Wingspan® Stent System

Stryker Neurovascular

FDA Neurological Devices Advisory Committee Meeting

23 March 2012

Stryker Introductions & Product Overview

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Disclosures:
Full time employee of Stryker Neurovascular

Agenda

- **Introduction and Product Overview**

  Ron Allen, PhD, Vice-President Regulatory Affairs, Stryker Neurovascular

- **Overview of Safety and Probable Benefit**

  Jon Hopper MB ChB, FRCSEd, Global Medical Director, Stryker Corporation

- **SAMMPRIS Design, Lessons Learned and Patient Implications**

  Michael Alexander, MD, FACS, Cedars-Sinai Medical Center

- **Conclusions**

  Jon Hopper MB ChB, FRCSEd, Global Medical Director, Stryker Corporation

Indications for Use

- The Wingspan Stent System with Gateway® PTA Balloon Catheter is indicated for use in **improving cerebral artery lumen diameter in patients** with intracranial atherosclerotic disease, **refractory to medical therapy**, in intracranial vessels with ≥50% stenosis that are accessible to the system.

- The Gateway PTA Balloon Catheter is indicated for balloon dilation of the stenotic portion of intracranial arteries prior to stenting for the purpose of improving intracranial perfusion.

Panel Objectives

- Per FDA Notice (Docket No. FDA-2012-N-001), the Committee is asked to:
  - **Discuss the comparability of the patient populations for the approved HDE and SAMMPRIS trial.**

    In its consideration of the approved indications for use of the Wingspan Stent System under the approved Humanitarian Device Exemption, the FDA required the SAMMPRIS trial to be conducted under an Investigational Device Exemption (IDE). This clearly indicates FDA's acknowledgement of the difference between the patient population for the approved HDE and the patient population that was studied in the SAMMPRIS trial.

Panel Objectives

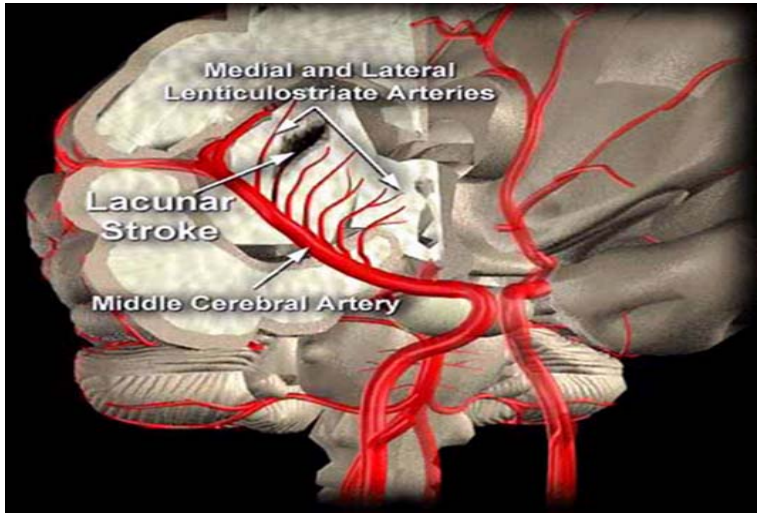
Per FDA Notice (Docket No. FDA-2012-N-001), the Committee is asked to:

- **Discuss the relevance of the SAMMPRIS trial results to the assessment of safety and probable benefit for the Wingspan Stent System with Gateway PTA Balloon Catheter HDE.**

  It is critical to appreciate that the Wingspan Stent System is approved as a Humanitarian Use Device that is not intended for the primary treatment of stroke due to ICAD. It is <u>only</u> approved for consideration as a therapy with probable benefit for patients who have experienced a stroke or TIA because they have failed medical therapy in the judgment of their treating physician.

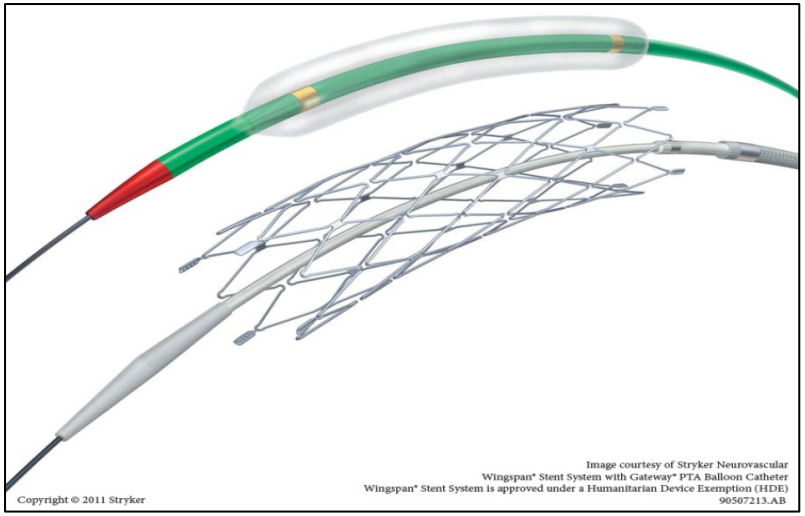
Wingspan Stent System

Complex Disease



- Tortuous, fragile vessels
- Many variables to consider
  - Vessel diameter
  - Plaque composition
  - Degree of stenosis
  - Symptom etiology
  - Patient co-morbidities
- Progressive

Designed for ICAD



- Designed for neurovascular access
- Gentle pre-dilation
- Highly conformable cell structure
- Active, controlled outward radial force (self-expanding stent)

Humanitarian Use Device Approval Requirements

Categories	HUD/ HDE	PMA	510(k)
Approval Steps	2	1	1
Available Alternative Devices	No	Yes	Yes
Require IRB Approval for Institutional Use	Yes	No	No
Require Continuing IRB Review (at least annual)	Yes	No	No
Demonstrate Probable Benefit vs. Effectiveness	Yes	No	No
Require Annual Reports to FDA	Yes	Yes	No
Limited to treating <4000 patients per year	Yes	No	No
Not-for-Profit Restriction	Yes	No	No

HDE Devices have the most regulatory and institutional oversight of all approved devices

Extremely Small Treatment Population

Total US Device Shipments

Period	Wingspan Stents
Aug 2005 - June 2006	1220
July 2006 - June 2007	2187
July 2007 - June 2008	1684
July 2008 - June 2009	2244
July 2009 - June 2010	2216
July 2010 - June 2011	1750
Total Shipped	**11,301**

2006 CMS Non-coverage decision issued; no reimbursement

Less than 4000 patients per year are eligible for treatment with the Wingspan device. On average, less than 2000 patients per year in the US receive a Wingspan Stent.

Safety and Probable Benefit Overview

Jon Hopper MB ChB, FRCSEd

Vice-President, Global Medical Director

Stryker Corporation

Disclosures:
Full time employee of Stryker Corporation, preserved pension rights from former employment in UK NHS and UK Department of Health's MHRA

Safety and Probable Benefit Overview

- Overview of Pre-approval (HDE) Study
- Comparison of SAMMPRIS and HDE study populations
- Review of Post-approval Data
  - Complaints
  - Clinical Literature
- Analysis
  - Relevance of SAMMPRIS to patients with HDE indication
  - Safety profile of Wingspan system in 2012
  - Risk-Probable benefit analysis for HDE population

Pre-approval (HDE) Study Design

- **Prospective, multicenter, single-arm trial**
  - Single-arm trial appropriate due to prior failure of medical therapy and no alternative treatments available for comparison
- **45 patients enrolled at 12 sites (Europe and Asia)**
  - Recurrent stroke attributed to target stenosis of ≥50%
  - Refractory to medical therapy (i.e., antithrombotics)
  - Greater than or equal to 7 days post-stroke
- **Independent event adjudication; Angio core lab; Data monitoring**
- **Primary Endpoint was Ipsilateral Stroke or Death at 30 days**
- **Served as the basis for HDE approval**

Angiographic Results

Measurement	Baseline (N=45)	Post-PTA (N=44)	Post-Stent (N=44)	6 Months (N=40)
Reference Vessel Diameter (mm) Mean ± SD Range (min, max)	3.1 ± 0.8 (1.3 , 4.8)	3.2 ± 0.8 (1.3 , 4.8)	3.2 ± 0.8 (1.3 , 4.8)	3.1 ± 0.8 (1.3 , 4.8)
MLD at Target Lesion (mm) Mean ± SD Range (min, max)	**0.8 ± 0.6** (0.0 , 2.0)	**1.6 ± 0.6** (0.5 , 2.9)	**2.1 ± 0.5** (1.3 , 3.2)	**2.2 ± 0.8** (0.4 , 4.0)
Gain in MLD from Baseline (mm) Mean ± SD Range (min, max)		-0.8 ± 0.6 (-3.0 , 0.2)	-1.3 ± 0.6 (-3.5 , -0.2)	-1.4 ± 0.7 (-3.5 , -0.0)
% Stenosis Mean ± SD Range (min, max)	**74.9 ± 9.8** (57.0 , 99.0)	**50.0 ± 16.2** (0.0 , 79.0)	**31.9 ± 13.6** (-8.0 , 49.0)	**28.0 ± 23.2** (-33.0 , 81.0)
≥50% Stenosis	**100% (45/45)**	**54.5% (24/44)**	**0.0% (0/44)**	**7.5% (3/40)**

MLD: Minimum Lumen Diameter; SD: Standard Deviation

Immediate significant increase in vessel lumen diameter sustained throughout study follow up

Clinical Outcomes

Endpoint	30 Days (N=45*)	6 Months (N=43*)
Death or Ipsilateral stroke	2 (4.4%)	3 (7.0%)
Major Ipsilateral stroke	2 (4.4%)	2 (4.7%)
Death	1 (2.2%)	1 (2.3%)
Ipsilateral stroke	2 (4.4%)	3 (7.0%)
Major ipsilateral stroke	2 (4.4%)	2 (4.7%)
Minor ipsilateral stroke	0	1 (2.3%)

*44 of 45 enrolled patients treated. One patient was enrolled but not treated due to problems with access through the patient's tortuous anatomy.

Low rates of death and ipsilateral stroke seen peri-procedurally and at 6 months

Comparison of Patient Populations

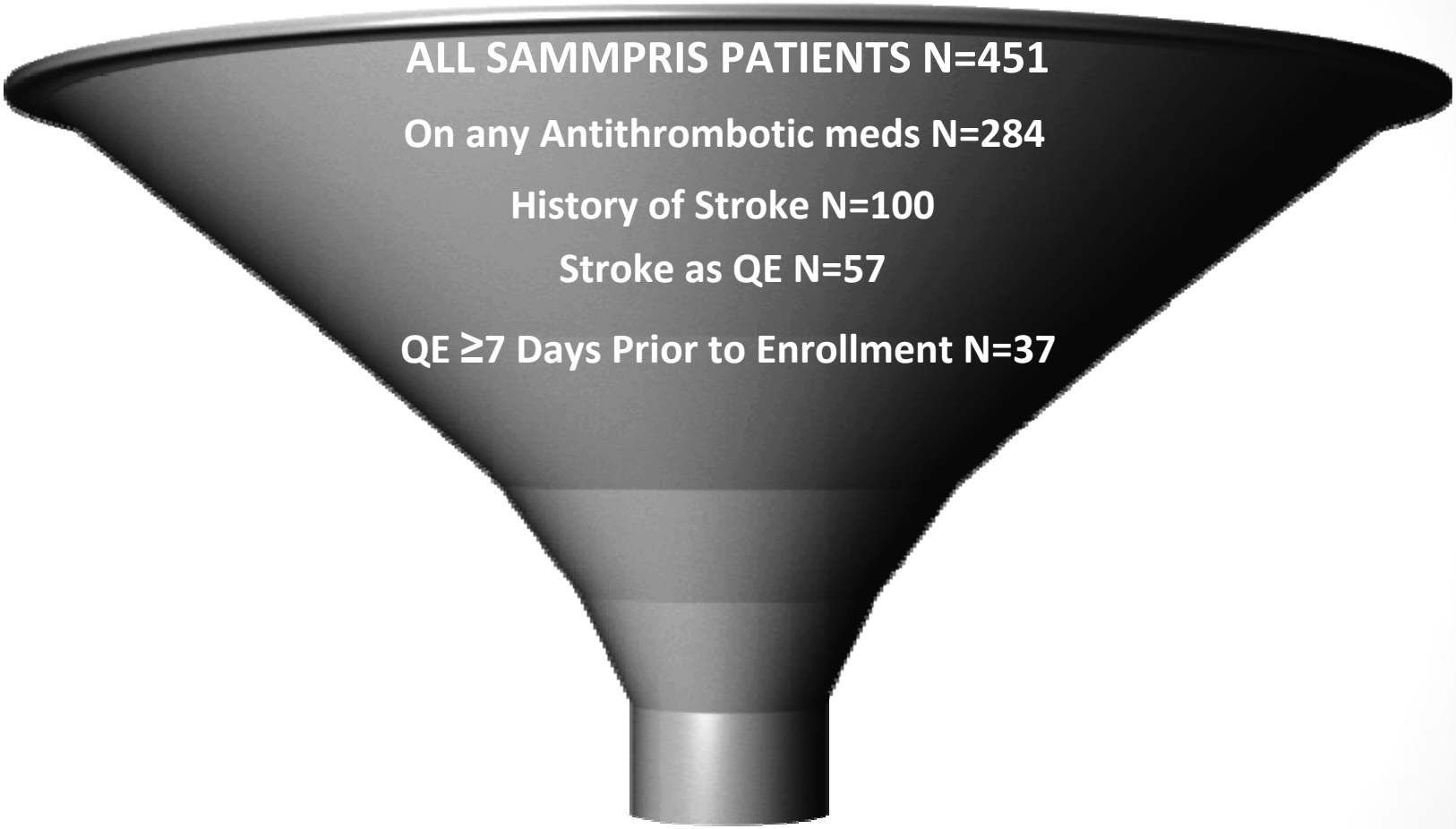
Key Inclusion Criteria Differences

HDE Study	SAMMPRIS
• Treatment of ICAD **following failed medical therapy**	• **Failure of medical therapy not required**
• Target vessel stenosis ≥50%	• Target vessel stenosis 70-99%

• **Recurrent stroke**
  • Eligible for enrollment after **more than one event**
	• **TIA or stroke** in the prior 30 days
	  • Eligible for enrollment after the **first stroke or TIA**

• At least 7 days post qualifying event prior to enrollment	• No exclusion for qualifying event in past 7 days

Patient Comparability SAMMPRIS and HDE Study



Only 8.2% of SAMMPRIS patients met the inclusion criteria for the HDE study

Clinical Characteristics Comparison

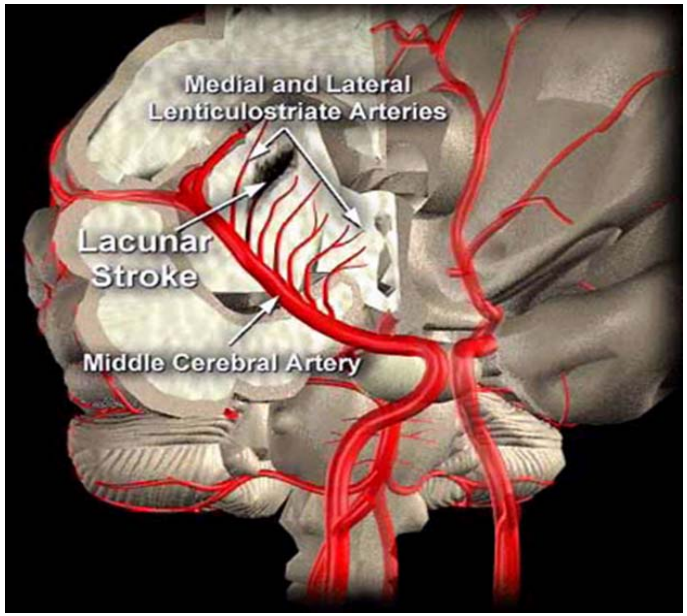
	HDE study (N=45)	SAMMPRIS PTAS (N=224)
Age (years), mean	66	61
Male, %	73	57
Hypertension, %	91	90
Hyperlipidemia, %	58	87
Diabetes, %	53	47
Stroke as the QE (%)	96	63
Median Time from QE to Treatment (days)	22 (12-59)	7 (4-16)

2 HDE patients had protocol violation for lack of stroke history (TIA only)

SAMMPRIS patients were stented significantly earlier than the HDE population, median 7 days compared to 22 days (mean 72.5) post QE

Angiographic Comparisons

Perforator Rich MCA Artery



Angiographic Comparisons

	HDE study (N=45)	SAMMPRIS PTAS (N=224)
Lesion location, %		
ICA	29	20
MCA	22	41
BA	20	22
VA	29	17
Baseline % Stenosis, mean	75	80
Lesion Length (mm), mean	7.2	UK
Post-stent Residual Stenosis, %	31.9	26.7

42% 63%

Significantly more perforator rich arteries (MCA, BA) were stented in SAMMPRIS

FDA Analysis of SAMMPRIS 30-day Stroke and Death Rates in HDE Subgroup

30 Day Results by Anti-Thrombotic Usage Group	Medical Therapy (#/n)	PTAS (#/n)	p-value
Overall (N=451)	5.8% (13/227) (3.4%, 9.7%)	14.7% (33/224) (10.7%, 20.1%)	0.009†
Medically refractory (N=284)	4.4% (6/140) (2.0%, 9.4%)	16.0% (23/144) (10.9%, 23.1%)	0.0276†
Medically refractory + history of stroke (N=100)	8.3% (4/49) (3.2%, 20.7%)	25.5% (13/51) (15.7%, 39.8%)	0.0136†
Medically refractory, history of stroke, Stroke QE (N=57)	13.9% (4/29) (5.5%, 33.0%)	17.9% (5/28) (7.9%, 37.7%)	.5918†

†p-value based on entire study follow-up

*The true HDE subgroup should be further subset to include time from QE to treatment ≥ 7 days

Only 37 patients in the SAMMPRIS trial were similar to HDE study population if time to treatment is considered. Sample size is too small for meaningful comparison.

Summary of Patient Comparability

- The patient population studied in SAMMPRIS is dissimilar to that studied in the HDE approval study
  - Only 8.2% of SAMMPRIS patients would have met the HDE inclusion criteria
  - Failed medical management of symptomatic ICAD was not a prerequisite for entry to SAMMPRIS
  - Many subtypes of patients treated with Wingspan Stent System under the approved HDE indication were severely under-represented in SAMMPRIS, making it difficult to draw any conclusions for these groups of patients
  - Timing of intervention, requirement of Stroke as a qualifying event are clinically important differences and possibly predictive of 30-day outcomes

Review of Post-approval Data

MDRs for Wingspan stent system from 2005 to Jan 2012

Total* reported MDRs	Total** MDRs	Stroke	Death	Stent occlusion due to thrombosis or restenosis	Technical issues (with or without vessel injury) dissection, perforation
321	291	119	57	93	81
units***	11,301 units shipped				
%	2.6	1.0	0.5	0.8	0.7

*Based on MDR analysis performed by FDA after excluding duplicate and literature MDRs

**Excludes off-label use

***Total number of devices shipped in US from Aug 2005 to June 2011

One MDR can report several events and total number of events is greater then number of MDRs, ex. Stent thrombosis, stroke, and death

Wingspan Clinical Data Review

- Literature search conducted spanning Jan 2006 – Feb 2012
- Nineteen datasets reporting on 30-day outcomes with Wingspan use were identified
  - 17 publications/press releases including SAMMPRIS and HDE study publications
  - 2 internal, unpublished studies
- Meta-analysis completed on reported results

Meta-analysis Methodology

- Derive 30 day stroke or death rate from each dataset
- Commercially available software: "Comprehensive Meta-Analysis version 2"*
- Used Random effect model to assign random weight to each study
- Conservatively more weight assigned to studies with larger sample sizes and higher event rates

* International package developed using NIH funding details available at www.meta-analysis.com

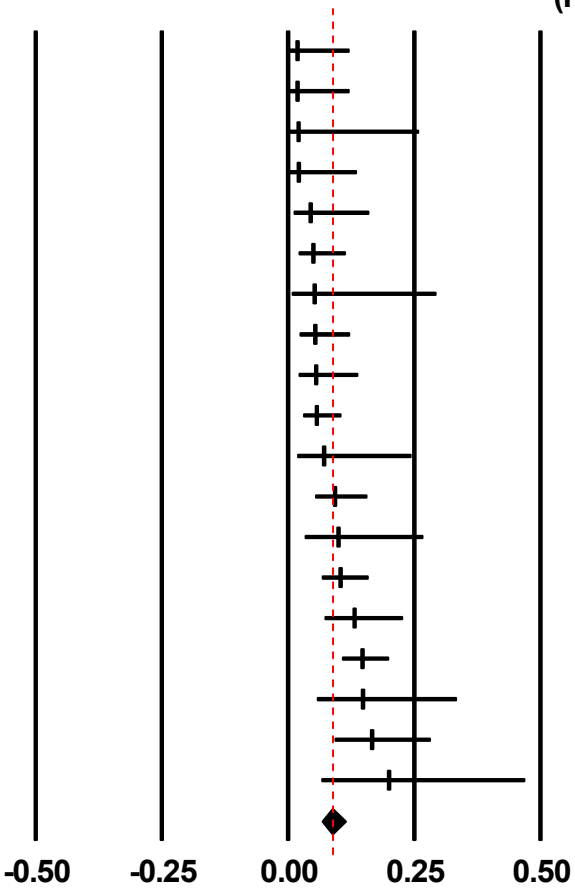
Meta-analysis Results

30-day Stroke or Death Outcomes (with SAMMPRIS)

Study name	Total	Event rate	Lower limit	Upper limit	Weight (Random)	Relative weight
Guo 2010	1 / 53	0.019	0.003	0.122	0.851	1.881
Zhang 2011	1 / 53	0.019	0.003	0.122	0.851	1.881
Qureshi 2011	0 / 23	0.021	0.001	0.259	0.455	1.005
Li 2010	1 / 47	0.021	0.003	0.136	0.849	1.877
Bose 2007	2 / 45	0.044	0.011	0.161	1.472	3.254
Jiang 2011	5 / 100	0.050	0.021	0.115	2.728	6.030
Tarlov 2011	1 / 19	0.053	0.007	0.294	0.825	1.824
ESASIS 2012	5 / 93	0.054	0.023	0.123	2.722	6.016
Yu 2010	4 / 72	0.056	0.021	0.139	2.377	5.253
Fiorella 2011	9 / 158	0.057	0.030	0.106	3.652	8.071
Yue 2010	2 / 28	0.071	0.018	0.245	1.440	3.183
Zadait 2008	12 / 129	0.093	0.054	0.157	4.034	8.916
Li 2011	3 / 30	0.100	0.033	0.268	1.900	4.199
WS Retrospective	18 / 173	0.104	0.067	0.159	4.587	10.138
IRISS	10 / 76	0.132	0.072	0.228	3.688	8.151
Chimowitz 2011	33 / 224	0.147	0.107	0.200	5.221	11.539
Zhao 2009	4 / 27	0.148	0.057	0.335	2.225	4.917
Costalot 2011	10 / 60	0.167	0.092	0.283	3.623	8.008
Lanfranconi 2010	3 / 15	0.200	0.066	0.470	1.746	3.859
Random Model	124 / 1425	0.086	0.066	0.112		
Weighted mean:		**0.0987**	**0.0746**	**0.1227**		

Statistics for each study

Event rate and 95% CI



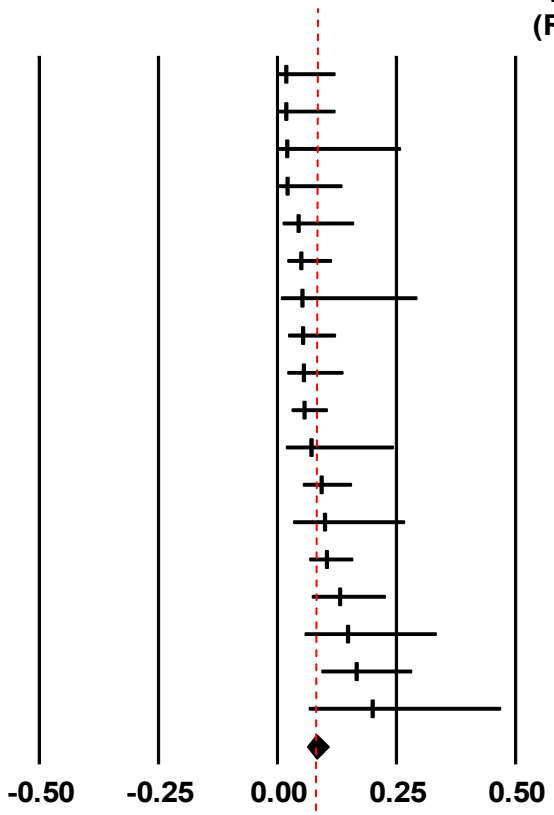
Meta-analysis Results

30-day Stroke or Death Outcomes (without SAMMPRIS)

Meta Analysis (Random effect)

Study name	Total	Event rate	Lower limit	Upper limit	Weight (Random)	Relative weight
Guo 2010	1 / 53	0.019	0.003	0.122	0.878	1.956
Zhang 2011	1 / 53	0.019	0.003	0.122	0.878	1.956
Qureshi 2011	0 / 23	0.021	0.001	0.259	0.463	1.030
Li 2010	1 / 47	0.021	0.003	0.136	0.876	1.952
Bose 2007	2 / 45	0.044	0.011	0.161	1.556	3.466
Jiang 2011	5 / 100	0.050	0.021	0.115	3.029	6.749
Tarlov 2011	1 / 19	0.053	0.007	0.294	0.851	1.896
ESASIS 2012	5 / 93	0.054	0.023	0.123	3.022	6.732
Yu 2010	4 / 72	0.056	0.021	0.139	2.602	5.798
Fiorella 2011	9 / 158	0.057	0.030	0.106	4.212	9.385
Yue 2010	2 / 28	0.071	0.018	0.245	1.520	3.386
Zadait 2008	12 / 129	0.093	0.054	0.157	4.729	10.536
Li 2011	3 / 30	0.100	0.033	0.268	2.041	4.547
WS Retrospective	18 / 173	0.104	0.067	0.159	5.507	12.269
IRISS	10 / 76	0.132	0.072	0.228	4.260	9.492
Zhao 2009	4 / 27	0.148	0.057	0.335	2.421	5.394
Costalot 2011	10 / 60	0.167	0.092	0.283	4.174	9.300
Lanfranconi 2010	3 / 15	0.200	0.066	0.470	1.865	4.155
Random Model	91 / 1201	0.082	0.062	0.106		
Weighted Mean		**0.093**	**0.069**	**0.117**		

Event rate and 95% CI



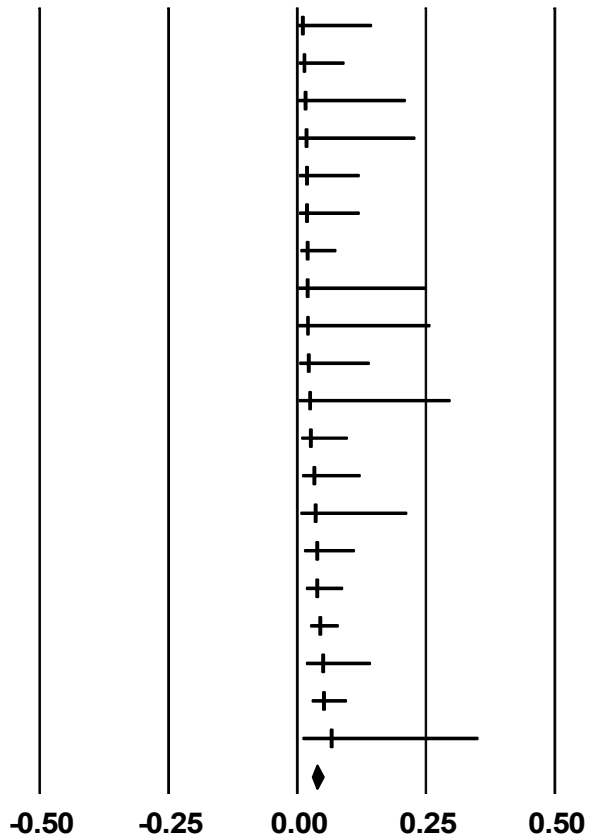
Meta-analysis Results

30 Day Intracranial Hemorrhage Rates

Meta Analysis (Random effects)

Study name	Total	Event rate	Lower limit	Upper limit	Weight (Random)	Relative weight
Li 2010	0 / 47	0.010	0.001	0.146	0.495	1.144
Yu 2010	1 / 72	0.014	0.002	0.092	0.986	2.281
Li 2011	0 / 30	0.016	0.001	0.211	0.492	1.138
Zhao 2009	0 / 27	0.018	0.001	0.230	0.491	1.136
Guo 2010	1 / 53	0.019	0.003	0.122	0.981	2.269
Zhang 2011	1 / 53	0.019	0.003	0.122	0.981	2.269
Jiang 2011	2 / 100	0.020	0.005	0.076	1.960	4.533
Leung 2009	0 / 24	0.020	0.001	0.251	0.490	1.133
Qureshi 2011	0 / 23	0.021	0.001	0.259	0.490	1.132
Bose 2007	1 / 45	0.022	0.003	0.142	0.978	2.262
Tarlov 2011	0 / 19	0.025	0.002	0.298	0.488	1.128
IRISS	2 / 76	0.026	0.007	0.099	1.947	4.504
Yu 2011	2 / 60	0.033	0.008	0.124	1.933	4.472
Yue 2010	1 / 28	0.036	0.005	0.214	0.964	2.230
Fiorella 2007	3 / 78	0.038	0.012	0.113	2.885	6.672
Zadait 2008	5 / 129	0.039	0.016	0.090	4.806	11.116
Chimowitz 2011	10 / 224	0.045	0.024	0.081	9.554	22.097
Costalot 2011	3 / 60	0.050	0.016	0.144	2.850	6.592
WS Retrospective	9 / 173	0.052	0.027	0.097	8.532	19.733
Lanfranconi 2010	1 / 15	0.067	0.009	0.352	0.933	2.159
Random model	42 / 1336	0.037	0.027	0.049		
Weighted mean		**0.039**	**0.033**	**0.045**		

Event rate and 95% CI



Summary of Meta-analysis Results

30 day stroke or death:

- Reported rates range from 0-20%
- 124 events reported for 1425 patients
- Overall mean rate of 30-day stroke or death is 8.6% (95% CI 6.6% – 11.2%)
- Weighted mean rate of 9.87% (95% CI 7.5% - 12.3%)
  - Weighted mean rate of 9.33% without SAMMPRIS (95% CI 6.9% - 11.7%)

30-day intracranial hemorrhage:

- Reported rates range from 0-6.7%
- 42 events reported for 1336 patients
- Overall mean rate of 30-day intracranial hemorrhage is 3.7% (95% CI 2.7% – 4.9%)
- Weighted mean rate of 3.9% (95% CI 3.3% - 4.5%)

Long Term Outcomes with Wingspan

Studies	# of Patients	# of Events*	Percent	Months to F/up
Guo	53	1	1.9%	6
Zhang	53	1	1.9%	9.8
Li (MCA)	47	3	6.4%	12.9
Bose (HDE)	42	3	7.1%	6
Jiang	100	9	9.0%	21.4
Li (Vertebrobasilar)	30	3	10.0%	17.8
Costalat	60	6	10.0%	13.2
Tarlov	19	2	10.5%	84
Zaidat	129	16	12.9%	6
Yu	60	8	13.3%	12
Fiorella	158	22	13.9%	14.2
IRISS	76	12	15.8%	12
Wingspan Retro	118	21	17.8%	12
Yue	28	5	17.9%	15.5
SAMMPRIS	224	46	20.5%	12
Total	**1197**	**158**	**13.2%**	

*Includes 30-day stroke or death plus ipsilateral stroke beyond 30 days

Long Term Outcomes (≥12 Months) with Wingspan

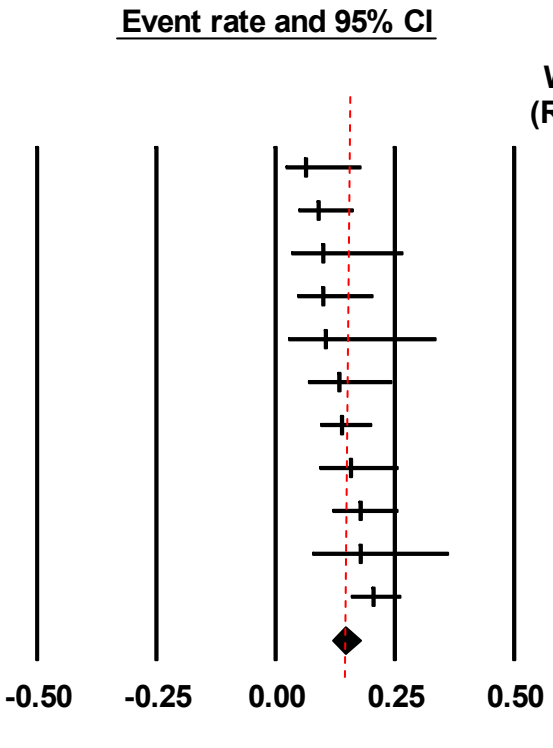
Studies	# of Patients	# of Events*	Percent	Months to F/up
Li (MCA)	47	3	6.4%	12.9
Jiang	100	9	9.0%	21.4
Li (Vertebrobasilar)	30	3	10.0%	17.8
Costalat	60	6	10.0%	13.2
Tarlov	19	2	10.5%	84
Yu	60	8	13.3%	12
Fiorella	158	22	13.9%	14.2
IRISS	76	12	15.8%	12
Wingspan Retro	118	21	17.8%	12
Yue	28	5	17.9%	15.5
SAMMPRIS	224	46	20.5%	12
Total	**920**	**137**	**14.9%**	

*Includes 30-day stroke or death plus ipsilateral stroke beyond 30 days

Meta-analysis Results

Wingspan Long-term Clinical Outcome (≥12 Months)

Study name	Total	Event rate	Lower limit	Upper limit	Weight (Random)	Relative weight
Li (MCA)	3 / 47	0.064	0.021	0.180	2.534	3.616
Jiang	9 / 100	0.090	0.047	0.164	6.221	8.879
Li (Vertebrobasilar)	3 / 30	0.100	0.033	0.268	2.445	3.490
Costalat	6 / 60	0.100	0.046	0.205	4.468	6.377
Tarlov	2 / 19	0.105	0.026	0.337	1.674	2.389
Yu	8 / 60	0.133	0.068	0.245	5.468	7.805
Fiorella	22 / 158	0.139	0.093	0.202	10.934	15.607
IRISS	12 / 76	0.158	0.092	0.258	7.267	10.373
Wingspan Retro	21 / 118	0.178	0.119	0.258	10.355	14.780
Yue	5 / 28	0.179	0.076	0.364	3.545	5.059
SAMMPRIS	46 / 224	0.205	0.157	0.263	15.150	21.625
Random Model	137 / 920	0.145	0.119	0.177		
Weighted Mean		**0.151**	**0.121**	**0.180**		



*Includes 30-day stroke or death plus ipsilateral stroke beyond 30 days

Long Term Outcomes with Medical Therapy

Author	Patients	Type of therapy	Type of outcome	Rate	Mean F/up
Thijs 2000	N=44	Failure of initial TX (AP/AC)	Stroke or TIA	21/44 (47.7%)	1.1 Years
	N=25	Failure of the second regimen	Stroke, TIA or vascular death	15/25 (60%)	1.1 Years
Kasner 2006 **WASID**	N=569	Warfarin or aspirin in 50-99% stenosis	Ischemic stroke in the territory	75/561 (13.5%)	1.8 Years
	N=203	Warfarin or aspirin in 70-99% stenosis	Ischemic stroke in the territory	39/203 (19.3%)	1.8 Years
Mazighi 2006 GESICA	N=102	Anti-platelets (AP)/ Anti-coagulants (AC)	Stroke in territory	14/102 (13.7%)	2 Years
	N=28	AP/AC in subset of hemodynamic stenosis	Stroke or TIA in territory	17/28 (60.7%)	2 Years
Samaniego 2009	N=58	Per guidelines	Stroke, TIA or vascular death	14/58 24.1%	1.2 Years

Long Term Outcomes with Medical Therapy

Author	Patients	Type of therapy	Type of outcome	Rate	Mean F/up
Kozak 2011	N=25	Per AHA guidelines, Endovascular TX deferred	Stroke	11/25 (44%)	1.3 Years
			Stroke	9/25 (36%)	30 day
Tang 2011	N=61	ASA/Plavix in 70-99% stenosis	Stroke/TIA vascular death	15/61 (24.6%)	1.4 Years
			Ischemic stroke in territory	7/61 (11.7%)	1 Years
Chimowitz 2011 SAMMPRIS	N=227	AMM: plavix, aspirin, BP meds, rosuvastatin, Life Style Mod.	Stroke and death up to 30 day and ipsilateral stroke up to 1 Year	28/227 (12.2%)	1 Years
			Stroke or death	13/227 (5.8%)	30 day

Summary of Long-term Results

Wingspan:

- Reported rates range from 1.9 - 20.5%
  - Includes 30-day stroke or death plus ipsilateral stroke beyond 30 days
  - FU time ranges from 6 - 84 months
- Overall mean rate 13.2%

Medical Management:

- Reported rates range from 11.7% - 60.7%
  - Includes ischemic stroke, TIA, vascular death
  - FU time ranges from 12-24 months
- Overall mean rate cannot be calculated due to variable endpoints reported
- Despite evolving medical therapy regimens, no treatment has been shown to eliminate the risk of stroke.
- Certain populations may be at higher risk for medical therapy failure.

ESASIS Trial

Early Stent-assisted Angioplasty in Symptomatic Intracranial Stenosis

Similar to SAMMPRIS*	Dissimilar to SAMMPRIS

• Inv. Initiated; external funding
• Randomized, controlled
  • Medical therapy vs. Medical therapy plus stenting
• Randomization within 28 days of TIA or stroke due to 70-99% ICAD stenosis
• Risk factor targets (HbA1c <65%, systolic BP< 140mmHg, LDL<70 mg/dl)
• DSMB, Independent central event adjudication
	• Single-center
	• Operators – min. 20 case experience with Wingspan
	• Medical therapy
	  • Aspirin 80mg daily during follow-up,
	  • Clopidogrel 75 mg/day from one-week before randomization.
	  • Medical arm: clopidogrel continued for one week
	  • Stent arm: clopidogrel for six weeks
	• 12 month angiogram for all participants
	• Primary endpoint: Composite ipsilateral fatal and nonfatal stroke based on neurological examination performed immediately after stenting, at 30 days and 12 months

*Based on publically available information; list may not be complete

ESASIS Trial Interim Results

Following SAMMPRIS clinical alert for enrollment halt, study DSMB met April 2011 to review 30-day data and concluded:

> "The safety data for the medical group is comparable to the 6% reported for the medical arm of the SAMMPRIS study, whereas the safety data for the stenting group is not comparable to the 14% reported for the stent arm of the SAMMPRIS study' and recommended that 'the ESASIS trial continues recruitment but with close monitoring of safety." (Leung, Int J Stroke 2011)

ESASIS Trial Interim Results

- Stenting results from 93 patients released January 2012*
  - Success rate of stenting procedure 95.7%.
  - 30-day stroke or death rate of 5.4%
  - Risk of stroke after treatment was 6.1% per year
    - Lower than event rate for SAMMPRIS medical therapy arm at one year (12.2%)

*ESASIS interim results. Chinese University of Hong Kong Press Release http://www.cpr.cuhk.edu.hk/en/press_detail.php?id=1225&s=. 12 Jan 2012. Accessed 17 Feb 2012

SAMMPRIS Design: Lessons Learned and Patient Implications

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Disclosures

Society: President–Elect, Society of NeuroInterventional Surgery,
Consulting/Device Proctoring: Stryker Neurovascular, Codman Neurovascular, EV3/Covidien Neurovascular, Penumbra, Siemens,
Research: Ahmanson Foundations (research grant), Cordis (SAPPHIRE WW carotid stent registry Investigator, MR Rescue – study Investigator, Penumbra – DSMB Chairman, PICS, and START study Investigator, Reverse Medical –study Investigator, SAMMPRIS trial – Initial NIH Steering Committee member and Study Investigator

The Clinical Issue

- The SAMMPRIS trial studied one medical regimen in one population but did not define the optimal and safest medical therapy.
- The question at hand is not whether stenting plus medical therapy is superior to medical therapy alone since medical therapy is the primary treatment for patients with ICAD who have experienced a stroke.
- The question at hand is whether physicians should have the therapeutic option of using the Wingspan Stent System for the treatment of patients who have experienced a stroke or TIA due to failed medical therapy.

Patient Selection in SAMMPRIS

- **SAMMPRIS Design**
  - IDE trial sought to answer a broad question of whether stenting plus medical therapy was superior to medical therapy alone.
  - Applied a previously untested, aggressive medical regimen across a mix of patients with ICAD.

- **Qualifying Events**
  - Heterogeneous mix of qualifying events (stroke or TIA) and etiologies not considered when determining study eligibility.

- **Clinical Practice**
  - Patient triage is more complex in the real world than was performed in the SAMMPRIS trial.
  - Some physicians determine antiplatelet therapy resistance and perfusion status to help guide treatment.
  - A single medical regimen may not be optimal for patients treated with and without endovascular methods.
  - Because SAMMPRIS did not incorporate these considerations, the outcome of the device on both 30 day and long term outcomes is not known.

Mechanisms of Stroke in ICAD Patients

Hemodynamic mechanism (perfusion failure)

Occurs when collateral circulation is unable to compensate for a severe stenosis. GESICA trial showed a 60.7% stroke/TIA rate at 2 years on medical therapy alone.

These patients are likely to experience probable benefit from stenting in comparison to continuation of failed medical therapy alone.

GESICA Study Overview

- Prospective study of symptomatic atherothrombotic intracranial stenoses of patients aged 18 to 80, enrolled with symptoms attributed to a single intracranial atherothrombotic stenoses of ≥50%.

- Stenoses involved the following intracranial arteries: VA (22.5%), BA (25.5%), MCA (26.5%), ICA (25.5%).

- 27.4% had clinical hemodynamic characteristics, as classified by a neurologist if symptoms related to the stenosis occurred during a change of position (supine to prone), upon effort, or following the introduction or increase of an antihypertensive medication.

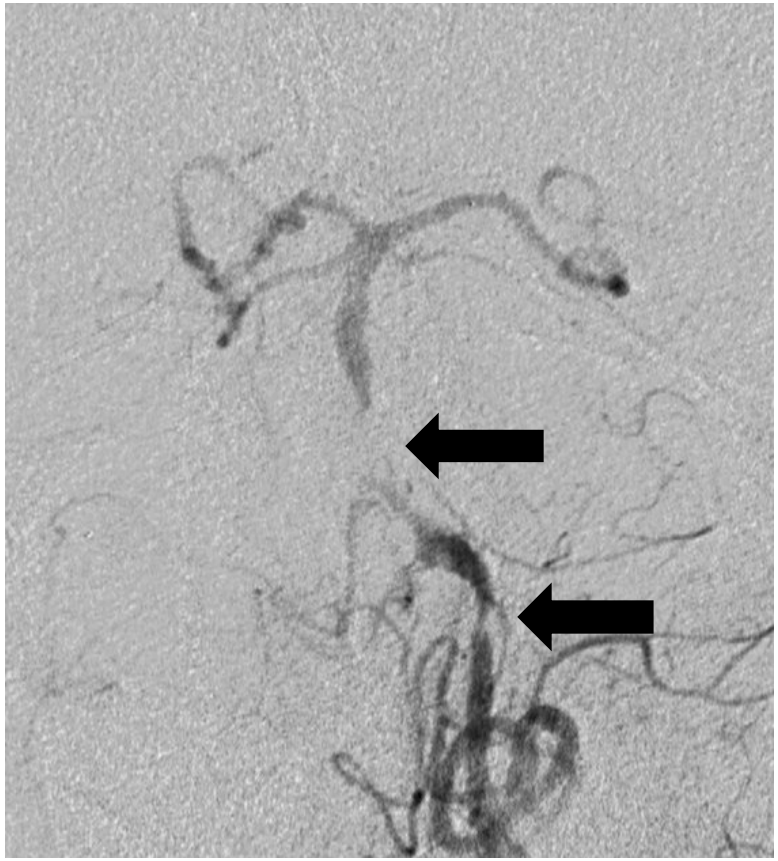
GESICA Study

Study Results

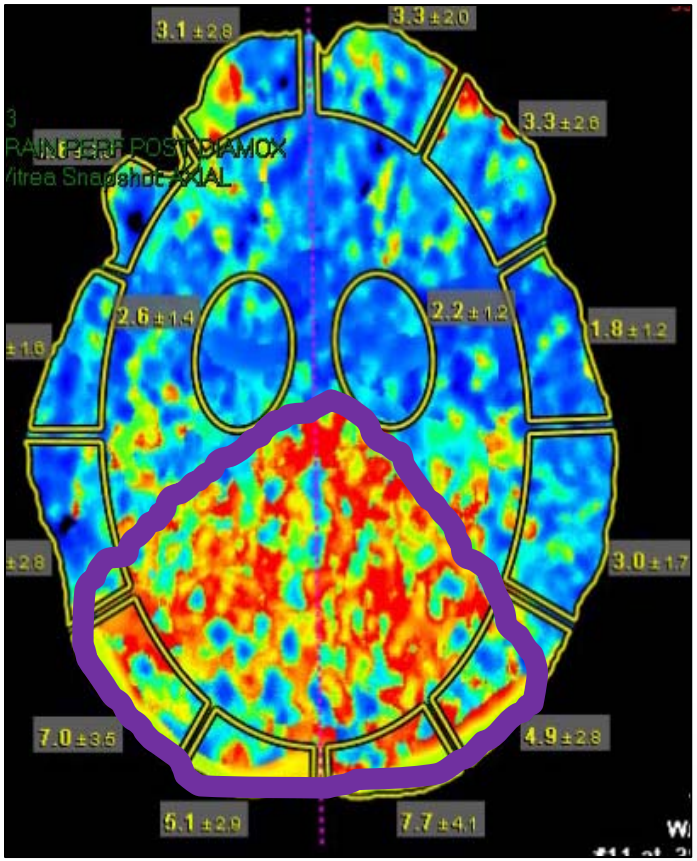
- At 23.4 months follow up:
  - 38.2% of patients had a cerebrovascular event
  - 13.7% of patients had a Ischemic stroke
  - 24.5% of patients had a TIA
  - **Of patients with a hemodynamically significant stenosis, 60.7% had a recurrent stroke or TIA in the territory of the stenotic artery**
    - This association was a significant variable in univariate analyses (p=0.009)
    - The median time to recurrent event was 2 years

Case example: Hemodynamic Stenosis

Patient with multiple posterior fossa strokes, tandem stenoses, requiring ICU management with intravenous pressors and heparin drip



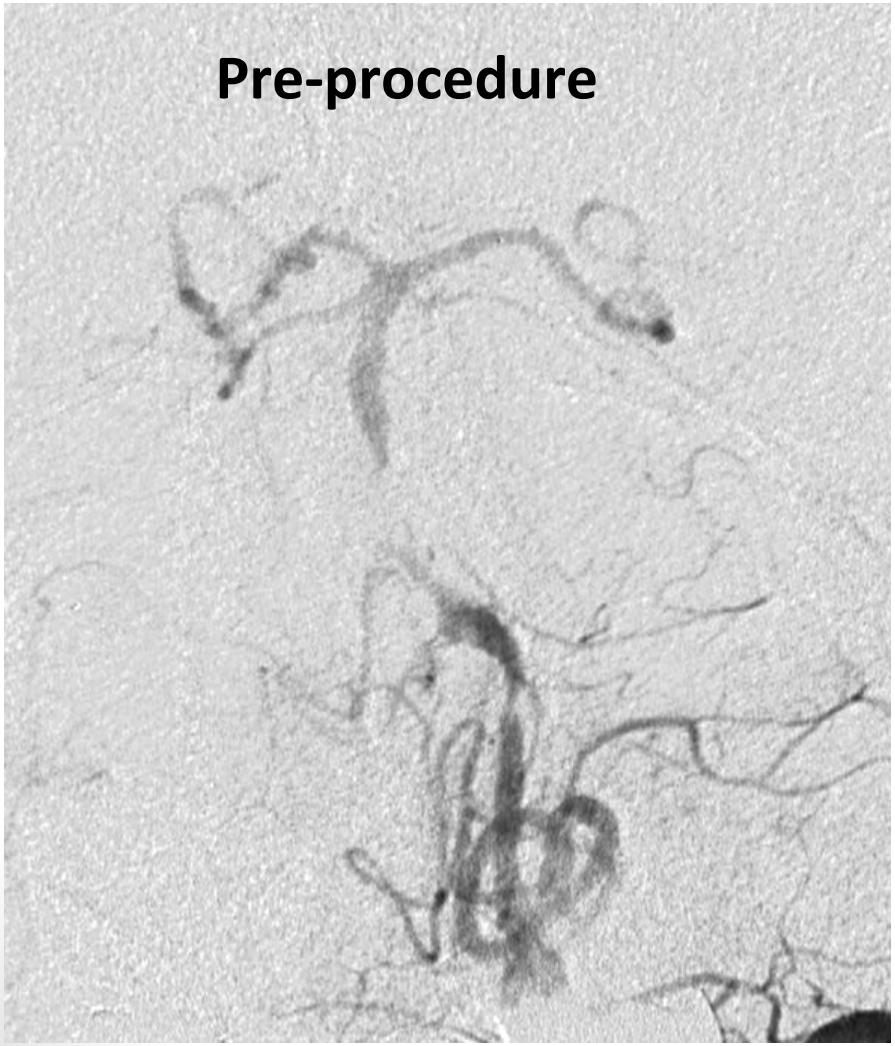
Angiography shows tandem vertebral and basilar stenosis and poor collaterals

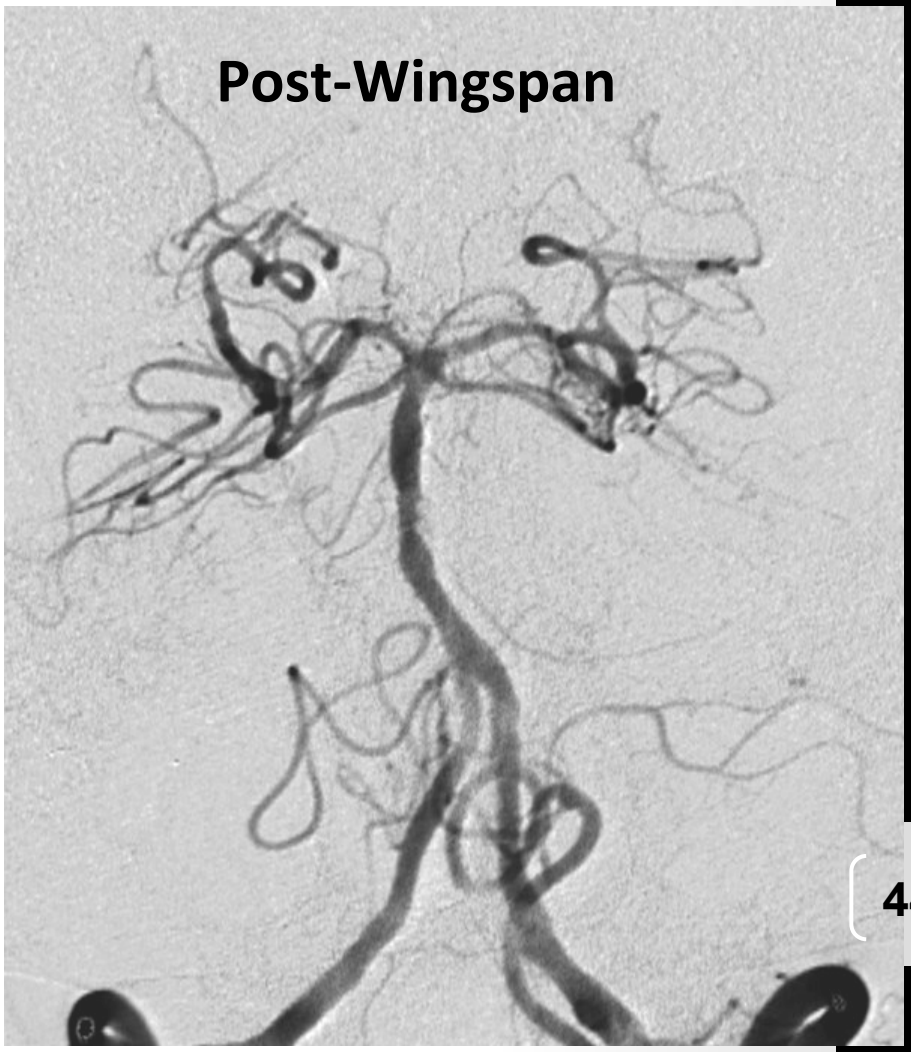


CT perfusion MTT study shows hypo-perfusion of the entire posterior fossa

Patient would not have qualified for SAMMPRIS

Following Wingspan treatment, patient was able to be weaned off pressors and discharged to rehab with no new infarcts over 4 year follow up





Mechanisms of Stroke in ICAD Patients

ICA stenosis associated with thromboembolic mechanism (local thrombosis with thromboembolism)

Those patients not tested for resistance to anti-platelet therapy are likely to do worse in stenting group.

This patient population may be effectively managed by medical management, however, in case of medical failure, these patients are likely to experience probable benefit from stenting

Mechanisms of Stroke in ICAD Patients

Perforator occlusion mechanism

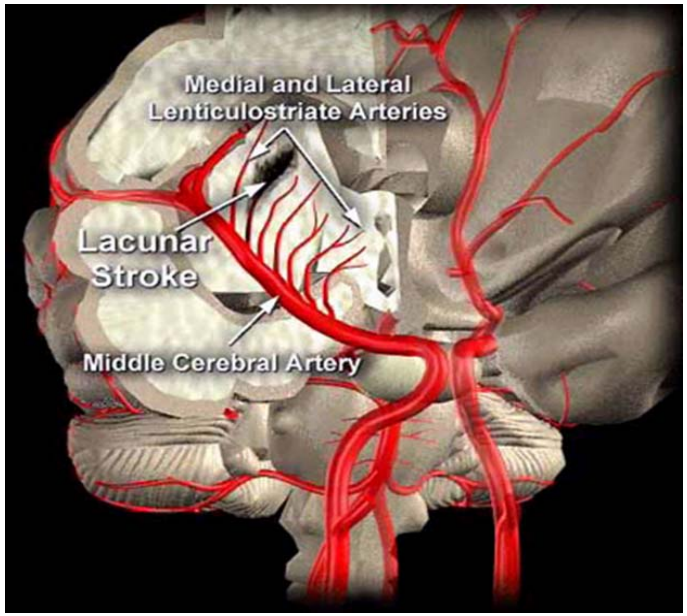
Occurs when there is occlusion of small arteries in the MCA and Basilar arteries from plaque.

In SAMMPRIS, 12 of 20 ischemic strokes at 30 days in patients who were treated with a stent were perforator strokes.

This patient population at risk for perforator occlusion may not experience probable benefit from stenting due to "snow plow" effect and was not considered in design of the SAMMPRIS trial

Angiographic Comparisons

Perforator Rich MCA Artery



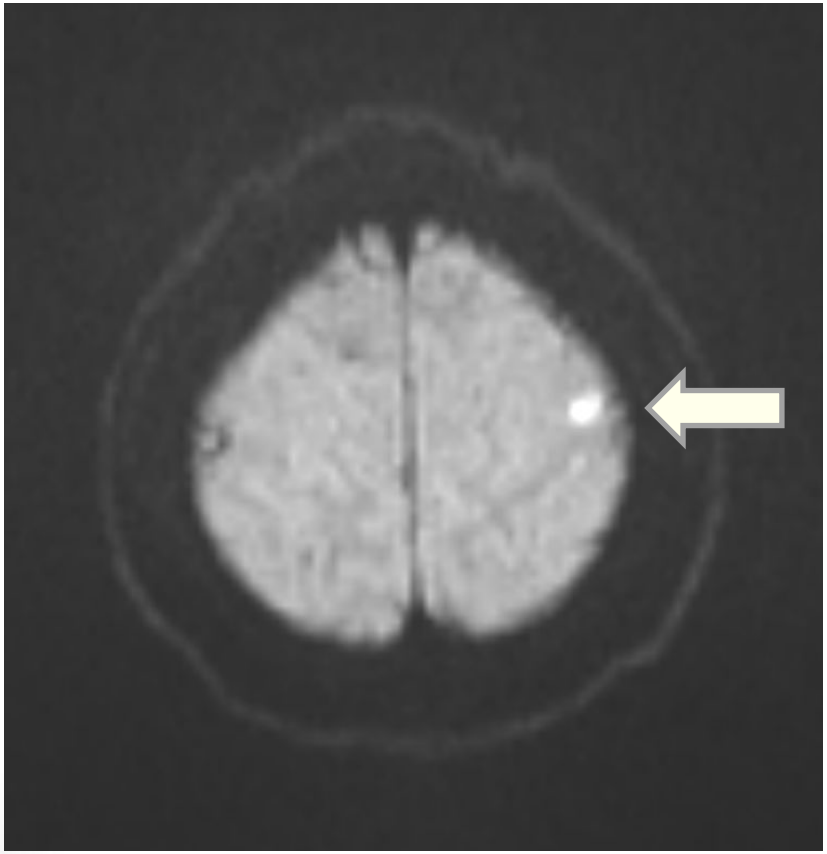
Angiographic Comparisons

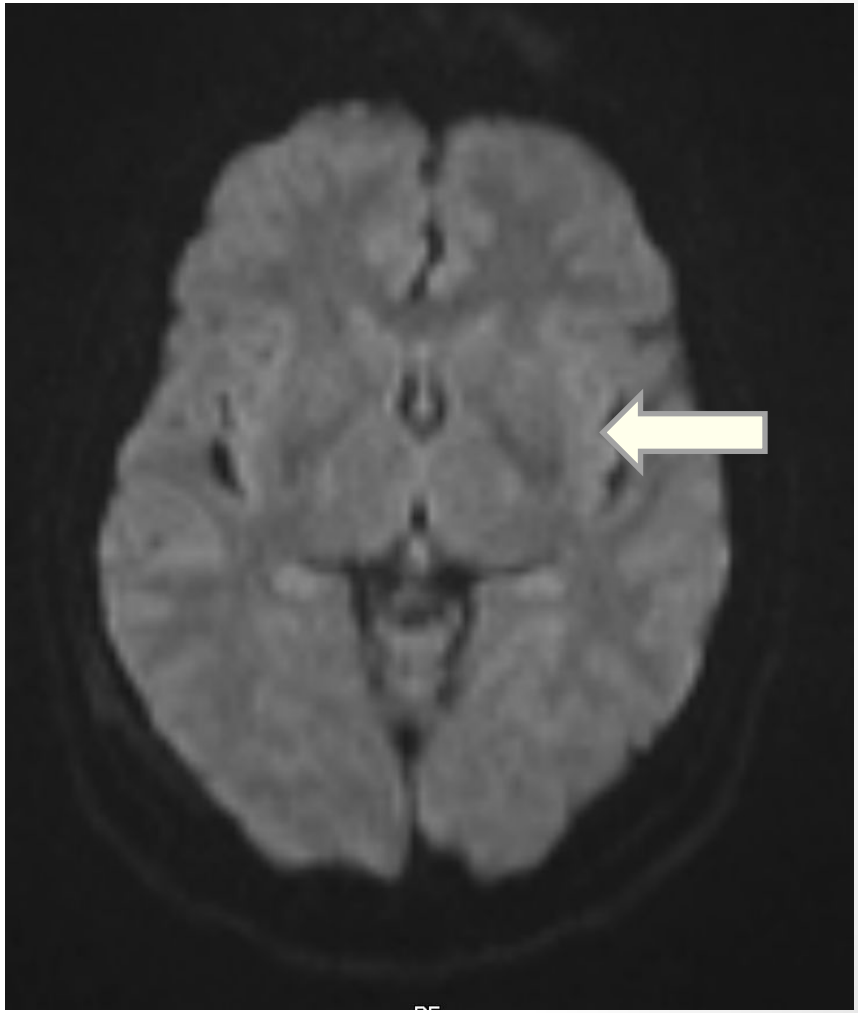
	HDE study (N=45)	SAMMPRIS PTAS (N=224)
Lesion location, %		
ICA	29	20
MCA	22	41
BA	20	22
VA	29	17
Baseline % Stenosis, mean	75	80
Lesion Length (mm), mean	7.2	UK
Post-stent Residual Stenosis, %	31.9	26.7

Significantly more perforator rich arteries (MCA, BA) were stented in SAMMPRIS may have contributed to high perforator stroke rate (12/20 ischemic strokes).

Case example: Perforator occlusion

Patient who presented with left frontal infarcts but no basal ganglia infarcts evident





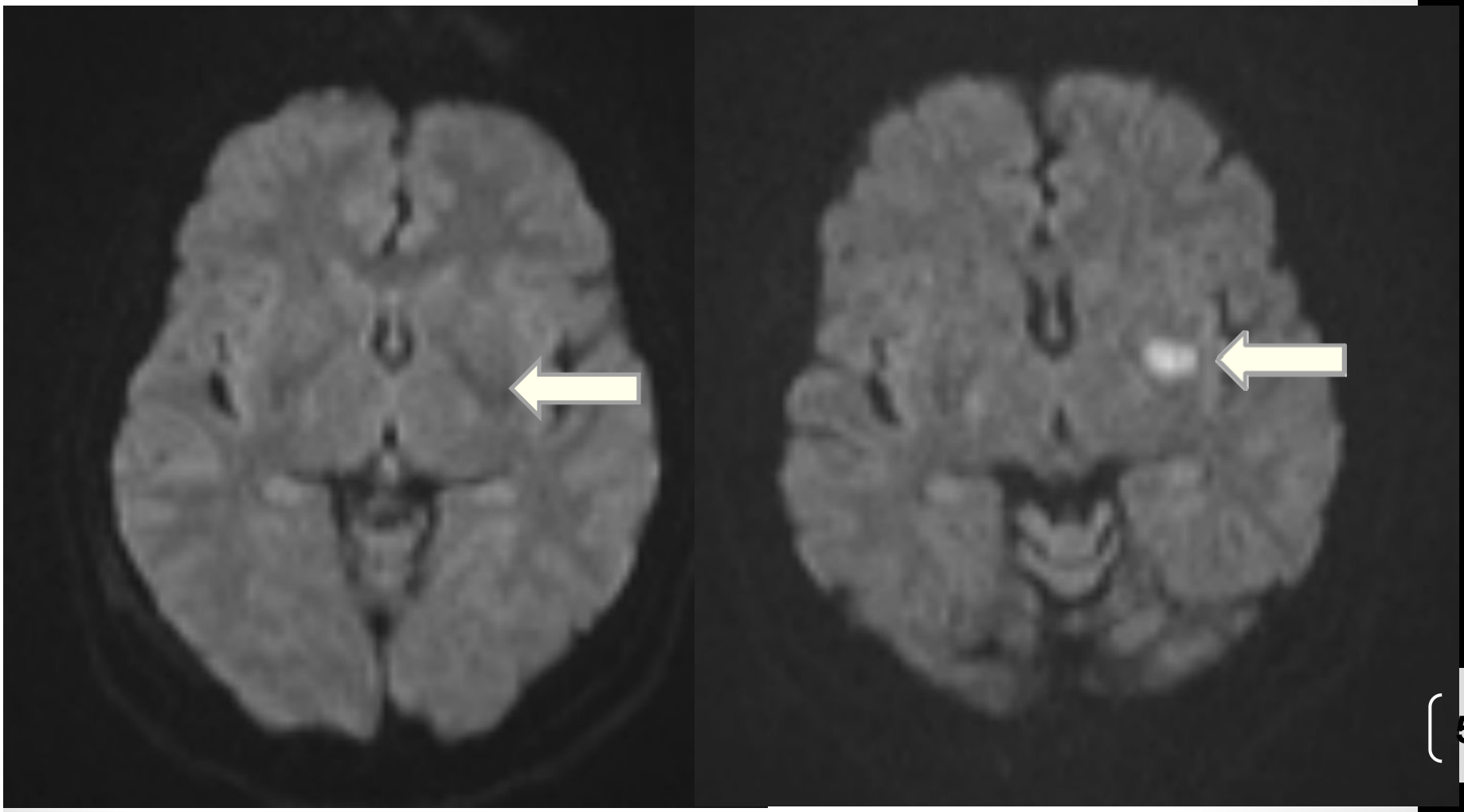
Middle Cerebral Artery Perforators

The Snow Plow Effect of Perforator Occlusion

Pre-treatment *Post-treatment*

Post-procedure left basal ganglia infarct

Pre-procedure ***Post-procedure***



Hemorrhagic Strokes in SAMMPRIS

10 out of 33 strokes (4.5%) in the PTAS arm were symptomatic brain hemorrhages (SAH and ICH)

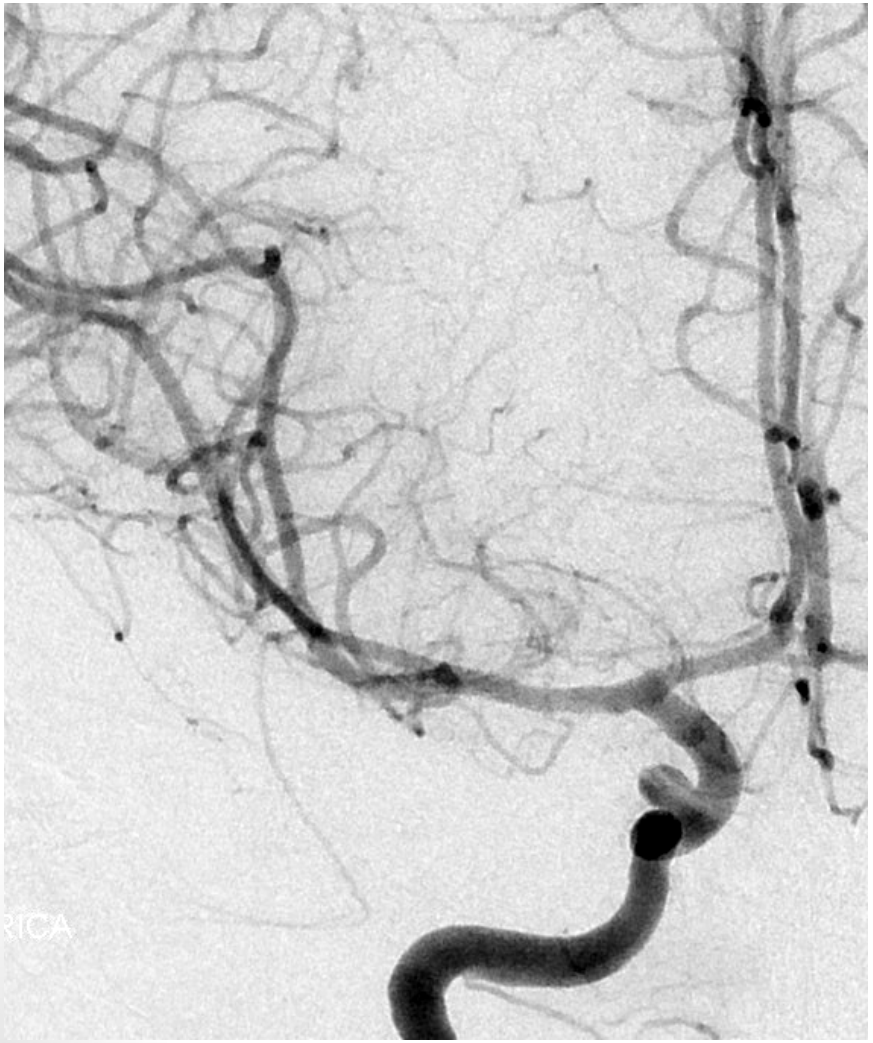
Subarachnoid hemorrhage (SAH): Usually occurs due to wire perforation during a procedure. Rate depends on physician experience. 4 of the 10 strokes (1.8%) in SAMMPRIS PTAS arm were SAH.

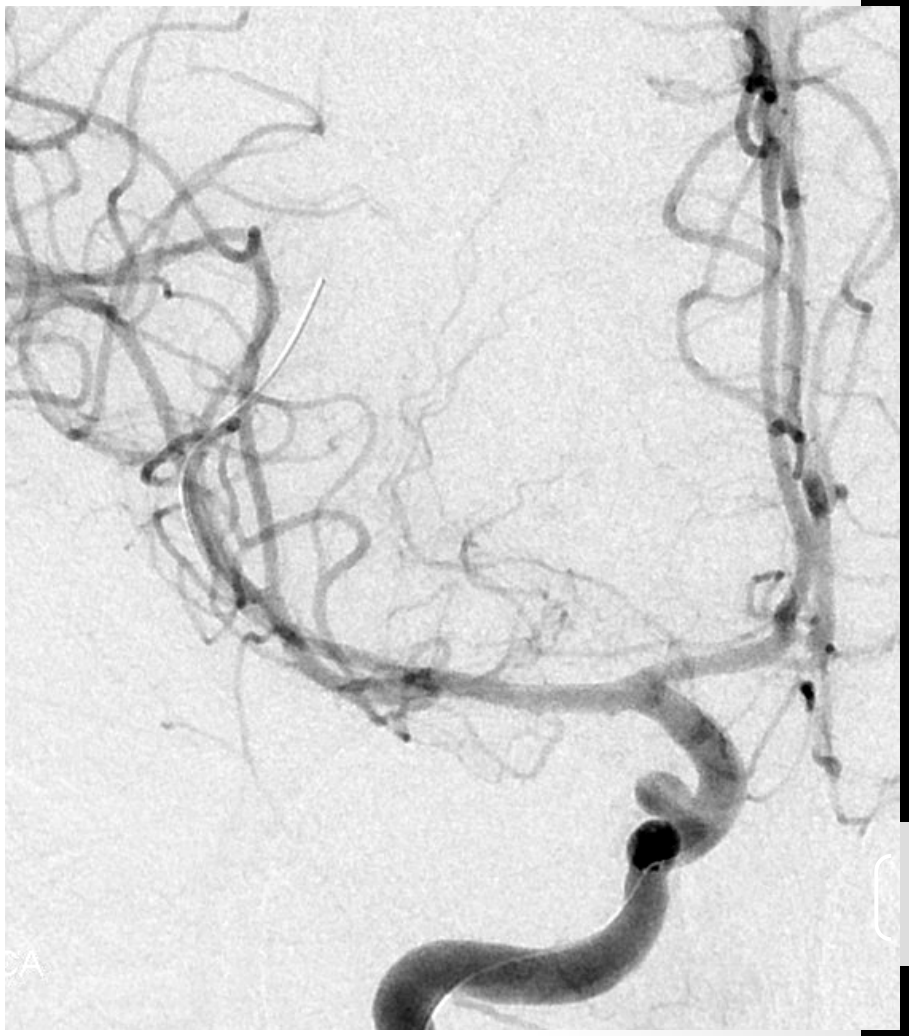
Intracerebral Hemorrhage (ICH): A reperfusion hemorrhage that usually occurs as a result of peri-procedural patient management. 5 of 6 strokes occurred within 24 hours.

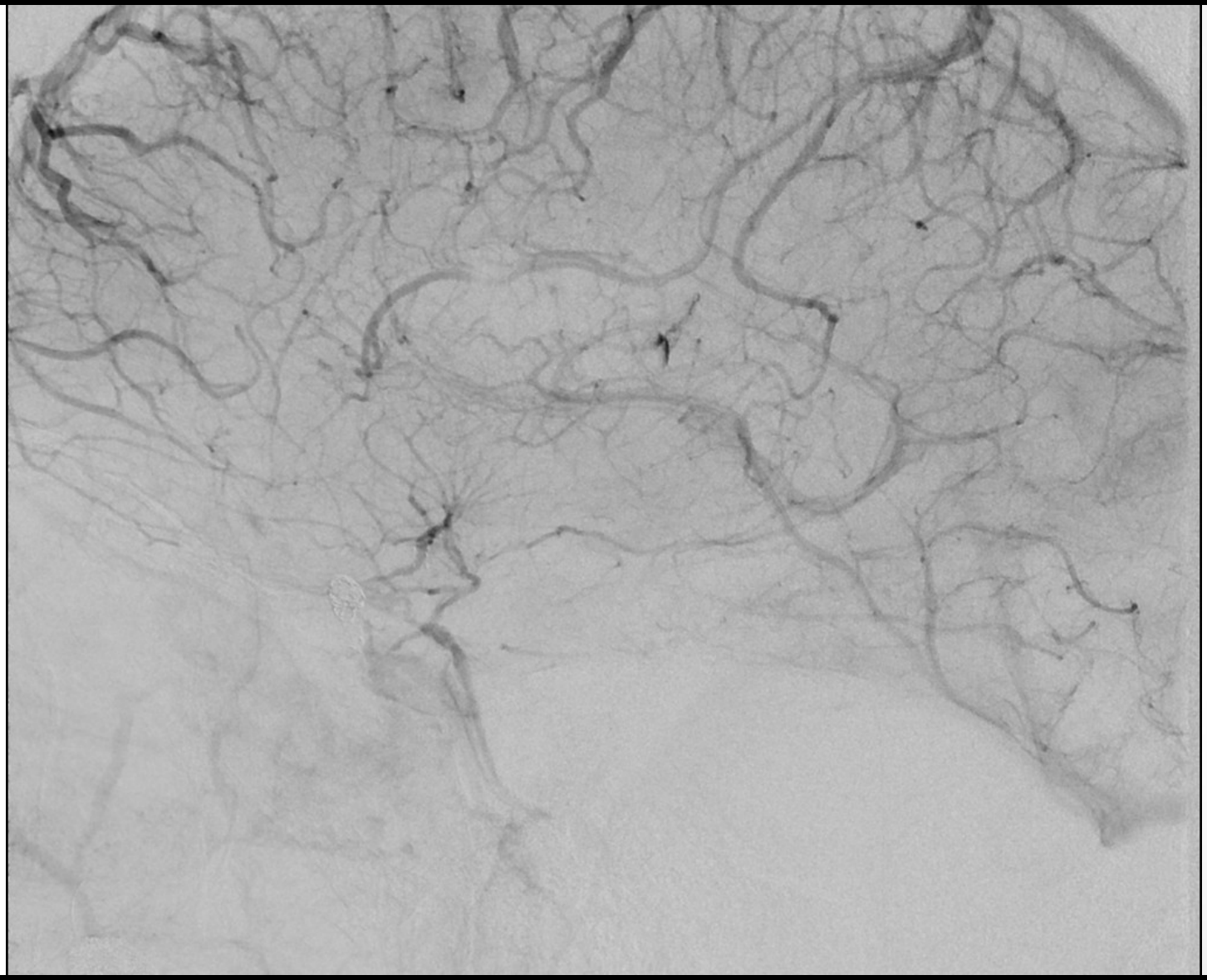
SAMMPRIS factors predictive of hemorrhagic strokes

- **Pre-stent lesion diameter** <0.6 mm (10%) vs ≥ 0.6 mm (0%); p=0.0006
- **Site enrollment** <12 patients 8/102 (8%) vs ≥ 12 patients (2%); p= 0.05
- **QE of TIA-** 7/79 (9%) vs Stroke 3/134 (2%); p=0.04

Physician experience: Intracranial hemorrhage







Results from case studies are not predictive of results in other cases. Results in other cases may vary.

Exchange wire perforation
Not re-perfusion hemorrhage

Physician experience – Wingspan case volume

- While there were several experienced interventionalists in SAMMPRIS the experience with the Wingspan stent system was limited
- The Requirement
  - 20 intracranial stent/angioplasty cases
  - Minimum of 3 Wingspan stents
- The Reality
  - Average of 10 Wingspan stent cases
- Compare to ESASIS study
  - Minimum of 20 Wingspan stent cases

Alternative Therapies

EC/IC bypass: Has not been shown to provide benefit

Balloon angioplasty: The safety and effectiveness of PTA treatment has not been demonstrated and there are no approved products available.

Alternative Therapies

Medical management:

- No medical therapy regimen has been shown to be 100% successful in eliminating the risk of stroke or death.
- Several studies of different drug combinations showed mixed results for long-term outcomes (≥12 months) from 12.2% (1 in 8 patients) in SAMMPRIS, 22% in WASID, to 60% in Thijs (2000).
- The SAMMPRIS trial has:
  - Not defined optimal medical therapy; single regimen applied to all patients
  - Did not examine whether aspirin alone (325 mg) is comparable but safer (less hemorrhage) than aspirin plus clopidogrel.
  - Failed to address known potential risks of hemorrhage with acute aggressive use of potent statin medication immediately after ICA stroke.

Considerations

- **SAMMPRIS Follow up:** Only 50% of patients had been followed out to 1 year at the time of the NEJM publication with 12.2% of AMM arm and 20.5% of stenting arm suffering a stroke or death.
  - Longer than one year follow-up is necessary to assess the safety and durability of stenting vs medical management therapy

- **Patient Selection:** Excess peri-procedural events in stenting arm can be reduced with careful patient selection, physician training, and careful medical management.

- **Appropriate Trial Design:** Need a trial which considers/requires:

1. Patients whom have had a stroke and have failed medical therapy
2. Selection for treatment according to mechanism of stroke
3. The most effective and safe medical arm comparator
4. Procedure issues which may affect early safety of stenting and patient outcomes

Application of SAMMPRIS Results to Wingspan Stent Usage

SAMMPRIS Key Learning	Wingspan Stent Usage
• AMM is effective as the primary therapy for ICA patients with stroke but does not eliminate the risk of recurrent events in patients with symptomatic ICAD (12.2%) • Stroke due to ICAD has multiple etiologies; these differences (embolic or ischemic) were not considered when defining the SAMMPRIS patient population or during the post hoc analyses. . Procedural issues with the potential to impact and affect early safety of stenting must be more carefully considered in future trials.	• Wingspan remains the only approved device to improve lumen diameter in patients consistent with the labeling • Wingspan continues to be used at Cedars Sinai and is still considered safe with probable benefit for the approved population. • Physicians must be experienced and continue to take into account multiple patient characteristics such as perfusion status, AP resistance, etc., as well as possess the technical abilities and case volumes to use the device.

Conclusions

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Vice-President, Global Medical Director

Stryker Corporation

Disclosures:
Full time employee of Stryker Corporation, preserved pension rights from former employment in UK NHS and UK Department of Health's MHRA

Conclusion

- Despite the different study populations, even including the results from the SAMMPRIS stenting arm in a safety analysis of published and reported evidence results in no material change on the safety profile for the use of Wingspan System.

- SAMMPRIS stenting arm falls within the range of data previously reported, and meta-analysis demonstrates that it does not materially increase the weighted mean rate of death and stroke which remains below 10% in the first 30 days post treatment.

- Thus the safety profile for the Wingspan Stent, based on the totality of currently available data, remains consistent with the safety profile of the device at the time of HDE approval in 2005.

Conclusion

- The SAMMPRIS study does not alter the evidence based **Risk / Probable Benefit** profile for use of the Wingspan stent in the indicated **HDE population**
  - It was not so designed and does not provide definitive information regarding patients who are refractory to medical management of symptomatic ICAD.

- The AMM in the medical arm of SAMMPRIS is relevant to the **Risk / Benefit analysis** for the primary management of symptomatic ICAD.
  - The single medical regimen studied may not be optimal for patients treated with and without endovascular methods.

Conclusion

- There continues to be a population of patients for whom the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use.
  - Examples include patients for whom AMM, as used in SAMMPRIS, has failed and those for whom this therapy is not appropriate but have failed another medical therapy regimen.

- The Wingspan Stent system should remain available for the Humanitarian Use treatment of this small group of patients defined by the approved indications for use.

Back up slides

Device Training Overview

Prior to a treating physician's use of the Wingspan Stent System, he/she must meet the following conditions:

1. Be currently licensed to practice medicine and have institutional privileges.
2. Have completed a Neuro-interventional fellowship.
3. Have completed the Stryker training program on the Wingspan® Stent System with Gateway® PTA Balloon Catheter which includes both didactic training on the device as well as case proctoring.

In-stent Restenosis Rates

- All ISR: 0 - 34.6%; 6-24 month mean FU
- Symptomatic ISR: 0 - 10.2%; 6-24 month mean FU