Cilostazol for Aneurysmal Subarachnoid Hemorrhage (CASH) trial

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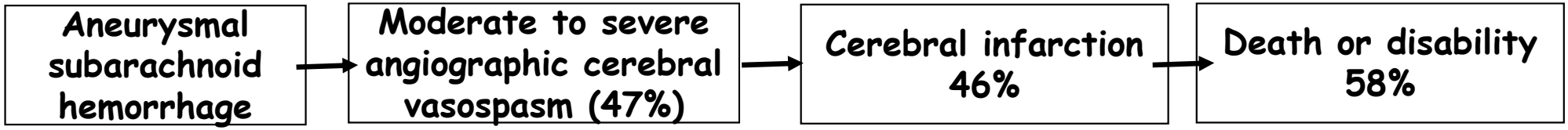
YP1

Background



Re: Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1) study (Stroke. 2011 Apr; 42(4):919-23).

- The American Heart Association/American Stroke Association guidelines for the management of aneurysmal subarachnoid hemorrhage acknowledge that cerebral ischemia *associated with arterial vasospasm, remains a major cause of death and disability in patients with* aneurysmal subarachnoid hemorrhage. *(Stroke. 2012;43:00-00). The guidelines also state that oral nimodipine is the only agent that has been shown to improve neurological outcomes (but not cerebral vasospasm) in patients with aneurysmal subarachnoid hemorrhage (Class I; Level of Evidence A). The guidelines acknowledge that both endothelin-1 antagonists (Lancet Neurol. 2011;10:618–625), magnesium sulfate. Lancet. 2012 Jul 7; 380(9836):44-9) and statin treatment (Lancet Neurol 13:666–675) have failed to demonstrate not shown any benefit in phase 3 clinical trials.*
- ***Therefore, further strategies need to be evaluated for reducing the death and disability associated with cerebral vasospasm and cerebral ischemia.***

Slide 2

YP1 Just reference the citations with numbers and add the actual citation info in the last slide? This is too hard to read.

Yuko Palesch, 4/9/2018

YP2

Cilostazol as an emerging therapeutic intervention

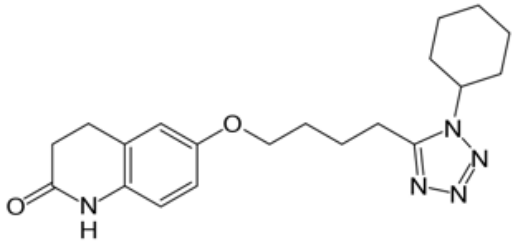
- Cilostazol, a phosphodiesterase III inhibitor reduced cerebral vasospasm and cerebral ischemia in in experimental studies (Cerebrovascular diseases (Basel, Switzerland). 2009;28(2):135-42) and small clinical studies in patients with subarachnoid hemorrhage *(J Neurol Sci. 2014 Jan 15; 336(1-2):146-51)*
- A more recent meta-analysis (Eur Radiol. 2017 Aug;27(8):3333-3342) including 26 randomized controlled trials, and 36 prospective and retrospective observational studies evaluated the efficacy of several therapeutic interventions on clinical outcomes of aneurysmal subarachnoid hemorrhage patients. The main endpoint was the proportion of unfavorable outcomes, defined as a modified Rankin score of 3–6 at last follow-up in 8,976 patients. **The only therapeutic intervention that was associated with lower relative risk (RR) of death or disability was cilostazol (RR=0.46; 95% CI, 0.25– 0.85; P=0.001;Q value, 1.5; I2 =0).**

Slide 3

YP2 I assume all studies in the meta analysis were in Japan? I'd note that here.
Yuko Palesch, 4/9/2018

YP3

Mechanism of action



Cilostazol

- Increased nitric oxide (NO) release from endothelial cells,
- Inhibition of vascular smooth muscle proliferation,
- Suppression of adhesion molecule expression on vascular membrane, and
- Inhibition of platelet derived growth factor (PDGF) production.

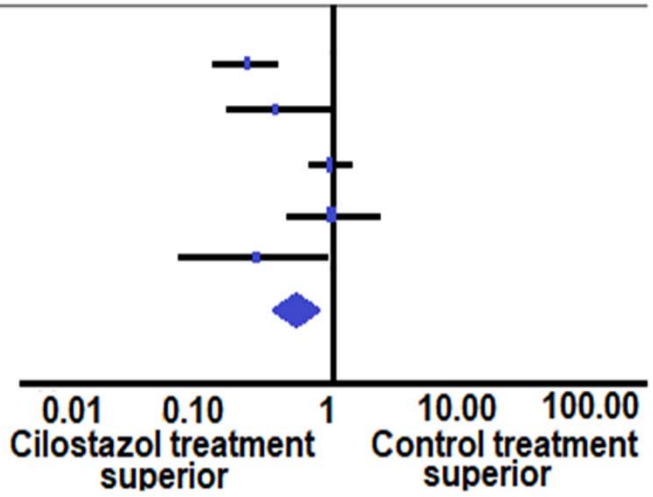
Slide 4

YP3 Much nicer format!
Yuko Palesch, 4/9/2018

Risk ratio of death or disability in subjects assigned to cilostazol and control treatments using random-effects model (5 studies included)—J Vasc Inter Neurol 2018;in press

Death or disability

Study name	Cilostazol treated Events	Total	Control treated Events	Total	Statistics for each study
Suzuki et al	10	49	27	51	0.385 (0.209-0.710)
Senbokuya et al	7	54	15	55	0.475 (0.210-1.074)
Kimura et al	32	62	48	68	0.731 (0.549-0.973)
Yoshimoto et al	4	26	5	24	0.738 (0.224-2.432)
Matsuda et al	4	74	13	74	0.308 (0.105-0.900)
Total	57	265	108	272	0.550 (0.386-0.783)



Matsuda et al, used Glasgow outcome scale at 3 months after onset of subarachnoid hemorrhage to determine the clinical outcome, and poor clinical outcome was defined by severe disability, vegetative state, and death

YP4

Adverse event profile-cilostazol

	Cilostazol (n=128)	Control (n=129)
Intracerebral hemorrhage	1	1
Epidural hemorrhage	1	1
Gastrointestinal hemorrhage	1	3
Sinus tachycardia	3	1
Other cardiovascular events	2	1
Hepatic enzyme elevation	5	6

J Neurosurg 118:121–130, 2013

Cerebrovasc Dis 2016;42:97–105

Slide 6

YP4 Format the number cells to align in the middle?

Yuko Palesch, 4/9/2018

Limitations of current data

- The studies were performed in predominantly Japanese population.
- Higher rate of neurosurgical treatment for intracranial aneurysm in Japan.
- Slightly higher rate of moderate to severe angiographic vasospasm in placebo treated groups was in Japanese and Korean patients than North American and European patients (80% and 66%, respectively). [Fujimura M, et al. Cerebrovasc Dis. 2017;44(1-2):59-67]
- Nimodipine was not used in these trials as not approved in Japan. Fasudil HCl was used in many of the patients.

Primary objective

- The primary objective is to determine if cilostazol (100 mg twice daily) administered within 72 hours of symptom onset and continued for 14 days increases the rate of favorable outcomes (defined by a modified Rankin scale of 0-2) at 3 months in patients with aneurysmal subarachnoid hemorrhage by 7% or greater compared to placebo controls.

YP6

Inclusion criteria

- Admitted to the neurological or neurosurgical units of one of the participating hospitals within 72 hours of symptom onset of aneurysmal subarachnoid hemorrhage.
- The diagnosis of subarachnoid hemorrhage by non-contrast computed tomography or magnetic resonance imaging. The presence of intracranial aneurysm by a catheter based angiography, computed tomographic angiography, or magnetic resonance angiography.
- The patients are required to have World Federation of Neurological Societies (WFNS) grades I–IV prior to randomization (WFNS grade V patients are excluded due to high early mortality rate).

Slide 9

YP6 Present in shorter sentence per criterion?

Yuko Palesch, 4/9/2018

World Federation of Neurological Societies (WFNS) grades

- *I – GCS 15, no motor deficit*
- *II – GCS 13-14, no motor deficit*
- *III – GCS 13-14, motor deficit*
- *IV – GCS 7-12 +/- motor deficit*
- *V – GCS 3-6, motor deficit present or absent*

YP7

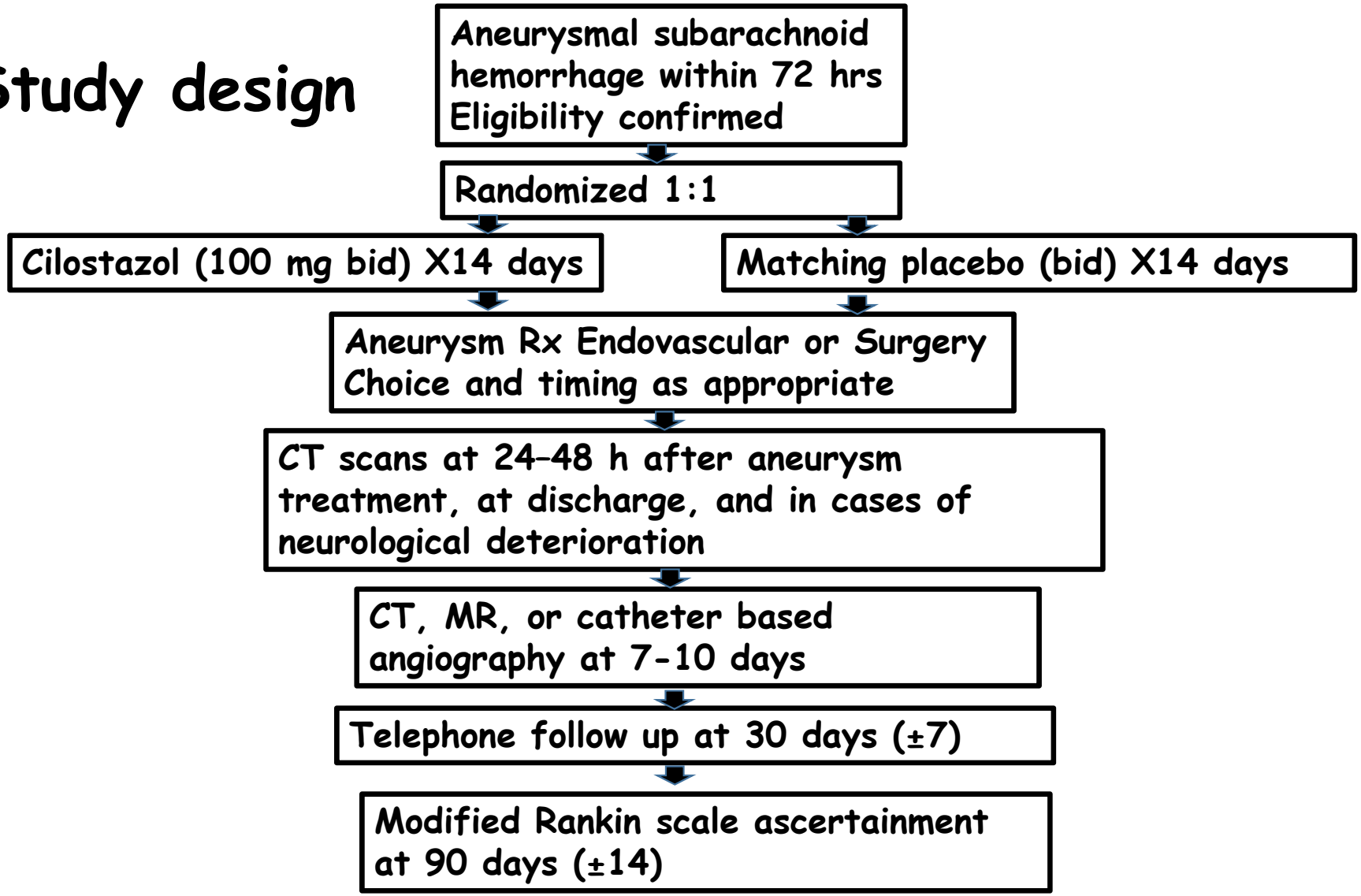
Exclusion criteria

- Subarachnoid hemorrhage due to non-aneurysmal causes.
- A modified Rankin scale of 2 or greater prior to occurrence of subarachnoid hemorrhage.
- Intraventricular or intracerebral hemorrhage without subarachnoid blood.
- Presence of moderate to severe vasospasm on screening angiogram.
- Known allergy to cilostazol.
- Pregnancy or post partum period.
- Known bleeding diatheses, hemorrhagic complications such as gastrointestinal bleeding, and severe concomitant diseases such as congestive heart failure.
- International normalized ratio >1.5 prior to randomization.
- Hepatic dysfunction manifesting as elevation in serum transaminases or bilirubin.

Slide 11

YP7 This is good.
Yuko Palesch, 4/9/2018

Study design



Study endpoints

Primary	**Favorable outcome (defined as a modified Rankin Scale score of 0-2) 90 days after subarachnoid hemorrhage.** 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 without assistance.
Secondary	**Composite of vasospasm-related cerebral infarction, vasospasm-related delayed ischemic neurological deficits and vasospasm-related neurological signs and symptoms leading to use of a valid rescue therapy.** New cerebral infarct(s) due to cerebral vasospasm as either the primary or relevant contributing cause, or not adjudicated to be entirely due to causes other than vasospasm Delayed ischemic neurological deficit due to cerebral vasospasm as either the primary or relevant contributing cause, or not adjudicated to be entirely due to causes other than vasospasm Neurological signs or symptoms (depending on state of consciousness) in the presence of confirmed cerebral vasospasm on angiography (digital subtraction angiography or computerized tomography angiography) leading to the administration of a valid rescue therapy **Vasospasm-related delayed ischemic neurological deficits during hospitalization.** The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies.(Stroke. 2010;41:2391–2395). **Health status by the EQ-5D and EQ-5D visual analog scale at 90 days.** Generic instrument that assesses 5 domains of HRQoL.(Neurosurgery. 2009;65:565–572). In addition, the EQ-5D visual analog scale will be used to record the respondent's assessment of their overall health status on a 20-cm scale anchored on 0 (worst imaginable health) and 100 (best imaginable health).

Primary endpoint

- **Modified Rankin scale versus Glasgow outcome scale**

Modified Rankin scale in clinical trials such as ISAT and SAHIT

doi:10.1002/ana.2467527129898

- **Time point of ascertainment**

3 months in recent clinical trials such as CONSCIOUS-2

https://doi.org/10.1016/S1474-4422(11)70108-9

- **Dichotomized versus ordinal endpoint**

dichotomized in previous clinical trials such as ISAT

https://doi.org/10.1016/S0140-6736(02)11314-6

Primary endpoint

- Modified Rankin scale (0-2) at 2 and 12 months in ISAT trial

https://doi.org/10.1016/S0140-6736(02)11314-6

Time point	Endovascular Rx	Surgical Rx
At 2 months	74.6%	63.6%
At 12 months	76.3%	69.4%

Outcome at 2 months in 1906 patients

	Endovascular treatment (n=959)	Neurosurgery (n=947)
Modified Rankin scale		
0 No symptoms	192 (20·0%)	138 (14·6%)
1 Minor symptoms	275 (28·7%)	245 (25·9%)
2 Some restriction in lifestyle	248 (25·9%)	219 (23·1%)
(0–2 inclusive)	*715 (74·6%)*	*602 (63·6%)*
3 Significant restriction in lifestyle	95 (9·9%)	172 (18·2%)
4 Partly dependent	29 (3·0%)	39 (4·1%)
5 Fully dependent	48 (5·0%)	55 (5·8%)
6 Dead	72 (7·5%)	79 (8·3%)
(3–6 inclusive)	*244 (25·4%)*	*345 (36·4%)*

Data in Italics are primary outcome.

Outcome at 1 year in 1594 patients (primary outcome)

	Endovascular treatment (n=801)	Neurosurgery (n=793)
Modified Rankin scale		
0 No symptoms	207 (25·8%)	152 (19·2%)
1 Minor symptoms	217 (27·1%)	220 (27·7%)
2 Some restriction in lifestyle	187 (23.4%)	178 (22·4%)
(0–2 inclusive)	*611 (76·3%)*	*550 (69·4%)*
3 Significant restriction in lifestyle	80 (10·0%)	106 (13·4%)
4 Partly dependent	24 (3·0%)	32 (4·0%)
5 Fully dependent	21 (2·6%)	25 (3·2%)
6 Dead	65 (8·1%)	80 (10·1%)
(3–6 inclusive)	*190 (23·7%)*	*243 (30·6%)*

Data in Italics are primary outcome.

Statistical consideration

- We assume that 66% (95% confidence interval 63%-70%) of the patients with subarachnoid hemorrhage will have favorable outcome (modified Rankin scale score 0-2) based on the rates observed in the placebo treated group in Magnesium for aneurysmal subarachnoid haemorrhage (MASH)-2 trial (*Lancet. 2012 Jul 7; 380(9836):44-9)*.
- We assume an absolute increase of 7% or greater based on the results of phase II trial by Senbokuya et al. (J Neurosurg 118:121–130, 2013). The trial demonstrated that 87% (47 of 54) and 73% (40 of 55) patients treated with cilostazol and placebo had achieved a modified Rankin scale of 0-2 at 3 months, respectively.
- A sample size of 1764 patients will be required with an alpha of 0.05 and beta of 80% to demonstrate the efficacy of cilastozal in reducing death and disability in patients with aneurysmal subarachnoid hemorrhage. The sample size adjusts for 10% loss to follow up and missing data and permits two interim analyses.

The sample size estimations under various assumptions:

Effect size	Power	0 interim	1 interim	2 interim
10	90	1052	1070	1106
10	85	899	905	945
				35
				67
				81
				43
8	90	1684	1689	1750
8	85	1439	1448	1512
8	80	1258	1272	1336
7	90	2224	2231	2311
7	85	1900	1913	1996
7	80	1662	1679	1764

The sample size estimations under various assumptions (three power estimates (90, 85, and 80), for effect size ranging from 10%-7%, and under the assumption of 0, 1, or 2 interim analyses) is provided in Table below

The sample size estimations under various assumptions:

Effect size	Power	0 interim	1 interim	2 interim
10	90	1052	1070	1106
10	85	899	905	945
10	80	786	795	835
9	90	1315	1320	1367
9	85	1124	1130	1181
9	80	983	993	1043
8	90	1684	1689	1750
8	85	1439	1448	1512
8	80	1258	1272	1336
7	90	2224	2231	2311
7	85	1900	1913	1996
7	80	1662	1679	1764

Adverse events were assessed in eight placebo-controlled clinical trials involving 2274 patients exposed to either 50 or 100 mg b.i.d. Cilostazol (n=1301) or placebo (n=973), with a median treatment duration of 127 days for patients on Cilostazol and 134 days for patients on placebo

Most Commonly Reported AEs (Incidence ≥2%) in Patients on CILOSTAZOL (CZL) 50 mg b.i.d. or 100 mg b.i.d. and Occuring at a Rate in the 100 mg b.i.d. Group Higher Than in Patients on Placebo

Adverse Events (AEs) by Body System	CZL 50 mg b.i.d. (N=303) %	CZL 100 mg b.i.d. (N=998) %	Placebo (N=973) %
BODY AS A WHOLE			
Abdominal Pain	4	5	3
Back pain	6	7	6
Headache	27	34	14
Infection	14	10	8
CARDIOVASCULAR			
Palpitation	5	10	1
Tachycardia	4	4	1
DIGESTIVE			
Abnormal stools	12	15	4
Diarrhea	12	19	7
Dyspepsia	6	6	4
Flatulence	2	3	2
Nausea	6	7	6
METABOLIC & NUTRITIONAL			
Peripheral edema	9	7	4
MUSCULO-SKELETAL			
Myalgia	2	3	2
NERVOUS			
Dizziness	9	10	6
Vertigo	3	1	1
RESPIRATORY			
Cough increased	3	4	3
Pharyngitis	7	10	7
Rhinitis	12	7	5

Drug interactions

- **No known interaction with cilostazol with either nimodipine or nicardipine.** https://www.drugs.com/interactions-check.php?drug_list=668-0,1713-0
- **No known interaction with milrinone, a phosphodiesterase inhibitor, with either nimodipine or nicardipine. (**https://doi.org/10.1161/STROKEAHA.107.492447 Stroke. 2008;39:893-898).