두개강내 스텐트 치료술- WEAVE 연구 후 고려해야할 사항은?

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Intracranial stenting: Is there any change after the WEAVE?

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Atherosclerosis

- Most common subtype of ischemic stroke
  - LAA > SVO > CE
- Annual recurrent stroke
  - 5-15 %/year
- Arterial wall thickening
  - Hemodynamic challenge
- Atheromatous plaque
  - Thromboembolism

Stroke recurrence in ICAD

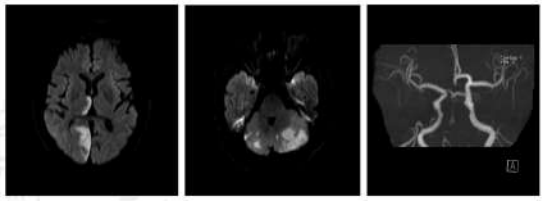
- Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial
  - Symptomatic ICAS (sICAS)
  - 50 to 99% sICAS treated with aspirin
  - Risk of recurrent stroke and death: 15% at 1 year
- CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) trial
  - Minor stroke or high-risk TIA patients treated with aspirin plus clopidogrel for 21 days followed by clopidogrel mono therapy for days 22 to 90
  - 11.3% within 3 months in those with ICAS, vs., 5.3% in those without ICAS

WASID

- Warfarin-Aspirin Symptomatic Intracranial Disease
- Medical therapy for symptomatic ICAD,
- Poor outcomes in both arms of medical therapy
- Stroke, bleed, and death rate (~1.8 years)
  - 22.1% in the aspirin group
  - 21.8% in the warfarin group.
  - Those with TIA: 14% of stroke at 1 year
  - Those with stroke: 23% of stroke at 1 year

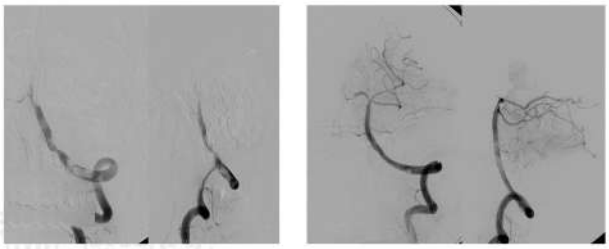
Angioplasty ~ Poor outcome?

M/71, visual disturbance
Onset: 6 HA, HT/DM, iNIHSS: 8



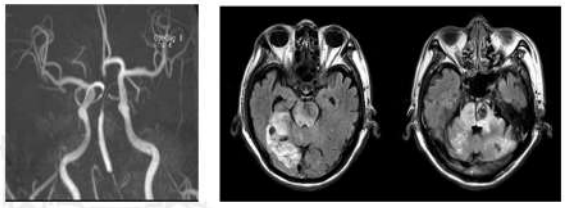
Plan

IA Thrombolysis: suction thrombectomy
Double stenting



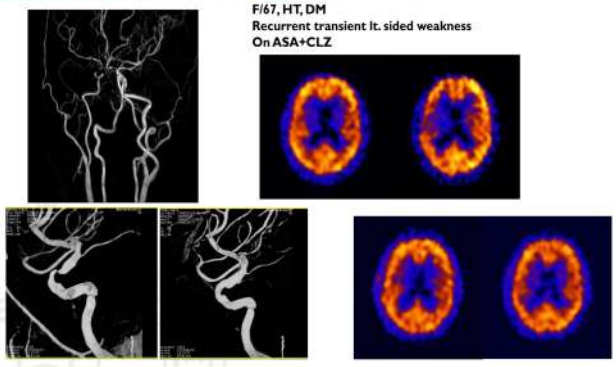
Outcome

NIHSS: 8→ 14 (D1)→ 28 (D5)
mRS (D30): 5

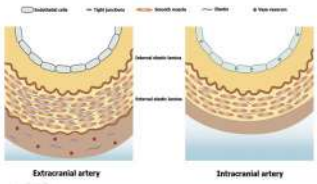


Angioplasty ~ good outcome?

F/67, HT, DM
Recurrent transient lt. sided weakness
On ASA+CLZ



ICAD

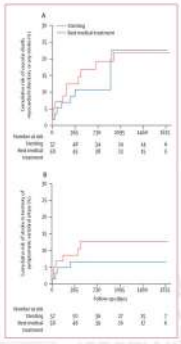


- ICAD is highly prevalent in black, Asian (China, Japan, South Korea, and India), and Hispanic populations.

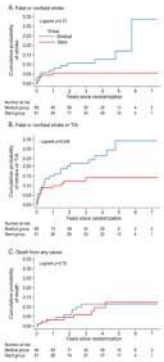
Table 2. Risk Factors of Intracranial Atherosclerosis

Nonmodifiable Risk Factors	Modifiable Risk Factors
Age	Hypertension
Race (black, Hispanic, Chinese, Korean, Japanese, and Indian)	Diabetes mellitus
	Metabolic syndrome
Male sex	Smoking
Family history of stroke[1]	Hyperlipidemia: low-density lipoprotein, high-density lipoprotein, total cholesterol, β-lipoprotein, and apolipoprotein (a)
Radiotherapy[2]	
Decreased s-adiponectin[3]	
Glutathione S-transferase omega-1 gene polymorphism[4]	Plasma homocysteine
Plasma endostatin/vascular endothelial growth factor ratio[5]	Physical inactivity

Extra+Intra, VA



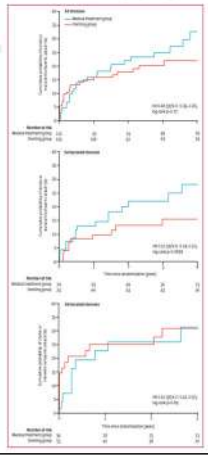
- Phase 2 vertebral artery stenting trial (VAST)
  - 96:19
- Stenting for symptomatic vertebral artery stenosis, The Vertebral Artery Ischaemia Stenting Trial (VIST)
  - 148:31



Compter A et al., Lancet Neurol, 2015; Markus HS et al., Neurology, 2017

Extra>>Intra, VA

- Preplanned pooled analysis
- Three studies: 179 patients from VIST, 115 patients from VAST, and 60 patients from SAMMPRIS (no patients had extracranial stenosis)
- The frequency of periprocedural stroke or death was higher for intracranial stenosis than for extracranial stenosis (ten (16%) of 64 patients vs one (1%) of 121 patients; p<0·0001).



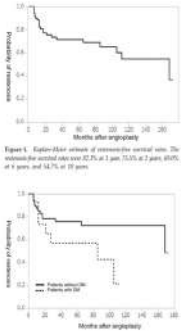
Markus HS et al., Lancet Neurol, 2019

Primary angioplasty

- Stroke or death within 30 days of angioplasty: 4-40%
- Re-stenosis: 24-40%
- Immediate elastic recoil of the artery, dissection, acute vessel closure, and residual stenosis >50% following the procedure.
- Coupled with the success of stenting in the coronary circulation

Primary angioplasty

- Japanese retrospective registry
- Balloon angioplasty without stenting for symptomatic MCA stenosis
- Low procedural risks (4.2%)
- A total of 23 (31.9%) patients had restenosis at a time point that varied from 6 to 111 months after treatment.



Ueda T et al, J Stroke Cerebrovasc Dis, 2018

Off label use of stent

- Balloon-mounted coronary stent
- Industry sponsored prospective phase I trial utilizing stents approved specifically for intracranial use
  - The Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) trial was a nonrandomized trial using the NEUROLINK stent in 61 patients with symptomatic (50-99%) intracranial stenosis or extra-cranial vertebral artery stenosis
  - The 30-day rate of death or stroke: 6.6%
  - The 1-year stroke rate: 10.9%
  - Restenosis (>50% luminal narrowing): 32%

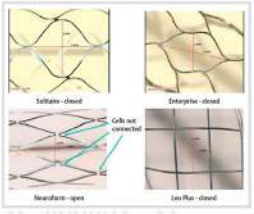
SSYLVIA Study Investigators, Stroke, 2004

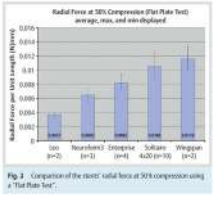
Evolution

- Lesion location and morphology
- Patient selection
- Experienced interventionist
- Stent type
  - Self-expanding nitinol stent: Wingspan stent (Stryker, Kalamazoo, MI) (Aug 2005)
  - Balloon-mounted stent
  - Drug-eluting stent: limited
- 4% periprocedural primary event safety benchmark set

Stent type

- Neuroform, Wingspan, Solitaire, Leo plus, Enterprise
- Radial force at 50% oversizing: L<N<E<S<W
- Wall apposition: E<N=W<S;
- Bending stiffness: N<L<W<S<E;
- Cell size: L<W<E<N<S;
- Ease of delivery: W<N<L<E<S.





Lesion, Mori classification

- Mori A, short and concentric stenosis: balloon-mounted stent
- Mori B, a tubular or extreme eccentric lesion with intermediate length (between 5 and 10 mm): self-expanding stent
- Mori C, a diffuse lesion with a long length (>10 mm): self-expanding stent
- Tortuous arterial access with Mori A lesions and a small target-vessel diameter of < 2.5 mm: balloon angioplasty alone

Mori et al., AJNR, 1998

Stent type per lesion

- Retrospective single arm registry analysis
- Balloon-mounted stent vs., Self-expanding stent
- Mori A lesion or smooth arterial access
- Mori C lesion or tortuous arterial access, lesion with a significant mismatch in the diameter between the proximal and the distal segments

Table 3. Comparison of clinical follow-up features.

	Patients treated with balloon-mounted stenting (n = 91)		Patients treated with balloon pre-dilation plus self-expanding stenting (n = 63)		
Variables	n	Means (SD)/(%)	n	Means (SD)/(%)	P-value
Re-stenosis features after 1 year	9	9.89	8	12.7	0.585
Degree of re-stenosis, %	9	47.51 ± 21.40	8	65.30 ± 20.12	0.099
Restenosis ≥50%	3	3.30	7	11.1	0.053
Restenosis ≥70%	2	2.20	3	4.76	0.377
Ischemic stroke	7	7.70	4	6.34	0.750
TIA	4	4.40	2	3.17	0.700
Hemorrhagic stroke	0	0	1	1.59	0.228
Death	1	1.10	2	3.17	0.359
Residual relative symptom	10	11.0	10	15.9	0.375

TIA: transient ischemic attack.

First wingspan study

- 45 patients
- Medically refractory intracranial artery stenosis
- 30-day rate of death or stroke: 4.5%
- 6-month rate of ipsilateral stroke or death: 7%
- Restenosis at 6 months was 7.5%.
- Approved by the Food and Drug Administration under a humanitarian device exemption (HDE)
- Used in practice in the USA for patients with 50-99% stenosis who had recurrent symptoms while on medical therapy, and were >7 days after their stroke

Bose A et al., Stroke, 2007

After FDA clearance

- Off-label use: patients who had not failed medical therapy, TIA without history of stroke, and patients earlier than 8 days after the event
- The National Institutes of Health Wingspan registry: 61%
- The US Wingspan registry: 58%

US registry study

- NIH Wingspan stent registry
  - Risk of any stroke or death within 30 days or any stroke in territory from 30 days to 6 months: 14%
  - Factors associated with increased risk of stroke: posterior circulation stenosis, treatment at low volume sites, stenting soon after a qualifying event, or stroke as opposed to transient ischemic attack (TIA) as the event leading to stenting
- US Multicenter registry
  - Of the 82 lesions treated, there were 5 (6.1%) major periprocedural neurological complications, 4 of which ultimately led to death within 30 days of the procedure
- Lack of medically treated controls

Zaidat et al., Neurology, 2008; Nahab et al., Neurology, 2008; Fiorella et al., Stroke, 2012

SAMMPRIS

- Stenting and Aggressive Medical Management for the Prevention of Recurrent Stroke in Intracranial Stenosis
- National Institutes of Health and performed at 50 sites in the United States
- Self-expanding Wingspan Stent, use of the Gateway angioplasty balloon
- Patients who had a recent transient ischemic attack or stroke attributed to stenosis of 70 to 99% of the diameter of a major intracranial artery
- Majority of patients stented would not have met the original HDE on label indication
- Primary endpoint at 30 days
  - Stent arm: periprocedural stroke, bleed, and death rate of 14.7%, 1-year stroke and death rate of 20.0%
  - Medical management only arm: 5.8%, 12.2%
- High periprocedural morbidity and not delayed events
  - Rate of death and disabling stroke beyond 30 days
  - Stenting group at 2.2%, Medical therapy group at 6.2%

Chimowitz A et al., N Engl J Med 2011

SAMMPRIS

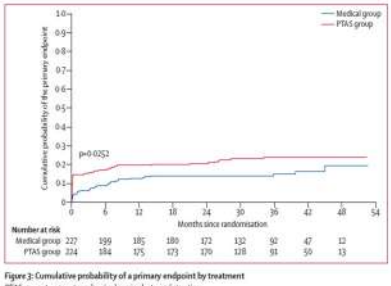


Figure 3: Cumulative probability of a primary endpoint by treatment
PTAS=percutaneous transluminal angioplasty and stenting.

In-stent restenosis

- SAMMPRIS stent cohort
- Symptomatic ISR
  - 9.6% at 1 yr
  - 11.3% at 2 yr
  - 14.0% at 3 yr

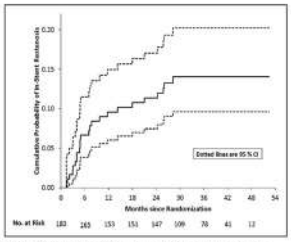
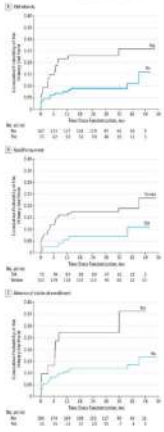


Figure. Kaplan–Meier in-stent restenosis curves. CI indicates confidence interval.

Derdeyn CP et al., Stroke 2017

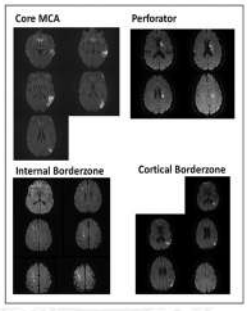
High risk patients

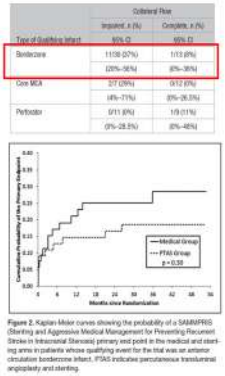
- Primary end point in medical treatment arm: 15% (32.7 mo)
- Factors for high risk patients
  - Old infarct in the territory (HR, 2.6; 95% CI, 1.3-5.3; P = .006)
  - Stroke as the qualifying event (HR, 3.0; 95% CI, 1.1-7.7; P = .03)
  - No statin use at enrollment (HR, 2.4; 95% CI, 1.1-5.2; P = .03)



Waters MF et al., JAMA Neurol 2016

High risk patients





Wabnitz AM et al., Stroke 2019

VISSIT

- Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) trial
- Industry-funded and conducted at sites in the USA, China, and Europe
- Vitesse balloon-expandable neurovascular stent system (Codman Neurovascular, Raynham, MA)
- Primary endpoint
  - The 1-year primary outcome of stroke or hard TIA occurred in more patients in the stent group (21/58; 36.2% [95% CI, 24.0-49.9]) vs the medical group (8/53; 15.1% [95% CI, 6.7-27.6]) (P = .02).

Zaidat OO et al., JAMA, 2015

Medical management

- Dual antiplatelet therapy with aspirin 81–325 mg daily as well as clopidogrel 75 mg for the first 90 days, followed by monotherapy with aspirin only for the duration of the study.
- Blood pressure targets were set at systolic blood pressure of less than 140 mm Hg (<130 mm Hg for diabetic patients in SAMMPRIS) and low-density lipoprotein cholesterol targets of <70 mg/dL in SAMMPRIS and < 100 mg/dL in VISSIT
- Lifestyle modification program focusing on smoking cessation, weight management, and exercise counseling

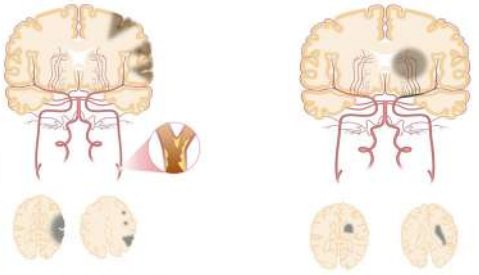
Reason for failure

- Poor patient selection
- Majority of postprocedural ischemic strokes after stenting: Perforator strokes
- Snow-plowing effect or reperfusion hemorrhage
- High 30-day stroke rates in both trials
  - 10.3% ischemic strokes and 4.5% hemorrhagic strokes in SAMMPRIS
  - 17.2% ischemic stroke and 8.6% hemorrhagic stroke in VISSIT
- Inexperience of the interventionists
- Underdeveloped standards of practice

- Delay in the stenting procedure for a recommended time of at least 3 weeks after the last event prior to the procedure
- Improved following advancement in PTAS techniques?

Lutsep HL et al., Stroke, 2015

ICAD-related stroke



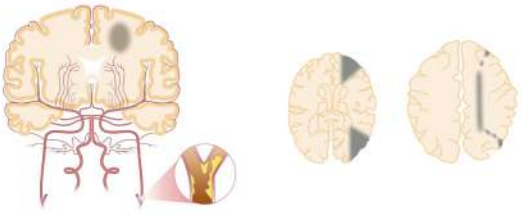
Artery to artery embolism

In situ thrombosis

ICAD-related stroke

Artery to artery embolism + in situ thrombosis

ICAD-related stroke



Low flow or hemodynamic

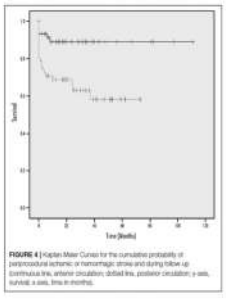
Patient selection

- Chinese stenting registry
- Patient selection
  - Patients with poor collateral flow, leading to hypoperfusion-related infarcts, are highly likely to fail medical therapy
- The primary outcome of any stroke, TIA, or death within 30 days was 4.3%
- Randomized controlled trial is underway in China to compare medical therapy with medical therapy plus intervention in patients with severe symptomatic ICAS and hypoperfusion symptoms

Miao Z et al., Stroke, 2015

Perforator-bearing segment

- Retrospective German cohort
- Ant (M1) vs Post (BA/V4)
- More patients treated for a posterior ICAS suffered a periprocedural or follow-up stroke [25% vs. 11.4%, p = 0.024].
- No difference between PTA alone or PTAS



Nordmeyer H et al., Front in Neurol, 2018

On label criteria revision

- March 2012
- Patients who had 2 strokes in the vascular territory of the stenotic intracranial artery
- Mandatory new postmarket surveillance trial of the Wingspan stent to reassess its safety
- Demonstrating specifically the periprocedural safety of the Wingspan stent, not longterm efficacy

WEAVE Trial

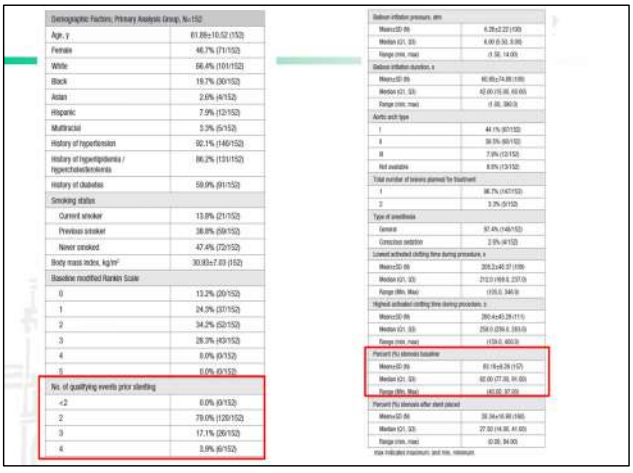
- Wingspan Stent System Post Market Surveillance
- Postmarket surveillance trial mandated by the Food and Drug Administration to assess the periprocedural safety
- Age 22 to 80 years, symptomatic intracranial atherosclerotic stenosis of 70% to 99%, baseline modified Rankin Scale score ≤3, ≥2 strokes in the vascular territory of the stenotic lesion with at least 1 stroke while on medical therapy, and stenting of the lesion ≥8 days after the last stroke
- Prestenting antiplatelet resistance testing (P2Y12, aspirin reactivity unit, or correlate testing), assessment of target lesion proximity to angiographically visible perforator arteries, plaque anatomy, presence of tandem lesions, aortic arch type, proximal tortuosity, cerebral perfusion testing or other assessment of collaterals, intraprocedural blood pressure, and demographic factors

Alexander MJ et al., Stroke, 2019

Key results

- Interim analysis of the first 100 patients: < 3% (expected primary analysis event rate)
- Bayesian analysis was used to redefine the safety benchmark for the study at a 4% primary analysis event rate for the first consecutive 150 patients.
- The trial was stopped early on October 25, 2017, when the second interim data analysis demonstrated that the safety benchmarks had been met.
- 72-hour stroke and death rate: 2.6% (4/152)

	Primary Analysis Trial / On Label
Enrolled	N=152
Subjects without stroke or death within 72 h	97.4% (148/152)
Subjects with death within 72 h	1.3% (2/152)
Subjects with stroke (without death) within 72 h	1.3% (2/152)
Total percentage of patients with stroke or death within 72 h	2.6% (4/152)



Demographic Factors, Primary Analysis Group, N=152	
Age, y	61.88±10.52 (152)
Female	46.7% (71/152)
White	66.4% (101/152)
Black	19.7% (30/152)
Asian	2.6% (4/152)
Hispanic	7.9% (12/152)
Multiracial	3.3% (5/152)
History of hypertension	92.1% (140/152)
History of hyperlipidemia / hypercholesterolemia	86.2% (131/152)
History of diabetes	59.9% (91/152)
Smoking status	
Current smoker	13.8% (21/152)
Previous smoker	38.8% (59/152)
Never smoked	47.4% (72/152)
Body mass index, kg/m²	30.83±7.03 (152)
Baseline modified Rankin Scale	
0	13.2% (20/152)
1	24.3% (37/152)
2	34.2% (52/152)
3	28.3% (43/152)
4	0.0% (0/152)
5	0.0% (0/152)
No. of qualifying events prior stenting	
<2	0.0% (0/152)
2	79.0% (120/152)
3	17.1% (26/152)
4	3.9% (6/152)

Technical issue

- More experienced group of interventionists
  - 10 stents (SAMMPRIS), 37 stents (WEAVE investigators)
- MCA stem
  - 22% (HDE trial), 41% (SAMMPRIS), 40.8% (WEAVE)
- Revised treatment paradigms
  - Underdilating middle cerebral artery lesions adjacent to angiographically visible perforators
  - 60% to 80% of the true luminal diameter
- Perforator stroke
  - 5.8% (SAMMPRIS), 0.7% (WEAVE)
- Time to stenting
  - 22 days (HDE trial), 7 days (SAMMPRIS), 22 days (WEAVE)
  - < 7 days after the qualifying event: ~50% (SAMMPRIS)
  - no patient stented before day 8 poststroke (WEAVE)

Early vs., Late

- Outcomes of early stenting (≤14 days) or late stenting (>14 days) in patients who underwent intracranial stent placement
- Prospective single-arm registry study with 20 participating stroke centers in China
- Self-expanding stent (Wingspan, Boston Scientific) and Apollo balloon-mounted stent (MicroPort Medical, Shanghai, China)

Table 3 Comparison of long-term follow-up clinical outcomes

Events	Early stent placement (n=41)	Late stent placement (n=74)	P value
Follow-up period, months, median (IQR)	26.0 (22.1–29.9)	25.3 (21.9–27.8)	0.709
Degree of restenosis ≥50%	8 (19.5%)	4 (5.41%)	0.018
Degree of restenosis ≥70%	2 (4.88%)	3 (4.05%)	0.836
Events	9 (22.0%)	6 (8.11%)	0.035
Ischemic stroke	5 (12.20%)	2 (2.70%)	0.041
TIA	1 (2.44%)	3 (4.05%)	0.651
Hemorrhagic stroke	1 (2.44%)	0 (0.00%)	0.177
Death	2 (4.88%)	1 (1.35%)	0.256

TIA, transient ischemic attack.

Zhang Y, et al. J NeuroIntervent Surg 2020

Drug eluting stent

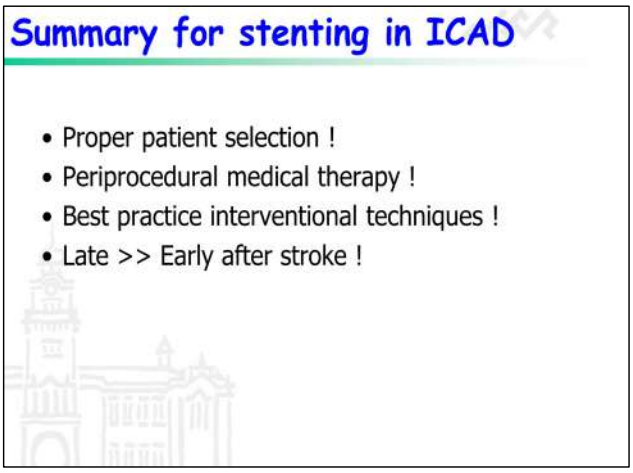
- Systematic review and metaanalysis (13 studies, N=336)
- Intravascular DES for sICAD can effectively reduce the risk of ISR, thereby reducing long-term complication rates, and will not increase perioperative complication risk.

Table 4
Comparison with other related clinical trial.

Study	NO. of patients in different groups	Any stroke or death rate within 30 days (%)	Any stroke, TIA or death rate within 30 days (%)	Primary endpoint events at 1 year (%)	Ischaemic stroke in the territory of the qualifying artery beyond 30 days (%)	ISR rate (%)
DES (this meta) (N = 364)	Total	6.0	8.1		2.2	4.1
	Moderate (N = 137)	1.0	2.2		1.2	3.0
	Severe (N = 227)	10.6	14.0	-	3.2	5.2
SAMMPRIS (N = 451)	Drug (N = 227)	5.8	-	12.2	6.4	-
	Stenos(N = 224)	14.7	-	20.0	5.3	-
VISIT* (N = 111)	Drug (N = 53)	-	9.4	13.3	5.7	-
	Stents (N = 58)	-	24.1	36.2	12.1	26.5
Chinese register†	Stents (N = 354)	-	4.3	-	-	-

VISIT trial defined any stroke and hard TIA after 2 days of randomization as a primary endpoint. A hard TIA was defined as a transient episode of neurological dysfunction caused by focal brain or retinal ischemia that lasts for at least 10 min but resolves within 24 h.
† Chinese register (Unique identifier: NCT01968122) defined any stroke (including ischemic or hemorrhagic stroke), TIA, and death after stenting within 30 days as primary outcome.

Ye G et al., J Clin Neurosci, 2019


Summary for stenting in ICAD
• Proper patient selection !
• Periprocedural medical therapy !
• Best practice interventional techniques !
• Late >> Early after stroke !