Stenting & Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis

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Aggressive Medical Management with or without Angioplasty and Stenting for Symptomatic Intracranial Atherosclerotic Stenosis: Long Term Results

Disclosures

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Individual disclosures monitored by COI committee and available in published results

Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial

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Study Design

Angioplasty and Stenting (Wingspan System) + Aggressive Medical Management

vs.

Aggressive Medical Management alone

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Aggressive Medical Management

Identical in both arms:

- Aspirin 325 mg / day for entire follow-up
- Clopidogrel 75mg per day for 90 days
- Aggressive, protocol driven risk factor management primarily targeting systolic blood pressure < 140 mm Hg (130 mm Hg diabetics) and low density cholesterol < 70 mg / dl
- Intervent USA – a lifestyle modification program

Hypothesis

Compared with aggressive medical therapy alone, intracranial stenting combined with aggressive medical therapy will decrease the risk of the primary endpoint * by 35% over a mean follow-up of two years in high-risk** patients with symptomatic stenosis of a major intracranial artery.

* Any stroke or death within 30 days after enrollment or after revascularization during follow-up OR stroke in the territory of the stenotic / stented artery beyond 30 days

** Patients with 70-99% stenosis and TIA or stroke within 30 days prior to enrollment. NOT required to have failed antithrombotic therapy.

Early Results

Enrollment was halted after randomization of 451 patients for safety concerns: 30-day rates of stroke and death were significantly higher in the stenting arm (14.7%) as compared to the medical arm (5.8%).

Approximately one half of enrolled patients had been followed out to one year.

Chimowitz et al. NEJM 2011

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Long term follow up

Follow up and medical treatment of all enrolled patients was continued out to a minimum of 2 years

Important to determine whether late strokes in the medical group narrowed the gap between interventional and medical arms

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Methods: Follow up

Outcomes assessed at entry, 4 days, 30 days and then every 4 months

Original plan for maximum of 3 years and minimum of 1 year but amended to minimum of 2 years after enrollment halted

Follow up in person unless unable to return (phone)

Potential adverse events or end points assessed by primary site neurologist – additionally, required blinded evaluation for potentially difficult to classify events (mild stroke or TIA > 1 hour)

All events centrally adjudicated

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Statistical Analysis

Original design for 35% relative risk reduction with PTAS compared to projected 24.7% rate in medical group at 2 years

Log-rank test to compare treatment groups. Cumulative probabilities based on Kaplan–Meier estimates at 1,2 and 3 years compared between treatments using a z-test

Subgroups for pre-specified baseline factors using Cox proportional hazards regression models

All analyses intent-to-treat, p values 2 sided without correction for multiple comparisons

Several sensitivity analyses for withdrawn/lost to follow up

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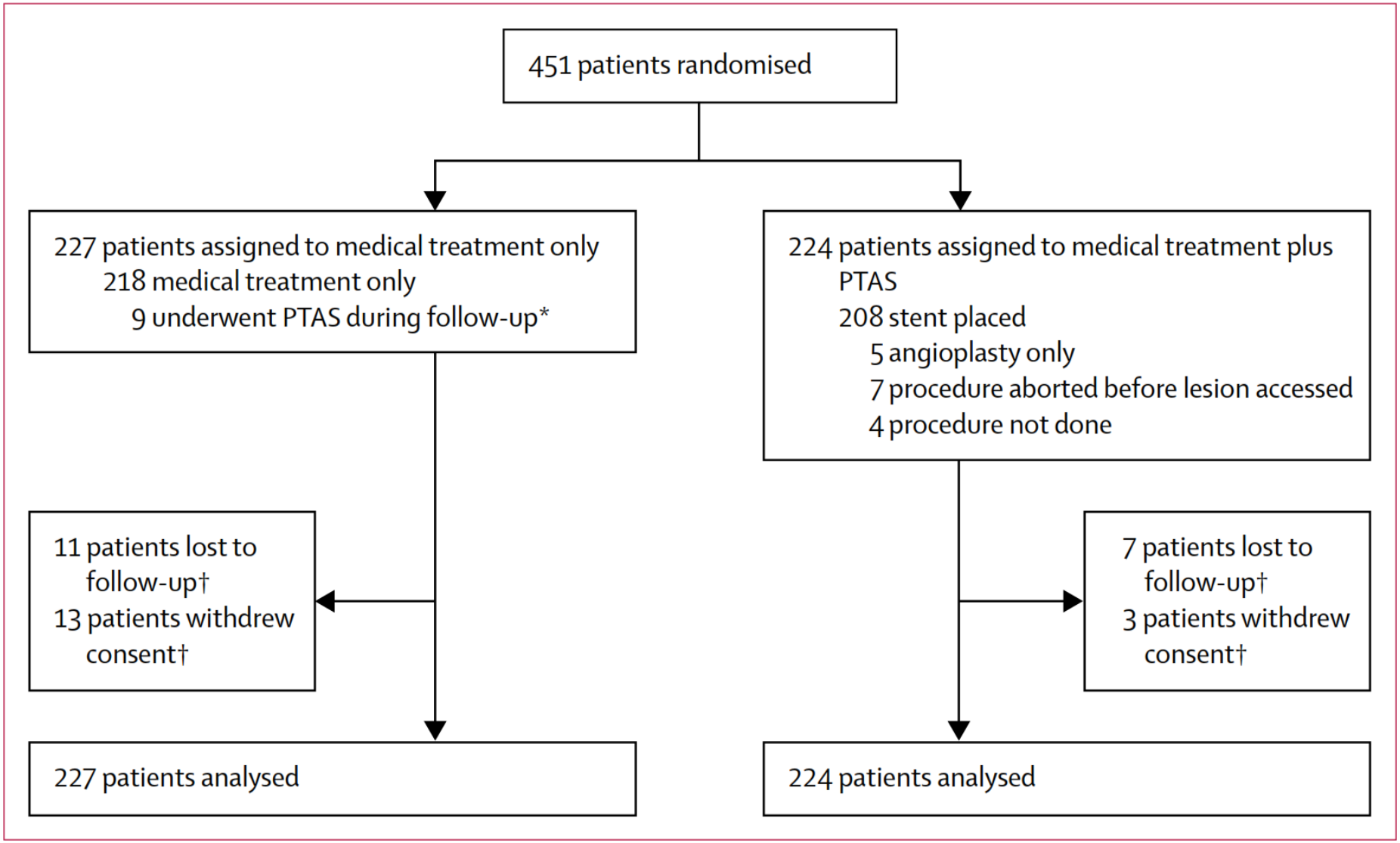
Trial Profile



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Withdrawn/Lost

	Medical Management n = 227	PTAS n = 224
Number of Lost Patients	11 (4.8%)	7 (3.1%)
Months of Follow-up for Lost Patients		
< 1	0 (0%)	0 (0%)
1 – 11.9	0 (0%)	2 (29%)
12 – 23.9	5 (45%)	0 (0%)
≥ 24	6 (55%)	5 (71%)
Number of Withdrawn Patients	13 (5.7%)	3 (1.3%)
Months of Follow-up for Withdrawn Patients		
< 1	4 (31%)	0 (0%)
1 – 11.9	3 (23%)	1 (33%)
12 – 23.9	2 (15%)	0 (0%)
≥ 24	4 (31%)	2 (67%)

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Duration of Follow-Up

- Medical group:
  - Median 32.7 months
  - IQR: 24.2 – 40.5months
  - Range: 0.03 – 52.6 months
- PTAS group:
  - Median: 32.2 months
  - IQR: 24.1- 40.5 months
  - Range: 0 – 52.4 months

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Baseline Characteristics

Characteristic	Medical Group (N=227)	PTAS Group (N=224)
Age (Yrs)	59.5 (11.8)	61.0 (10.7)
Gender (Male)	145 (64)	127 (57)
Race **		
Black	49 (22)	55 (25)
White	162 (71)	160 (71)
Other	16 (7)	9 (4)
History of Hypertension (Yes)	203 (89)	200 (89)
History of Lipid Disorder (Yes)	202 (89)	195 (87)
Smoking		
Never	78 (34)	90/223 (40)
Previously	80 (35)	79/223 (35)
Currently	69 (30)	54/223 (24)
Diabetes (Yes) [ϕ]	103 (45)	105 (47)
Systolic Blood Pressure (mmHg)	146.8 (21.8)	143.9 (20.6)
Low Density Lipoprotein Cholesterol (mmol/L [×])	2.53 (0.95)	2.49 (0.99)
High Density Lipoprotein Cholesterol (mmol/L [×])	1.00 (0.26)	0.98 (0.27)
Non-High Density Lipoprotein Cholesterol (mmol/L [×])	3.02 (1.04)	3.01 (1.14)
Glycosylated Hemoglobin in Diabetic Patients (%)	8.2 (2.3) n=105 [b]	7.8 (2.1) n=111 [b]
Body Mass Index (kg/m^2)	30.7 (6.3)	30.3 (6.2)

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Baseline Characteristics

Characteristic	Medical Group (N=227)	PTAS Group (N=224)
History of Coronary Artery Disease (Yes)	59 (26)	47 (21)
History of Stroke (Not Qualifying Event) (Yes)	58 (26)	60 (27)
Qualifying Event		
Stroke	152 (67)	142 (63)
TIA	75 (33)	82 (37)
On Antithrombotic Therapy at Qualifying Event (Yes)	140 (62)	144 (64)
Time from Qualifying Event to Randomization (Days)	7 (4-19)	7 (4-16)
Symptomatic Qualifying Artery		
Internal Carotid Artery (ICA)	49 (22)	45 (20)
Middle Cerebral Artery (MCA)	105 (46)	92 (41)
Vertebral Artery	22 (10)	38 (17)
Basilar Artery	51 (22)	49 (22)
Percent Stenosis of Symptomatic Qualifying Artery †	81 (7)	80 (7)
Categories of Percent Stenosis of Symptomatic Qualifying Artery †		
70-79%	102 (45)	107/223 (48)
80-89%	97 (43)	92/223 (41)
90-99%	28 (12)	24/223 (11)

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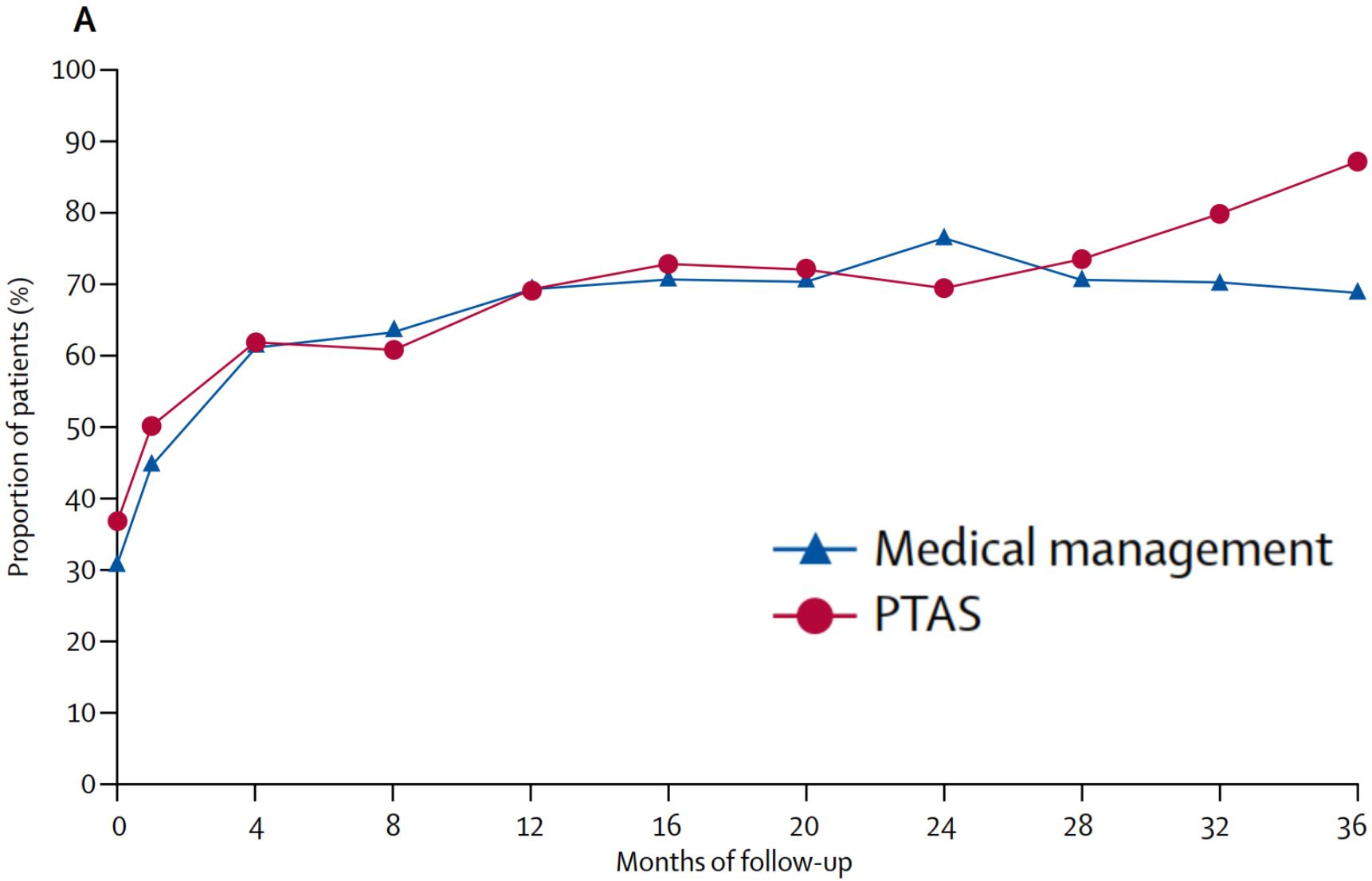
Systolic BP control



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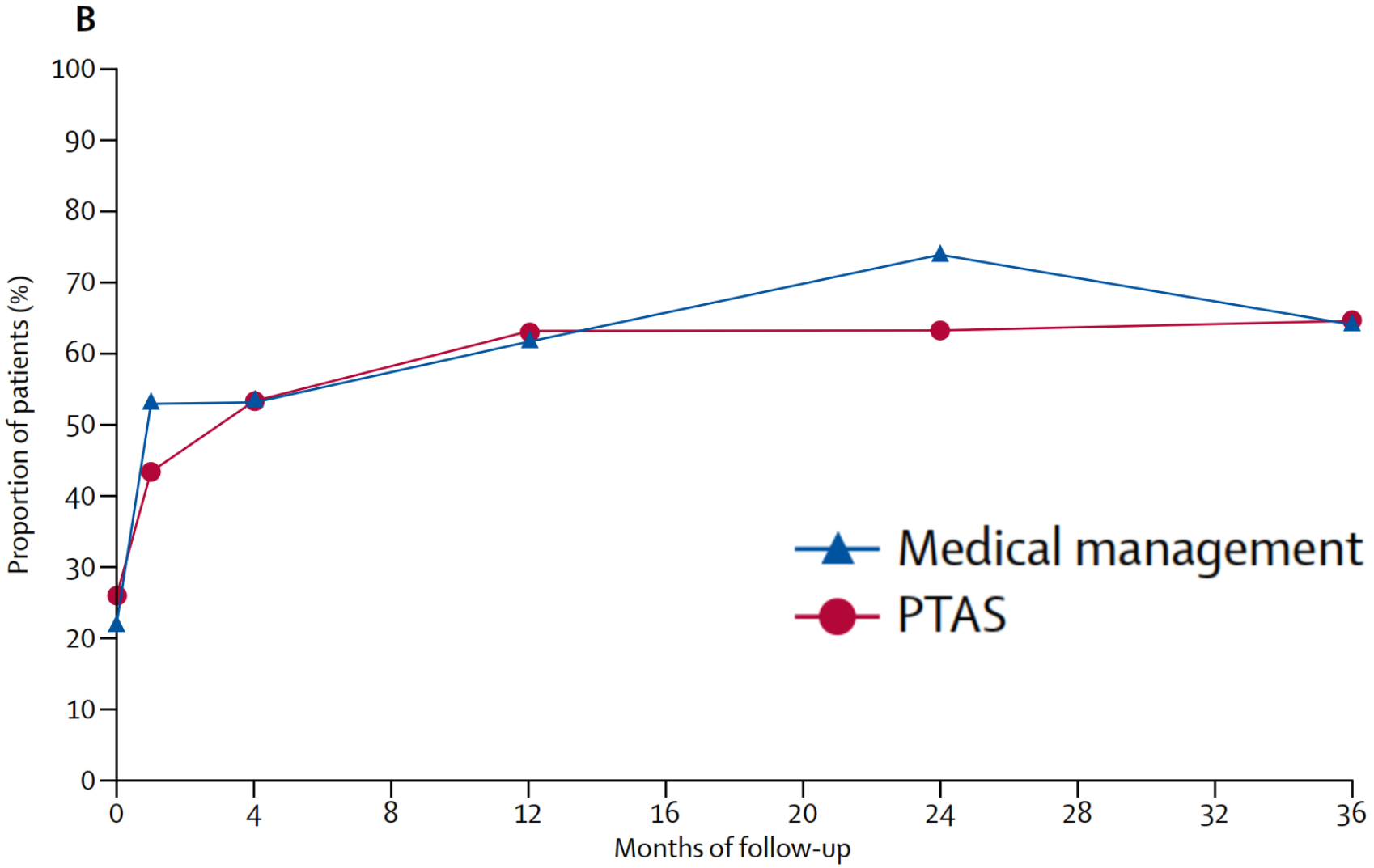
LDL control



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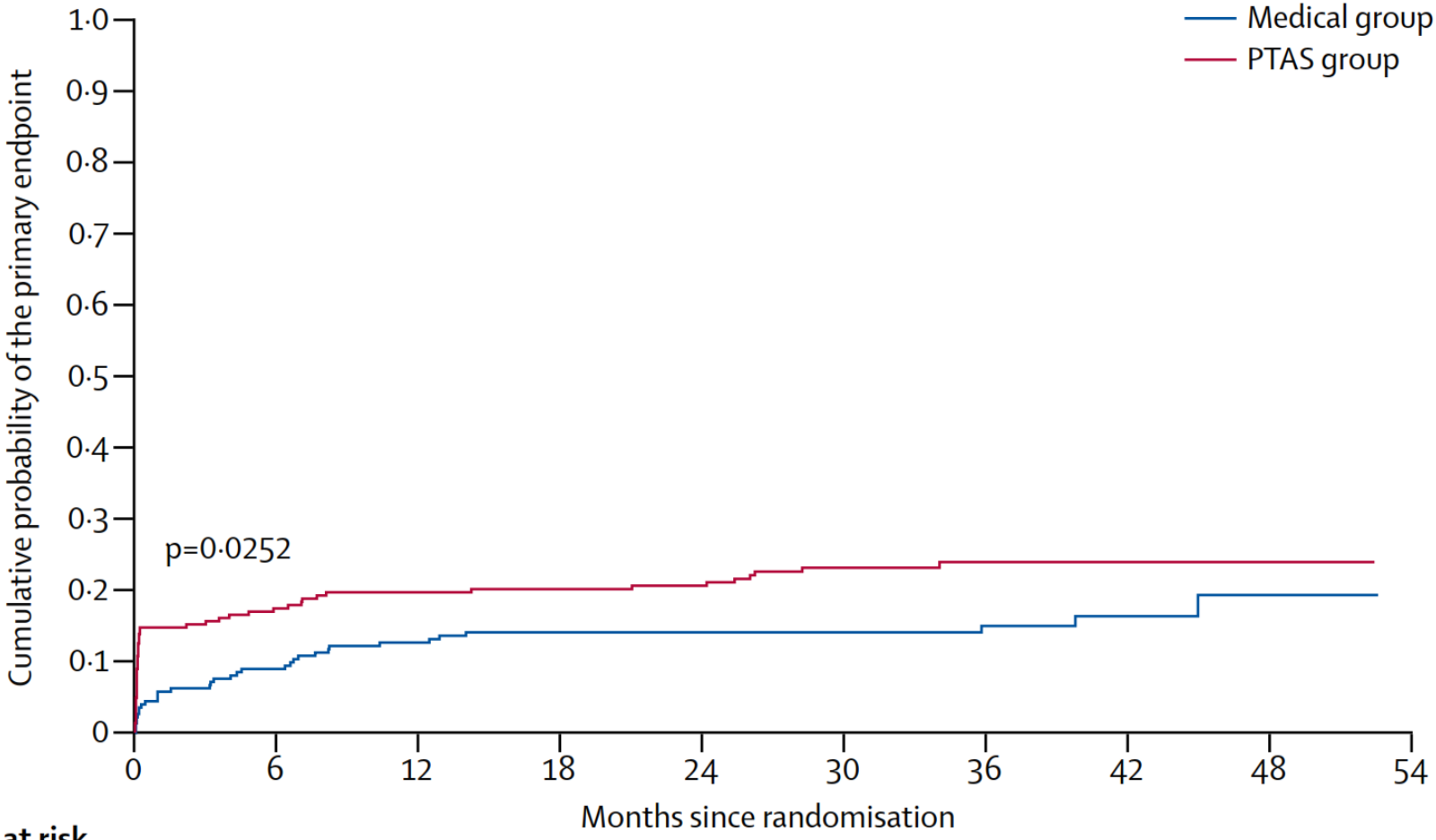
Primary Endpoint



Number at risk

Medical group	227	199	185	180	172	132	92	47	12
PTAS group	224	184	175	173	170	128	91	50	13

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Primary Endpoints Beyond 30 Days After Enrollment

- Beyond 30 days:
  - 21 (10%) of 210 patients in medical group and 19 (10%) of 191 patients in the PTAS group had a primary endpoint
- Beyond 1 year:
  - 6 (3%) of 185 patients in the medical group and 8 (5%) of 175 patients in the PTAS group had a primary endpoint

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Primary Endpoint Rates Over Time

Period	PTAS	Medical	Absolute RR	P-value
30 Days	14.7%	5.8%	8.9%	0.002
Year 1	19.7%	12.6%	7.1%	0.04
Year 2	20.6%	14.1%	6.5%	0.07
Year 3	23.9%	14.9%	9.0%	0.02

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Sensitivity Analysis

Scenario	Medical Group (n=227)		PTAS Group (n=224)		log-rank p-value
	Patients with Event n (%)	Probability by 2 Yrs (95% CI)	Patients with Event n (%)	Probability by 2 Yrs (95% CI)	
Assign primary endpoint to all lost and withdrawn	58 (25.6%)	20.1% (15.4% - 26.0%)	62 (27.7%)	21.9% (17.0% - 27.9%)	0.50
Assign primary endpoint to all Medical lost and withdrawn	58 (25.6%)	20.1% (15.4% - 26.0%)	52 (23.2%)	20.6% (15.9% - 26.5%)	0.79
Assign primary endpoint to all PTAS lost and withdrawn	34 (15.0%)	14.1% (10.1% - 19.4%)	62 (27.7%)	21.9% (17.0% - 27.9%)	0.0016
Censor all lost and withdrawn at last contact. (Primary analysis for paper)	34 (15.0%)	14.1% (10.1% - 19.4%)	52 (23.2%)	20.6% (15.9% - 26.5%)	0.025

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Sensitivity Analysis

Simulate the outcome of each lost or withdrawn patient beyond their last study contact, using the observed data from patients that remained in the study. Repeated 10,000 times

As most were after the first month (when most events occurred), most simulations had no events in the lost/ withdrawn). PTAS was never superior.

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Primary, Secondary Endpoints and MAEs

	Medical group	PTAS group
Primary endpoint (n [%])	34 (15%)	52 (22%)
Within 30 days of enrolment		
Ischaemic stroke in territory of qualifying artery	10	23 (1 fatal*)
Ischaemic stroke in other territory	2	0
Symptomatic brain haemorrhage†	0	10‡ (4 fatal*)
Non-stroke death	1§	0
After 30 days of enrolment		
Ischaemic stroke in territory of qualifying artery	21 (2 fatal*)	18 (1 fatal*)
Symptomatic brain haemorrhage after revascularisation procedure†	0	1‡
Any stroke	42 (19%)	59 (26%)
Ischaemic stroke in territory of qualifying artery	31	41
Ischaemic stroke in other territory	10	7¶
Symptomatic brain haemorrhage†	1	11

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Primary, Secondary Endpoints and MAEs

	Medical group	PTAS group
Disabling or fatal stroke**	18 (8%)	21 (9%)
Ischaemic stroke in territory of qualifying artery	12	10
Ischaemic stroke in other territory	5	3
Symptomatic brain haemorrhage†	1	8
Major non-stroke haemorrhage‖	9 (4%)	16 (7%)
Subdural	1	0
Gastrointestinal	5	6††
Genitourinary	2	2
Angiogram access site	0	4
Associated with surgery	0	2
Ocular	1	1‡‡
Lingual haematoma	0	1§§
Any major haemorrhage¶¶	10 (4%)	29 (13%)
Symptomatic brain haemorrhage†	1	12***
Asymptomatic brain haemorrhage‖‖	0	2
Major non-stroke haemorrhage	9	15

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Comparison of Primary and Secondary Endpoints and MAEs

(Probability by 2 Years)

Endpoint	Medical Group	PTAS Group	log-rank p-value
Primary Endpoint	14.1%	20.6%	0.0252
Any Stroke or Death	19.8%	24.1%	0.13
Any Death	4.5%	4.6%	0.90
Any Stroke	17.2%	23.3%	0.0468
Disabling or Fatal Stroke	7.8%	10.1%	0.51
Myocardial Infarction	3.4%	2.7%	0.34
Major Non-Stroke Hemorrhage	3.0%	7.9%	0.11
Any Major Hemorrhage	3.5%	13.1%	0.0009

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Subgroup Analysis

Factor	Medical Group		PTAS group		p-value[§]
	n	Probability by 2 Years[*]	n	Probability by 2 Years[*]	
Age (years)					0.75
< 60[‡]	119	11.9%	107	15.9%	
≥ 60	108	16.5%	117	24.8%	
Gender					0.40
Male	145	10.7%	127	18.2%	
Female	82	20.1%	97	23.7%	
Symptomatic Artery					0.63
ICA	49	23.2%	45	29.0%	
MCA	105	12.8%	92	14.2%	
Vertebral	22	9.5%	38	21.1%	
Basilar	51	9.9%	49	24.5%	
Qualifying Event					0.12
TIA	75	7.0%	82	20.7%	
Stroke	152	17.5%	142	20.5%	

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Subgroup Analysis

Factor	Medical Group		PTAS group		p-value[§]
	n	Probability by 2 Years[*]	n	Probability by 2 Years[*]	
Days from Qualifying Event to Enrollment					0.55
≤ 7[‡]	115	13.4%	115	22.7%	
> 7	112	14.7%	109	18.4%	
Old Infarct in the Territory of Symptomatic Artery †					0.35
No	147	9.1%	146	15.8%	
Yes	75	23.1%	69	27.6%	
On Antithrombotic at Time of Qualifying Event					0.68
No	87	11.6%	80	18.8%	
Yes	140	15.6%	144	21.6%	
Old Infarct in Territory and Stroke as Qualifying Event While On Antithrombotic Therapy					0.21
No	186	9.9%	185	17.3%	
Yes	36	34.7%	30	33.3%	

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Discussion

- Early benefit of aggressive medical therapy (AMM) persisted over a median duration of follow-up of 32.4 months
- No closure of efficacy gap beyond 30 days after enrollment → even if peri-procedural risk had been as low as anticipated (i.e., similar to 5.8% in medical group), PTAS would still not have been more effective than AMM

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Discussion

- Lower than projected primary endpoint rate in medical group (14.1% at 2 years vs. 24.9% at 2 years) likely attributed to dual antiplatelet Rx for 90 days plus sustained control of vascular risk factors over duration of follow-up
- Risk of stroke beyond 1 year in medically treated patients is very low even in this high risk population

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Discussion

No subgroup appeared to benefit from PTAS compared to AMM

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Conclusions

- The early benefit of AMM over PTAS with the Wingspan system persists over extended follow-up
- These results support the use of AMM rather than PTAS with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis

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Metro Areas with SAMMPRIS Sites

THANK YOU FOR YOUR CONTRIBUTION!!