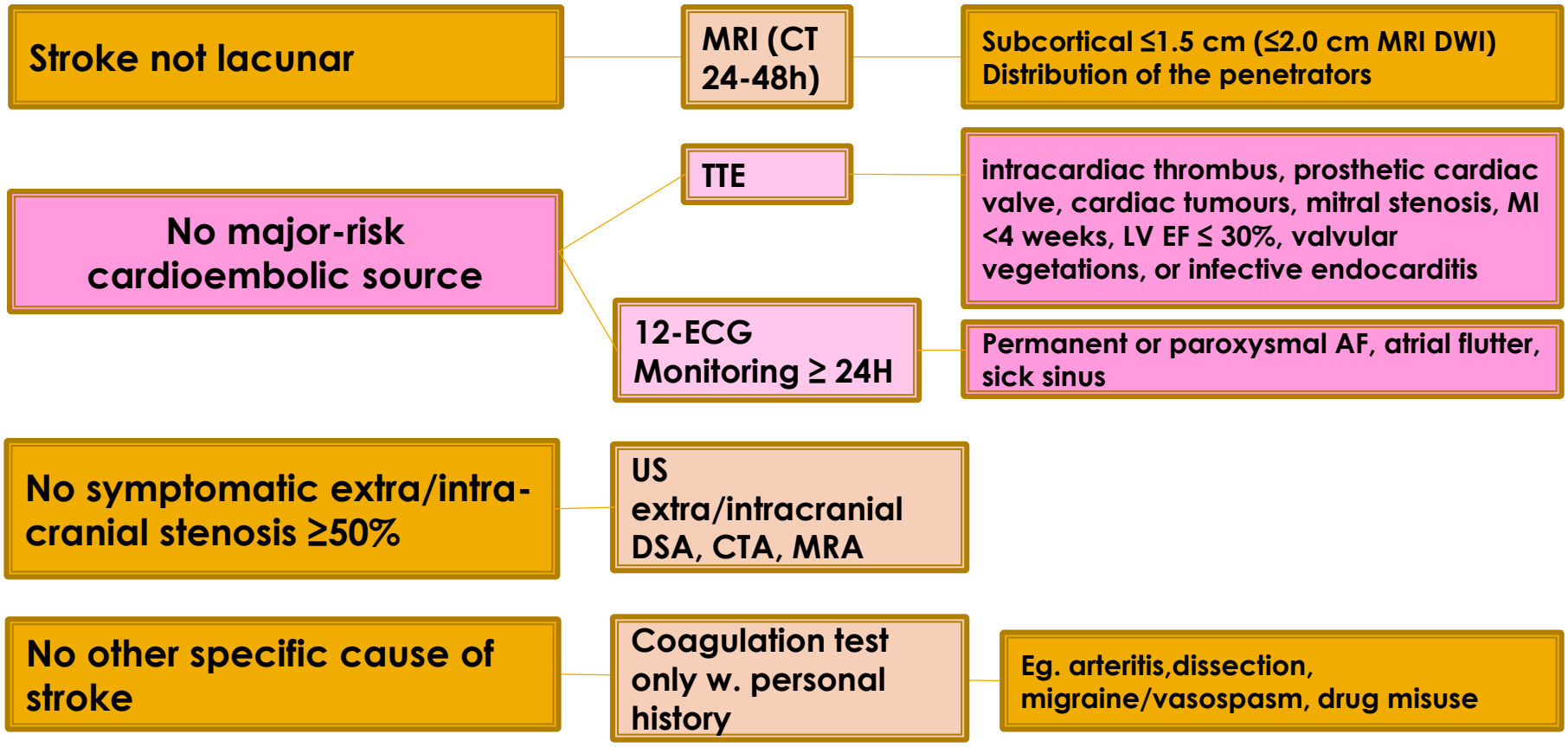
Embolic strokes of undetermined source: the case for a new clinical construct

Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O'Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

Cryptogenic (of unknown cause) ischaemic strokes are now thought to comprise about 25% of all ischaemic strokes. Advances in imaging techniques and improved understanding of stroke pathophysiology have prompted a reassessment of cryptogenic stroke. There is persuasive evidence that most cryptogenic strokes are thromboembolic. The thrombus is thought to originate from any of several well established potential embolic sources, including minor-risk or covert cardiac sources, veins via paradoxical embolism, and non-occlusive atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries. Accordingly, we propose that embolic strokes of undetermined source are a therapeutically relevant entity, which are defined as a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources, with a clear indication for anticoagulation. Because emboli consist mainly of thrombus, anticoagulants are likely to reduce recurrent brain ischaemia more effectively than are antiplatelet drugs. Randomised trials testing direct-acting oral anticoagulants for secondary prevention of embolic strokes of undetermined source are warranted.

Hart RG et al. Lancet Neurol 2014.

ESUS Diagnostická kritéria a vyšetřovací panel



Hart RG et al. Lancet Neurol 2014.

Základní fakta o ESUS

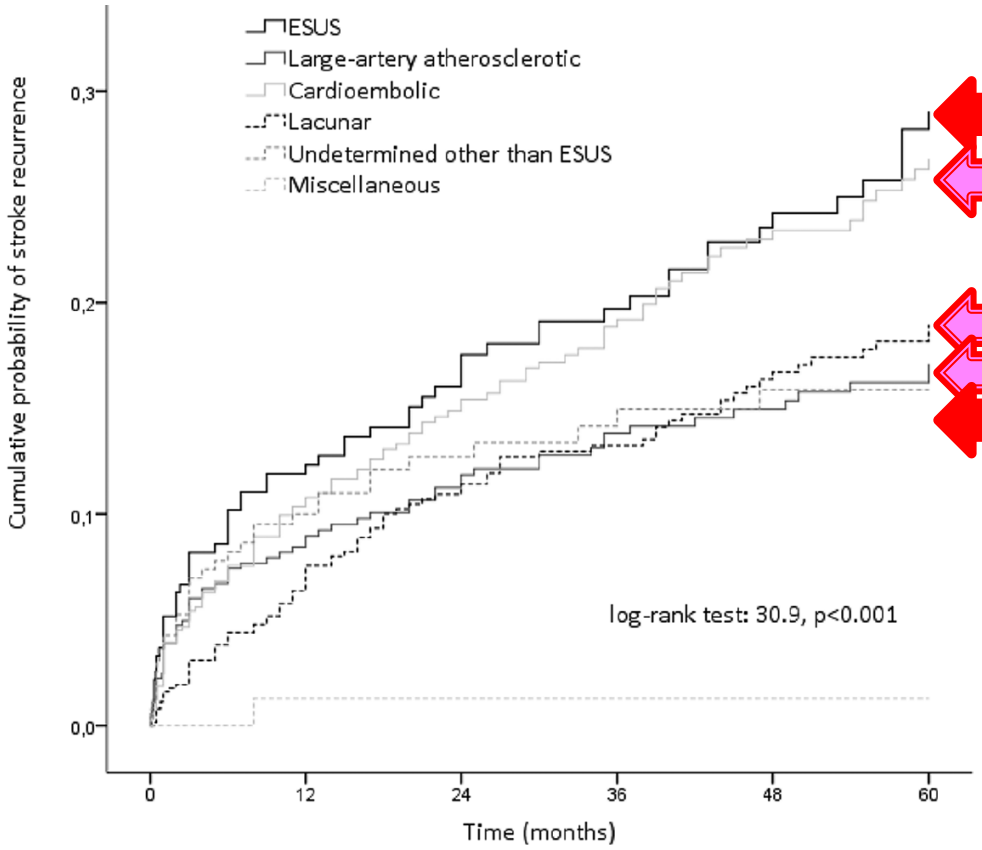
Study	Design	Population	Cardiac Rhythm Monitoring	% ESUS* (n)	Comments
Ntaios et al[13]	Retrospective, single-center, inpt stroke registry, 1992–2011	2731 Greek pts with first ischemic stroke; mean age 71 y	71% inpt telemetry for 7 d or discharge; 52% 24 h Holter ECG	10 (275)	29% of ESUS pts had AF detected during f/up
Mahagne et al[14]	No details	1074 French pts, no details published	Holter ECG as inpt (mean 7 d)	23 (243)	28% ESUS if only a 24 h Holter ECG done
Li et al[15]	Population-based, ischemic stroke or TIA, 2002–2014	1607 strokes and 948 TIAs in the UK; mean age 74 y	Ambulatory home monitoring in 20% first 8 y, 80% thereafter	7 (189)	Nonlacunar TIAs could be ESUS; most cryptogenic pts did not have the required cardiac rhythm monitoring
Putaala et al[16]	Retrospective, single center, inpts, 2010–2012	540 Finnish pts, mean age 69 y	44% continuous ECG monitoring	9 (46)	NAVIGATE ESUS trial criteria used.[2] Most cryptogenic pts did not have the required cardiac rhythm monitoring
Ladeira et al[17]	Retrospective, single center, ages 18-55 y, 2010–2014	100 young Portuguese pts with ischemic stroke, mean age 46 y	NR	42 (42)	Minor risk potential cardioembolic sources not more frequent in young stroke patients with ESUS
Takasugi et al[18]	Retrospective, single center, 2012–2014	623 Japanese acute ischemic stroke pts; mean age NR	Continuous ECG monitoring for ≥3 days in all	13 (81)	
Perera et al[19]	Retrospective, 19 international stroke units, 2014–2015	2144 pts with ischemic stroke; mean age 67 y	33% only inpt telemetry for ≥24 h, 59% 24 h Holter ECG, 8% >24 h monitoring	16 (351)	Excluding pts with incomplete diagnostic testing required for ESUS, 19% were ESUS
Montero et al[20]	Retrospective, single-center stroke unit pts during 2010	318 Spanish pts with ischemic stroke; mean age NR	No details	19 (60)	Support for a cardioembolic mechanisms for most ESUS
Coutinho et al[21]	Retrospective, single-center stroke registry, 2012–2015	1038 Canadian pts with ischemic stroke, mean age NR	Minimum of 24 h of automated rhythm monitoring	12 (128)	Support for nonstenotic carotid plaques as causing ESUS
Ueno et al[22]	Retrospective, single-center inpt stroke registry, 2008–2014	1158 Japanese pts with acute ischemic stroke, mean age NR	Cardiac telemetry ≥24 h	25 (292)	
Masina et al[12]	Retrospective, single-center stroke unit, 2010–2012	337 Italian ischemic stroke pts, mean age 78 y†	72 h continuous inpt telemetry without automated rhythm detection	25 (84)	41 (49%) ESUS pts had minor risk cardioembolic sources identified by echocardiography
Arauz et al[23]	Retrospective, single-center stroke registry, 2003–2015	1673 Mexican ischemic stroke pts, mean age NR	At least 24 h of Holter monitor	9 (149)	60 additional patients with cryptogenic stroke were not ESUS due to incomplete evaluation

SYSTEMATIC REVIEW OF ESUS (n=2045 patients):

- Frequency **17%** (9-25%)
- Mean age **65** years
- Mean admission NIHSS **5**
- Annual recurrent stroke on antiplatelet **4.5%**

Hart RG et al. Stroke 2017;48:867-872.

Prognóza ESUS – 5-leté sledování



Rekurence CMP – 5 let

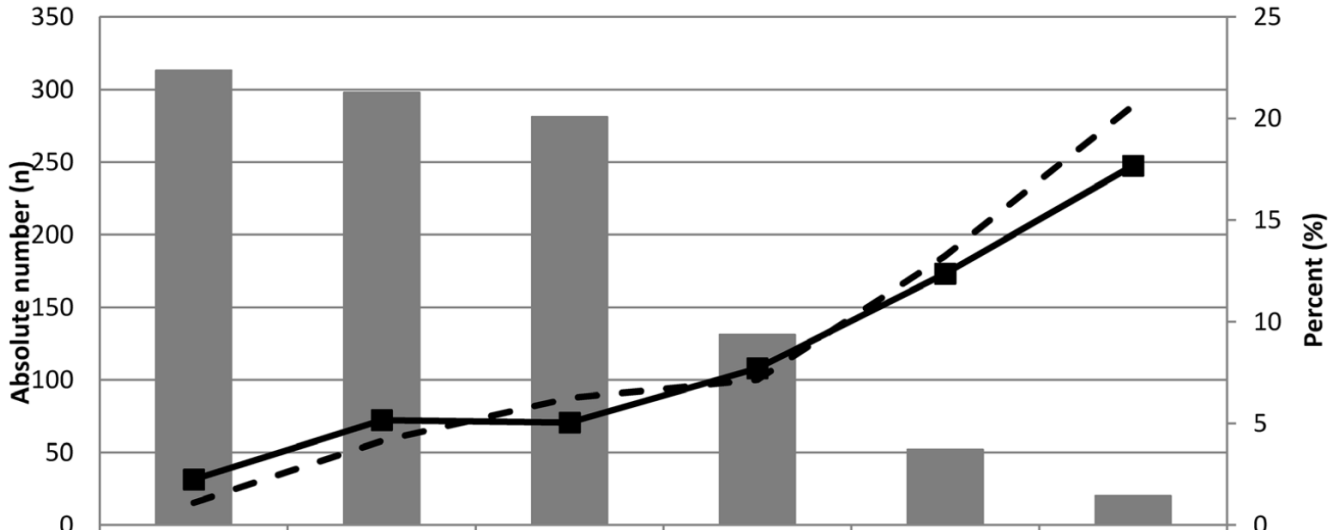
ESUS	29.0%
CARDIOEMBOLIC	26.8%
LACUNAR	18.9%
LVD	17.1%
UND – ne ESUS	15.9%

Ntaios G et al. Stroke. 2015;46:2087-2093.

Stratifikace rizika u ESUS pacientů?

The risk of stroke recurrence and death in patients with a CHA2DS2-VASc score ≥2 is much higher compared with that in patients with a score of 0, approximately 3-fold and 15-fold, respectively.

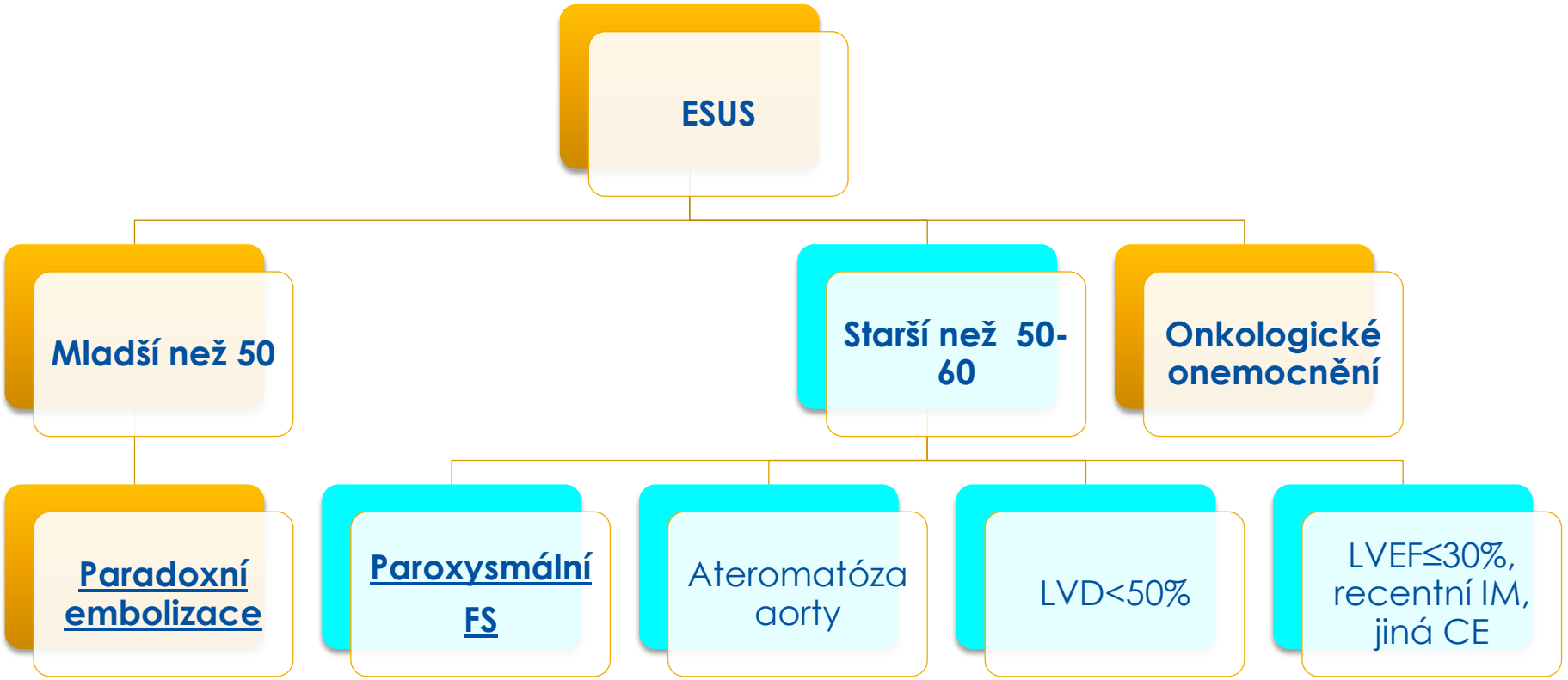
A



	0	1	2	3	4	5&6
CHADS2 (n)	313	298	281	131	52	20
CHADS2 - Recurrence (% per year)	2,2	5,2	5,0	7,7	12,4	17,7
CHADS2 - Mortality (% per year)	1,1	4,1	6,3	7,1	13,2	20,6

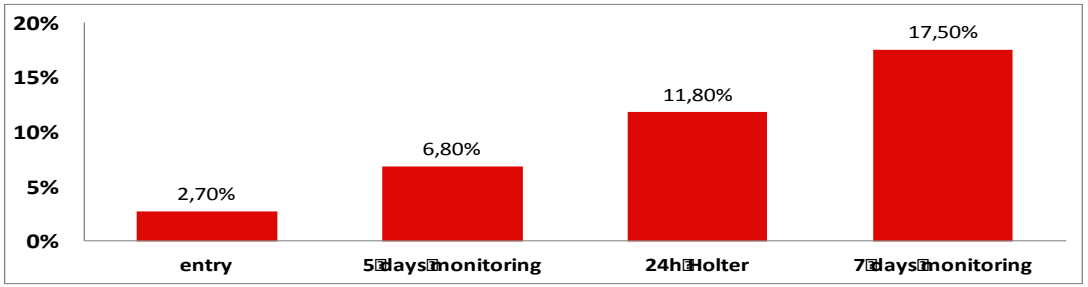
Ntaios G et al. Stroke. 2016;47:2278-2285.

Co je možná příčina ESUS?

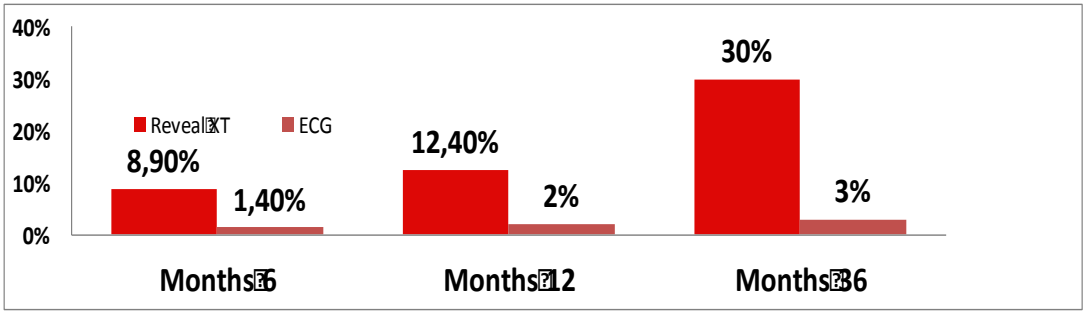


Detekce FS – čím déle, tím více

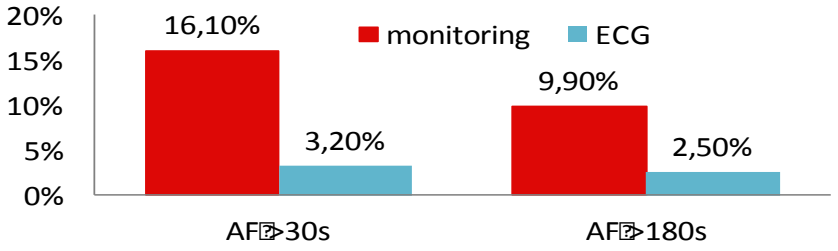
Jabaudon et al 2004.
8 days = 14.8%



CRYSTAL-AF
3 years = 30%



EMBRACE
30 days = 16.1%



Diagnóza FS u ESUS pacientů?

Table 2. Potential Causes of ESUS

Minor-Risk Potential Cardioembolic Sources	
Mitral valve	
Myxomatous valvulopathy with prolapse	5 (1.8%)
Mitral annular calcification	8 (2.9%)
Aortic valve	
Aortic valve stenosis	3 (1.1%)
Calcific aortic valve	12 (4.4%)
Non-atrial fibrillation atrial dysrhythmias and stasis	
Atrial asystole and sick-sinus syndrome	3 (1.1%)
Atrial high-rate episodes	7 (2.6%)
Atrial appendage stasis with reduced flow velocities or spontaneous echodensities	6 (2.2%)
Atrial structural abnormalities	
Atrial septal aneurysm	10 (3.6%)
Chiari network	0
Left ventricle	
Moderate systolic or diastolic dysfunction (global or regional)	42 15.4%)
Ventricular noncompaction	12 (4.4%)
Endomyocardial fibrosis	1 (0.4%)
Covert paroxysmal atrial fibrillation (detected during follow-up)	
Atrial fibrillation detected on stroke recurrence	30 (11.0%)
Atrial fibrillation detected on monitoring during follow-up	50 (18.3%)
Atrial fibrillation not confirmed but strongly suspected	38 (13.9%)
Cancer-associated	
Covert nonbacterial thrombotic endocarditis	1 (0.4%)
Tumor emboli from occult cancer	2 (0.8%)
Arteriogenic emboli	
Aortic arch atherosclerotic plaques	9 (3.3%)
Cerebral artery nonstenotic plaques with ulceration	29 (10.6%)
Paradoxical embolism	
Patent foramen ovale	11 (4.0%)
Atrial septal defect	3 (1.1%)

28.3% AF in Athens ESUS registry, where 10% of strokes were classified as ESUS (n=275)

Covert paroxysmal atrial fibrillation (detected during follow-up)	
Atrial fibrillation detected on stroke recurrence	30 (11.0%)
Atrial fibrillation detected on monitoring during follow-up	50 (18.3%)
Atrial fibrillation not confirmed but strongly suspected	38 (13.9%)

Ntaios G et al. Stroke. 2015;46:176-181.

Jak léčit ESUS pacienty? Současná doporučení….

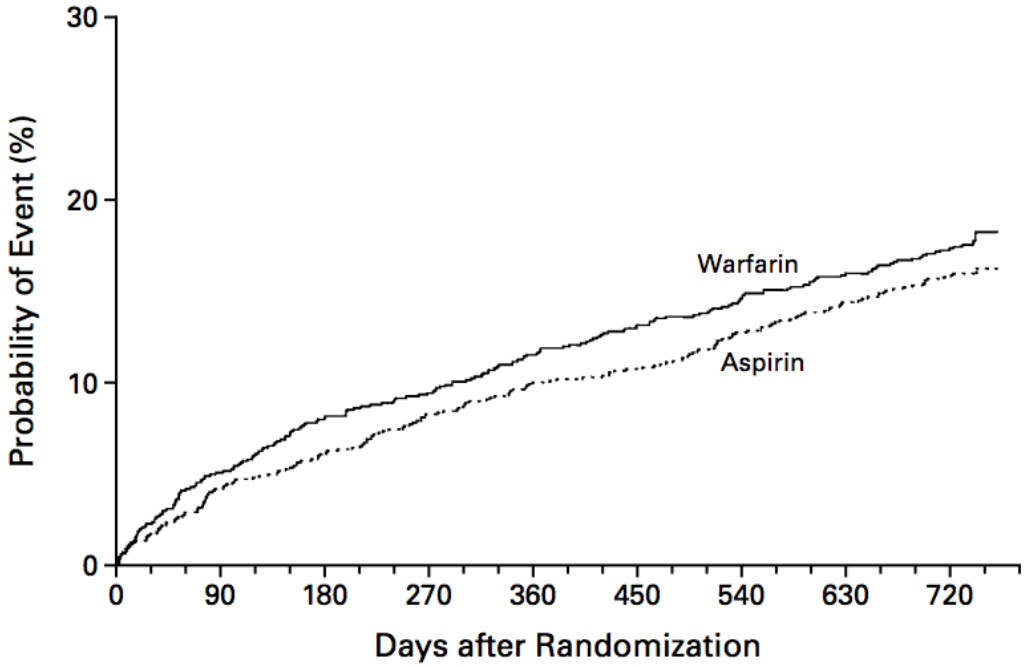
Antiplatelet Agent Recommendations

For patients with non-cardioembolic ischemic stroke or TIA, **the use of antiplatelet agents rather than oral anticoagulation is recommended** to reduce the risk of recurrent stroke and other cardiovascular events

(Class I; Level of Evidence A)

AHA-ASA - Kernan WN et al. Stroke 2014

WARSS: Proč vůbec léčíme nekardioembolické CMP antiagregační léčbou?



No. at Risk									
Warfarin	1103	1047	1013	998	972	956	939	924	885
Aspirin	1103	1057	1032	1004	984	974	951	932	900

Warfarin vs. ASA 325mg

- primary end point of recurrent **ischemic stroke or death** from any cause within two years.

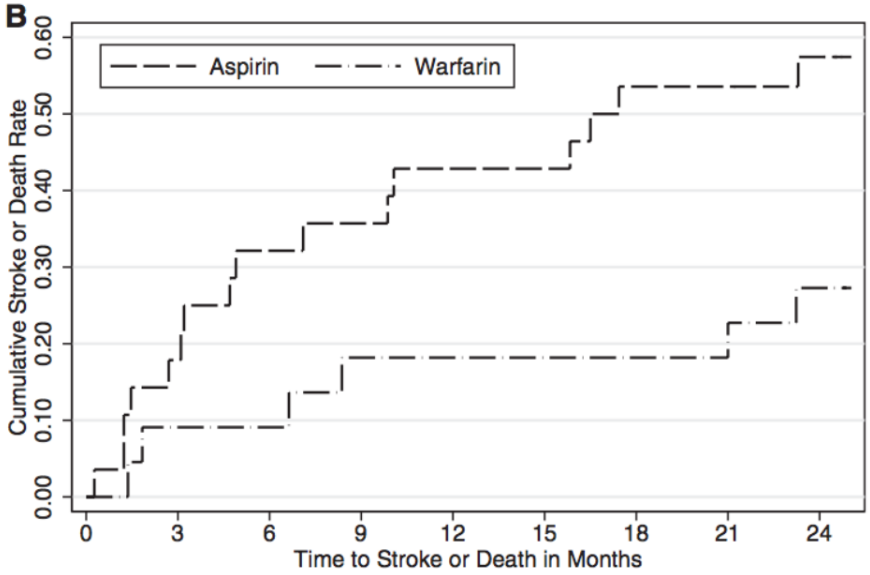
Mohr JP et al. N Engl J Med 2001;345:1444-51.

Analysis	Events		Probability of Event at 2 Yr*		Hazard Ratio (95% CI)†	P Value‡
	Warfarin	Aspirin	Warfarin	Aspirin		
	no. with events/total no.					
Primary and secondary analyses						
Recurrent ischemic stroke or death	196/1103	176/1103	17.8	16.0	1.13 (0.92–1.38)	0.25
Recurrent ischemic stroke or death or major hemorrhage	222/1103	196/1103	20.0	17.8	1.15 (0.95–1.39)	0.16
Recurrent ischemic stroke or death, with data from patients lost to follow-up censored	195/1103	174/1103	17.6	15.9	1.13 (0.92–1.39)	0.24
Recurrent ischemic stroke or death (model including interaction of treatment assignment and interruption of treatment)	196/1103	176/1103				
Subgroup analyses for primary end point						
Sex						
Male	122/656	101/653	18.5	15.4	1.23 (0.95–1.61)	0.12
Female	74/447	75/450	16.2	16.8	0.98 (0.71–1.36)	0.92
Race or ethnic group						
Black	70/338	59/325	20.2	18.4	1.14 (0.81–1.62)	0.45
White	98/627	90/626	15.5	14.3	1.10 (0.83–1.47)	0.50
Hispanic	21/105	21/118	20.1	17.9	1.14 (0.62–2.09)	0.66
Other	7/33	6/34	21.2	17.6	1.18 (0.40–3.50)	0.77
Cause of prior stroke						
Cryptogenic	42/281	48/295	15.0	16.5	0.92 (0.61–1.39)	0.68
Small vessel or lacunar	107/612	95/625	17.1	15.2	1.15 (0.88–1.52)	0.31
Large artery, severe stenosis, or occlusion	27/144	18/115	18.8	15.7	1.22 (0.67–2.22)	0.51
Other determined cause	11/30	7/33	36.7	21.2	1.99 (0.77–5.15)	0.15
Conflicting mechanism	9/36	8/35	25.0	23.0	1.14 (0.44–2.96)	0.79

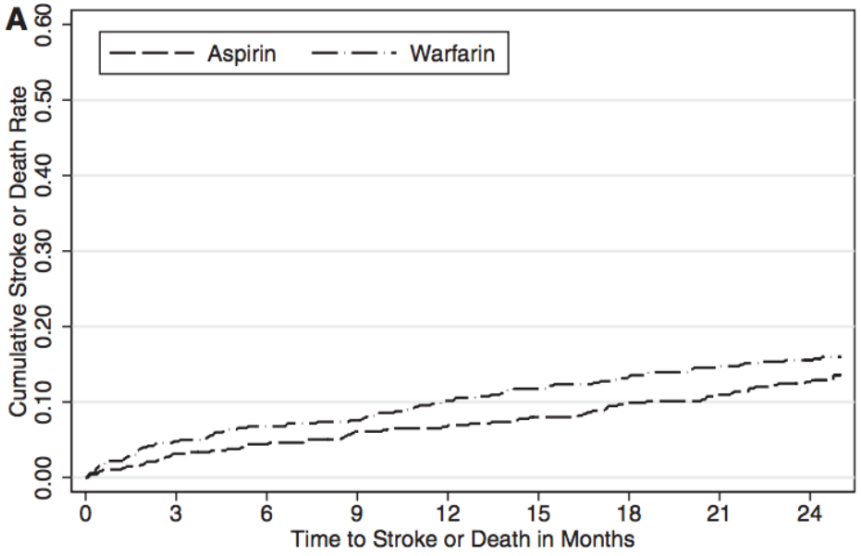
Mohr JP et al. N Engl J Med 2001;345:1444-51

WARSS: "Pacienti s "kardiopatií"

NT-proBNP >750 ng/dL



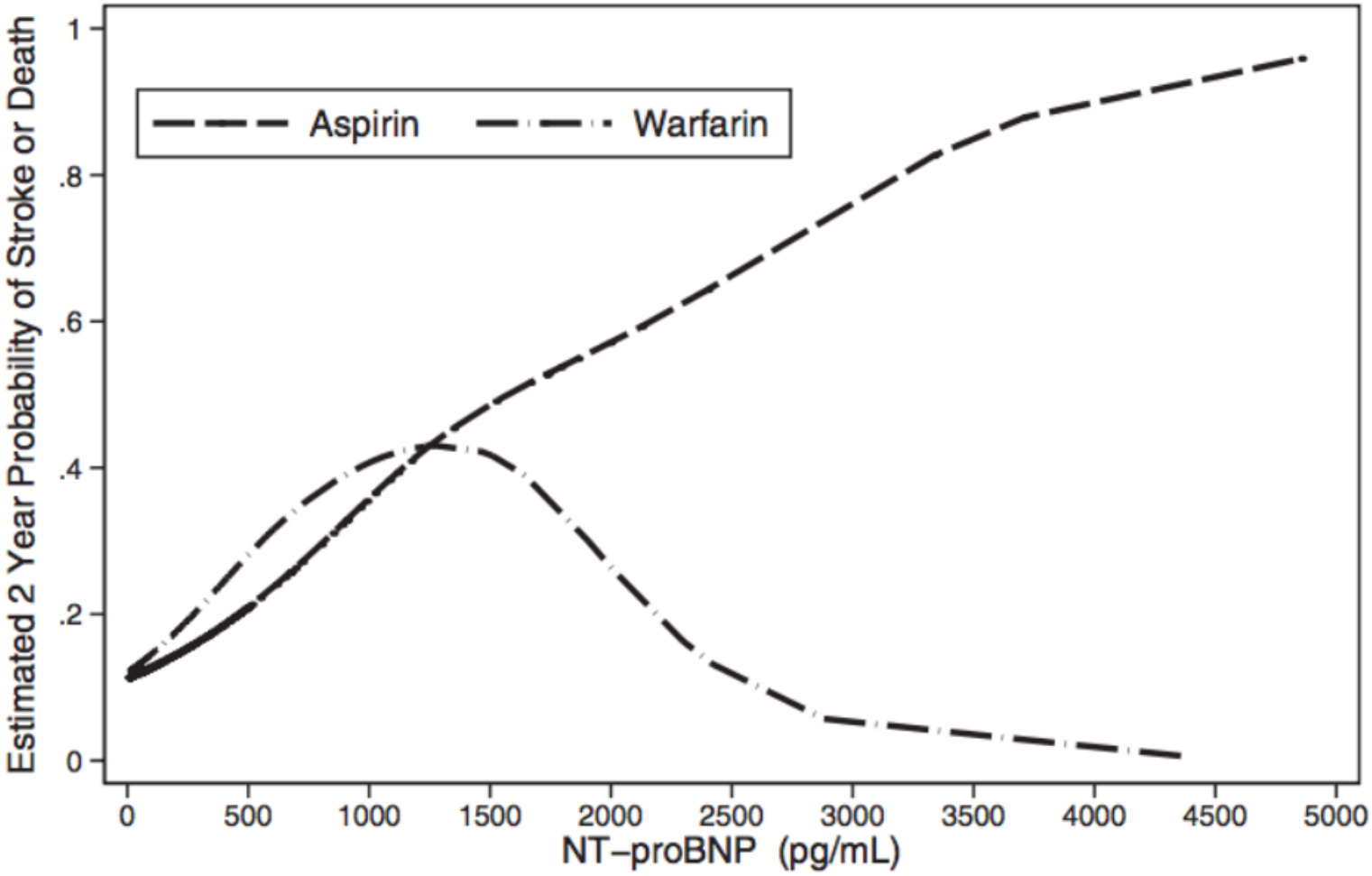
NT-proBNP <750 ng/dL



Warfarin was superior to aspirin in reducing the risk of stroke or death at 2 years

Longstreth WT et al. Stroke 2013;44:714-719.

WARSS: Recidiva CMP/smrt – podle hladiny NT-proBNP



Longstreth WT et al. Stroke 2013;44:714-719.

NOAC ESUS studie (clinicaltrials.gov)

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
4	☐	Terminated	Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (**ESUS**)	• Stroke	• Drug: Rivaroxaban (Xarelto, BAY59-7939) • Drug: Aspirin (Acetylsalicylic acid, BAY1019036) • Other: Rivaroxaban-Placebo • Other: Aspirin-Placebo	• Tucson, Arizona, United States • Long Beach, California, United States • Stanford, California, United States • (and 451 more...)
5	☑	Active, not recruiting	Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source (RE-SPECT **ESUS**)	• Stroke • Secondary Prevention	• Drug: optional ASA as comedication • Drug: placebo to ASA • Drug: placebo to optional ASA as comedication • (and 3 more...)	• Bronislava Shafran, MD PC Phoenix, Arizona, United States • University of Arkansas for Medical Sciences Little Rock, Arkansas, United States • Westside Medical Associates of Los Angeles Beverly Hills, California, United States • (and 590 more...)

Závěr

- I nejlepší léčba může selhat, je nutné být připraven
  - Ischemie na dabigatranu = IVT s podáním idarucizumabu
  - Krvácení na dabigatranu = idarucizumab
- Koncept ESUS
  - může nám potenciálně zjednodušit život, ubyde dlouhodobých monitorací rytmu (RESPECT-ESUS)