31 GIORNATE CARDIOLOGICHE TORINESI

TURIN
October
24th-26th
2019

THE CHALLENGE

A patient with migraine, positive MR and PFO:

What to do?

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- Recurrent of **migraine without aurea**

- Multiple areas of altered signal hyperintense at T2 acquisitions, in the **white matter**

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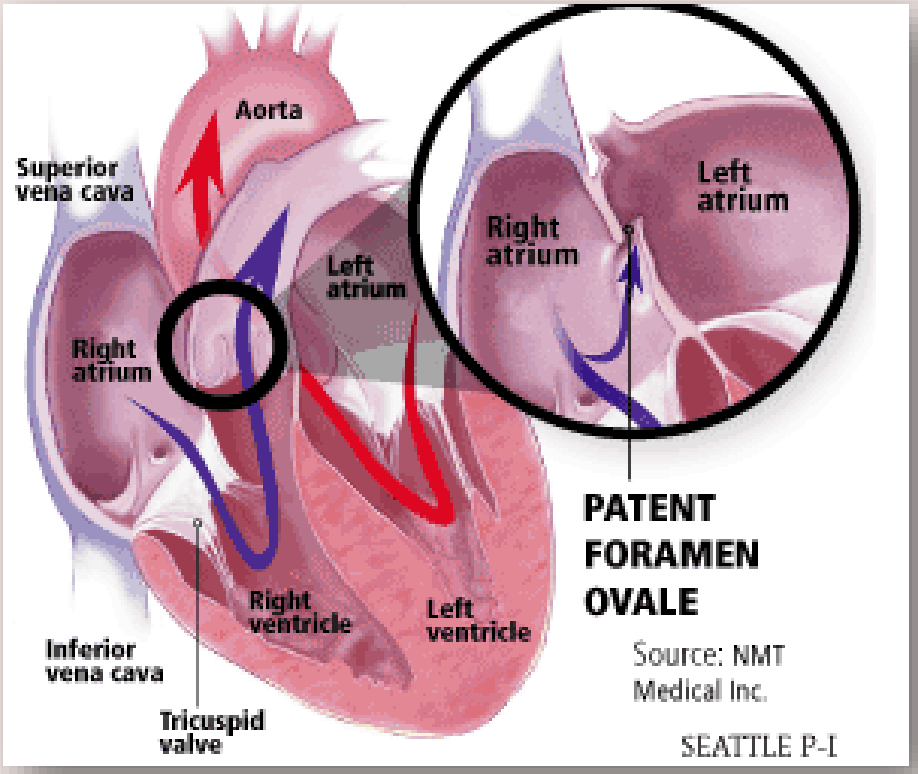


PFO prevalence ~27%

Paradoxical embolism

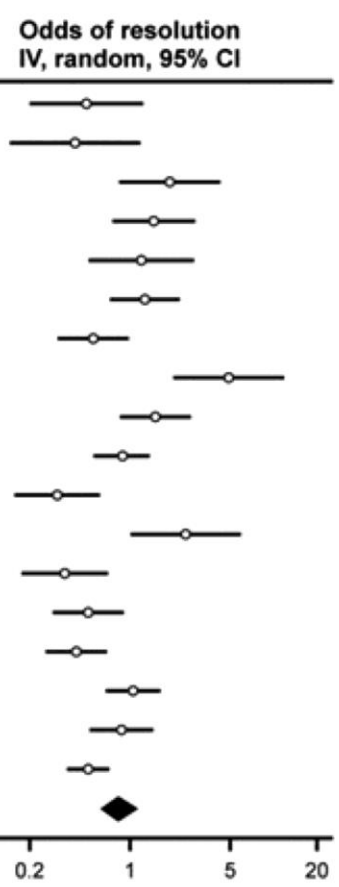
Right to left shunt of circulating factors

Migraine

PFO closure and Migraine *NO* ***RESOLUTION***

Author	Log (odds of resolution)	SE	Resolved (n)	Total (N)	Weight (%)	Odds of resolution IV, random, 95% CI	Year
Wilmshurst	-0.69	0.46	7	21	4.4	0.50 (0.20-1.24)	2000
Morandi	-0.88	0.53	5	17	3.9	0.42 (0.15-1.18)	2003
Post	0.64	0.41	17	26	4.9	1.89 (0.84-4.24)	2004
Azarbal	0.38	0.33	22	37	5.6	1.47 (0.76-2.83)	2005
Mortelmans	0.18	0.43	12	22	4.7	1.20 (0.52-2.78)	2005
Reisman	0.24	0.28	28	50	6.0	1.27 (0.73-2.22)	2005
Anzola	-0.58	0.29	18	50	5.9	0.56 (0.32-1.00)	2006
Donti	1.58	0.45	29	35	4.5	4.83 (2.01-11.64)	2006
Slavin	0.41	0.29	30	50	6.0	1.50 (0.85-2.64)	2007
Jesurum	-0.13	0.23	36	77	6.5	0.88 (0.56-1.37)	2008
Dubiel	-1.16	0.35	11	46	5.5	0.31 (0.16-0.62)	2008
Luermans	0.89	0.45	17	24	4.5	2.43 (1.01-5.86)	2008
Chessa	-1.04	0.35	11	42	5.4	0.35 (0.18-0.71)	2009
Vigna	-0.66	0.29	18	53	6.0	0.51 (0.29-0.91)	2009
Trabattoni	-0.85	0.25	23	77	6.4	0.43 (0.26-0.69)	2011
Rigatelli	0.05	0.22	41	80	6.6	1.05 (0.68-1.63)	2012
Nagpal	-0.13	0.26	28	60	6.3	0.87 (0.53-1.45)	2013
Wahl	-0.66	0.17	51	150	7.0	0.52 (0.37-0.72)	2013
Total (95% CI)			**404**	**917**	**100.0**	**0.85 (0.64-1.14)**	

Heterogeneity: Tau^2=0.29; Chi^2=71.69, df=17 (P<0.00001); I^2=76%



Kanwar SM, Clin Trials Regul Sci Cardiol 2016;1;15:7-13

PFO closure and Migraine *possible* ***IMPROVEMENT***

Author	Log (odds of improvement)	SE	Improved (n)	Total (N)	Weight (%)	Odds of improvement IV, random, 95% CI	Year
Wilmshurst	0.92	0.48	15	21	4.6	2.50 (0.97-6.44)	2000
Morandi	2.01	0.75	15	17	2.5	7.50 (1.72-32.80)	2003
Schwarzmann	0.99	0.32	35	48	7.0	2.69 (1.42-5.09)	2004
Reisman	0.85	0.31	35	50	7.3	2.33 (1.27-4.27)	2005
Azarbal	1.13	0.38	28	37	6.0	3.11 (1.47-6.59)	2005
Donti	2.37	0.60	32	35	3.4	10.67 (3.27-34.83)	2006
Anzola	1.99	0.44	44	50	5.2	7.33 (3.13-17.21)	2006
Slavin	1.39	0.35	40	50	6.5	4.00 (2.00-8.00)	2007
Kimmelstiel	1.61	0.55	20	24	3.9	5.00 (1.71-14.63)	2007
Jesurum	0.79	0.25	53	77	8.5	2.21 (1.36-3.58)	2008
Dubiel	1.90	0.44	40	46	5.2	6.67 (2.83-15.72)	2008
Luermans	3.14	1.02	23	24	1.5	23.00 (3.11-170.31)	2008
Vigna	1.88	0.41	46	53	5.7	6.57 (2.97-14.55)	2009
Chessa	1.30	0.38	33	42	6.1	3.67 (1.75-7.66)	2009
Trabattoni	0.39	0.23	46	77	8.8	1.48 (0.94-2.34)	2011
Rigatelli	1.24	0.27	62	80	8.1	3.44 (2.04-5.82)	2012
Wahl	1.30	0.20	118	150	9.5	3.69 (2.50-5.45)	2013
Total (95% CI)			**685**	**881**	**100.0**	**3.63 (2.80-4.71)**	

Odds of improvement IV, random, 95% CI

Heterogeneity: $Tau^2=0.14$; $Chi^2=35.14$, df=16 (P=0.004); $I^2=54\%$

0.02 0.1 1 10 50

Kanwar SM, Clin Trials Regul Sci Cardiol 2016;1;15:7-13

MIST Study 2008	*PRIMA Study 2016*	*PREMIUM Study 2017*
• PFO closure (Starflex) vs Sham 1:1	• PFO (Amplatzer) vs Medical 1:1	• PFO closure (Amplatzer) vs Sham
• N=147 migraine w/aura	• N=107 migraine w/aura	• N=230 migraine w/ and w/out aura
• EP1 cessation of symptoms	• EP1 reduction of migraine days	• EP1 -50% migraine episodes/month
N=3 vs 3 cessations	**2.9 vs 1.7 days p=0.17**	**38% vs 32% p=0.30**
N=10 procedure related sAE	**N=5 procedure related sAE**	**N=1 transient Afib**
Dawson A. et al Circulation. 2008;117:1397–404.	Mattle HP et. al. Eur Heart J. 2016;37:2029–36.	Tobis JM et. al. JACC. 2017;5:2766–74

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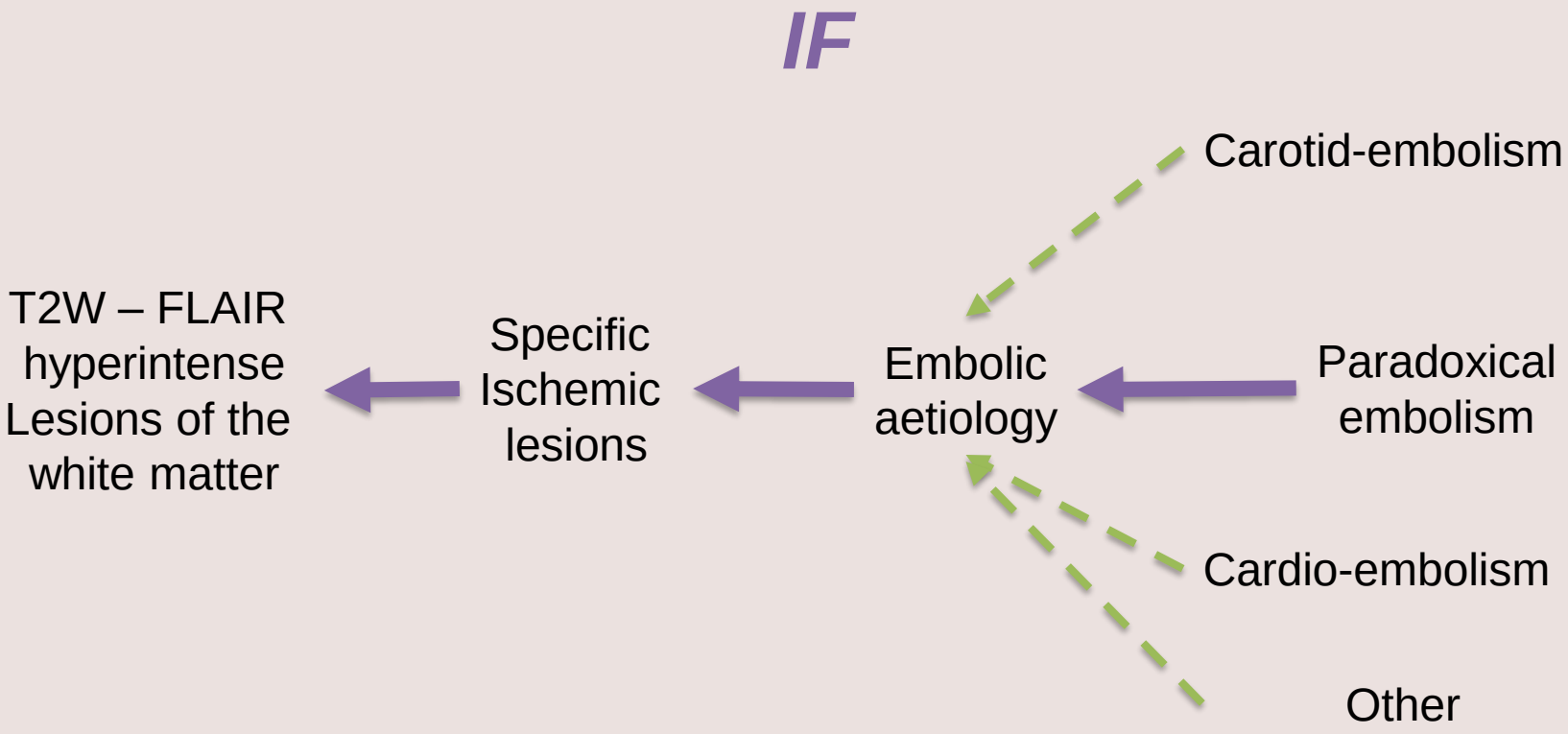
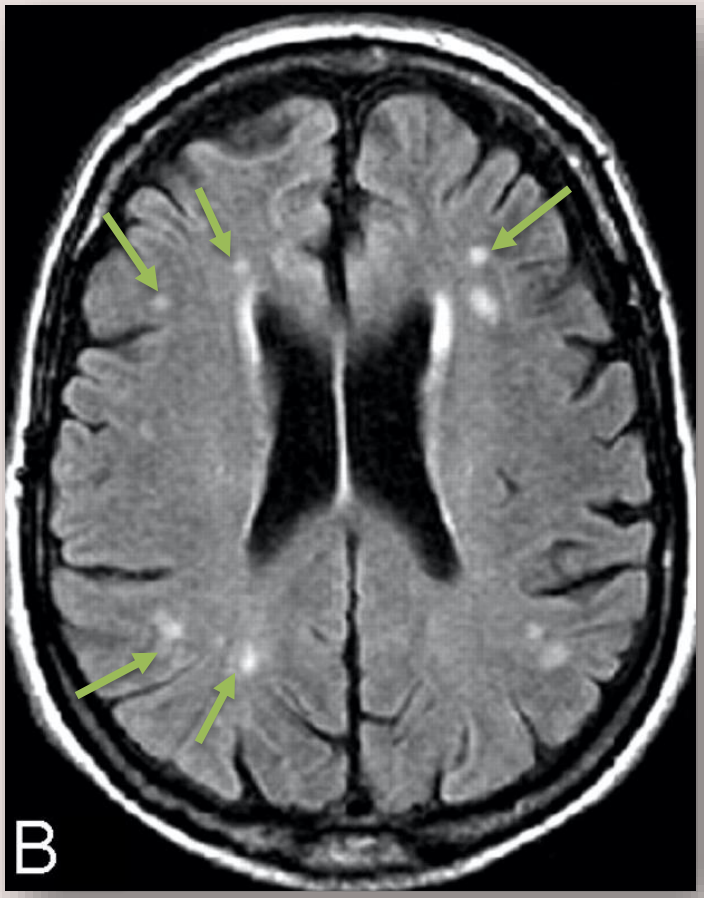
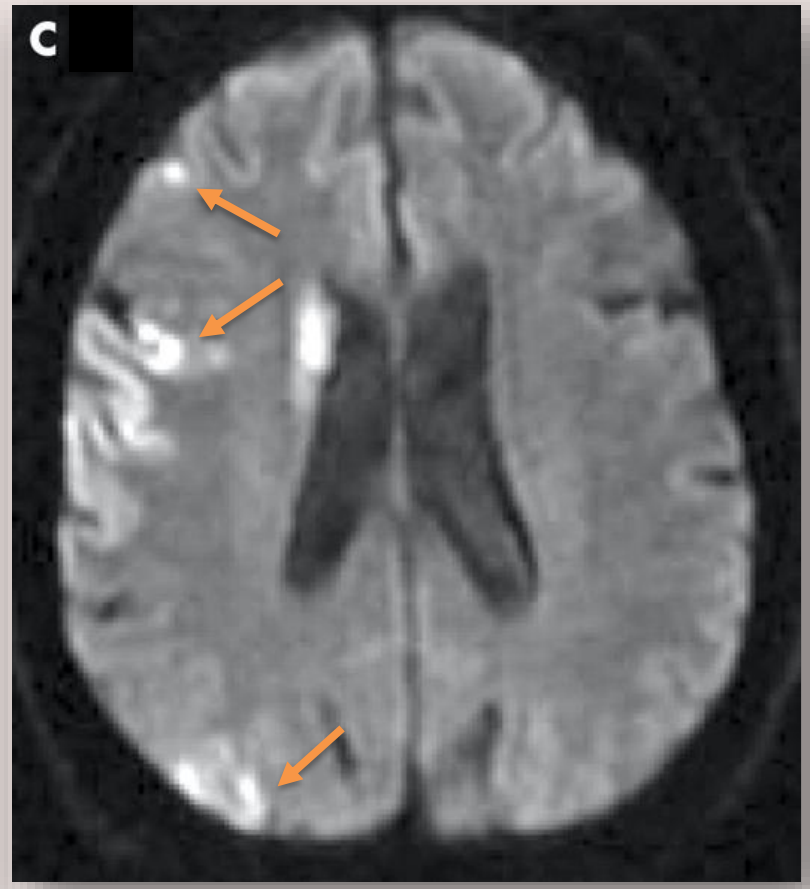
PFO closure would make sense



Black *or* ***White*** *MATTER!*





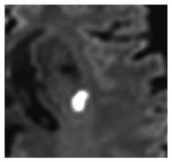
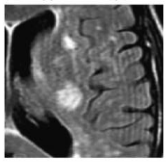
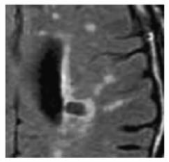
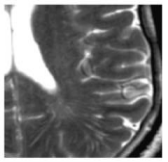
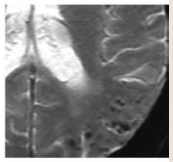
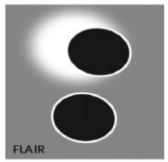
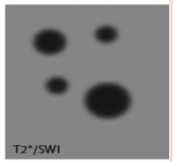
White matter lesion = Leukoaraiosis = gliosi

Table 2 Population-based studies of white matter abnormalities

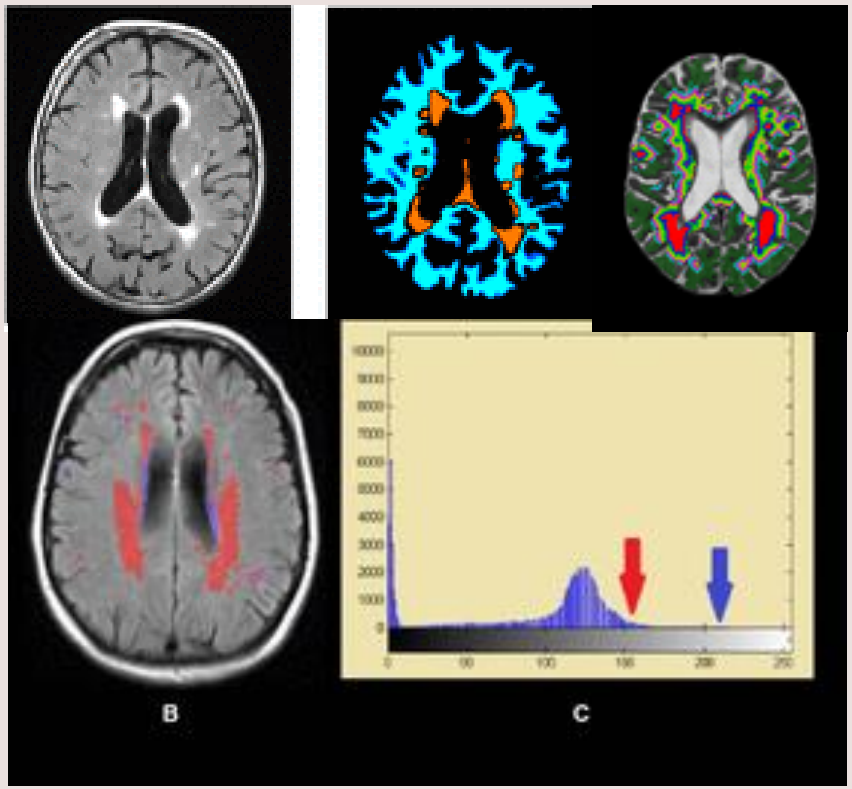
Study name (year)	Imaging	Number (%) of WMAs			Proportion of migraine group and controls (mean age, years); OR and *p* values; possible associations with migraine-related variables
		MA	MO	Control	
CAMERA-1[10] (2004)	1.5-T MRI	34 (21)	31 (23)	22 (16)	MA, n = 161; MO, n = 134; controls, n = 140 (73% women; mean age 48.3 years); the number of deep WMAs is presented (%); migraineurs compared to controls: MA (OR 2.0; 95% CI 1.0–4.3) and MO (OR 2.1; 95% CI 1.0–4.7) compared to controls (OR 1.0)[a]; no association between WMAs and migraine subtype; an association between WMAs and attack frequency: ≤1 attack per month (OR 1.6; 95% CI 0.8–3.5) vs ≥1 attack per month (OR 2.6; 95% CI 1.2–5.7) (p = 0.008).
CAMERA-1[11] (2006)	1.5-T MRI	8 (5)	5 (4)	1 (1)	MA, n = 161; MO, n = 134; controls, n = 140 (73% women; mean age 48.3 years); the number of IHLs is presented (%); an association between migraine and IHLs (p = 0.04); no association between IHLs and migraine subtype, attack frequency, age at onset, or antimigraine therapy.
EVA-MRI[13] (2011)	1.0-T MRI	10 (59)	38 (38)	190 (31)	MA, n = 17; MO, n = 99; nonmigraine headaches, n = 47; controls, n = 617 (59% women, mean age 69 years); the number of deep WMAs is presented (%); migraineurs and nonmigraine headache compared to controls: MA (OR 12.4; 95% CI 1.6–99.4; p = 0.005), MO (OR 1.6; 95% CI 0.9–2.7; p = 0.11), and nonmigraine headache (OR 2.1; 95% CI 1.0–4.4; p = 0.03) compared to controls (OR 1.0); an association between WMAs and severe history of headaches (p = 0.002); an association between WMAs and MA (p = 0.005); attack frequency is not reported.
CAMERA-2[14] (2012)	1.5-T MRI	84 (74)	68 (76)	54 (65)[b]	MA, n = 114; MO, n = 89; control, n = 83 (71% women, mean age 57 years).
		11 (10)	15 (17)	2 (2)[c]	The number of deep WMAs[b] and IHLs[c] are presented; migraineurs compared to controls: WMA progression (OR 2.1; 95% CI 1.0–4.1; p = 0.04)[a,b]; migraineurs compared to controls: IHL progression (OR 7.7; 95% CI 1.0–59.5; p = 0.05)[a,c]; no association between WMA progression and attack frequency, attack duration, type of attack, and antimigraine therapy; no association between IHL progression and migraine subtype and attack frequency.

Bashir A et. al. Neurology 2013;81;1260-1268

What are White Matter Hyperintensities Made of?

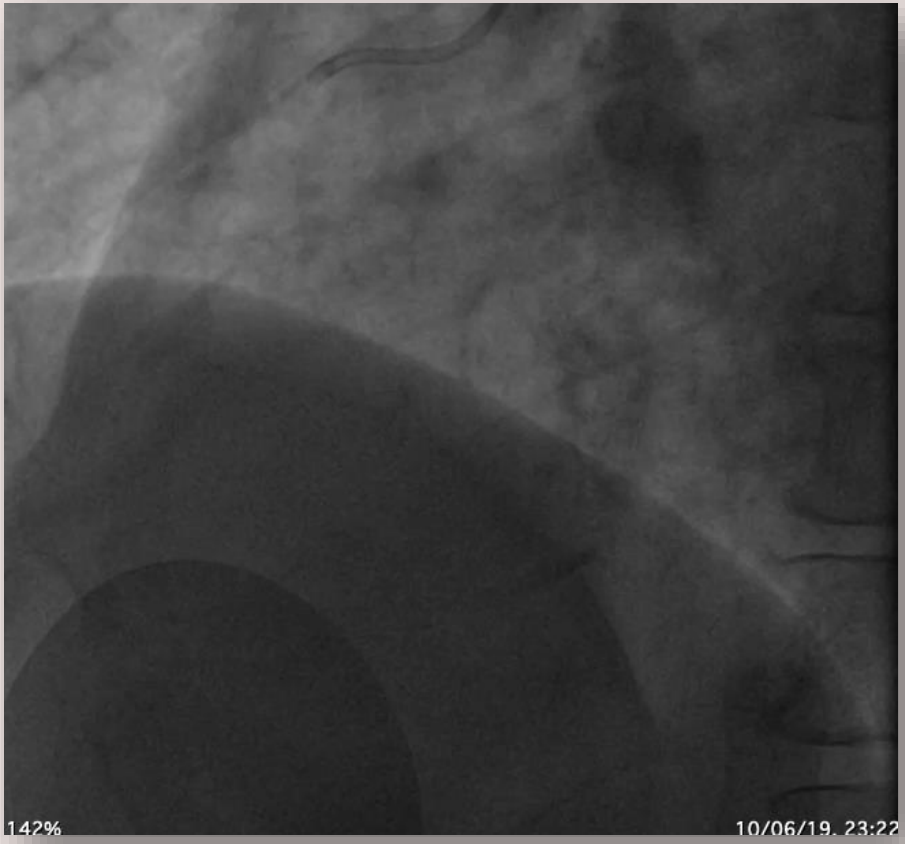
	Recent small subcortical infarct	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleed
Example image					
Schematic	 DWI	 FLAIR	 FLAIR	 T2 T1/FLAIR	 T2*/SWI
Usual diameter	≤20 mm	Variable	3–15 mm	≤2 mm	≤10 mm
Comment	Best identified on DWI	Located in white matter	Usually have hyperintense rim	Most linear without hyperintense rim	Detected on GRE seq., round or ovoid, blooming
DWI	↑	↔	↔/(↓)	↔	↔
FLAIR	↑	↑	↓	↓	↔
T2	↑	↑	↑	↑	↔
T1	↓	↔/(↓)	↓	↓	↔
T2*-weighted GRE	↔	↑	↔ (↓ if haemorrhage)	↔	↓↓

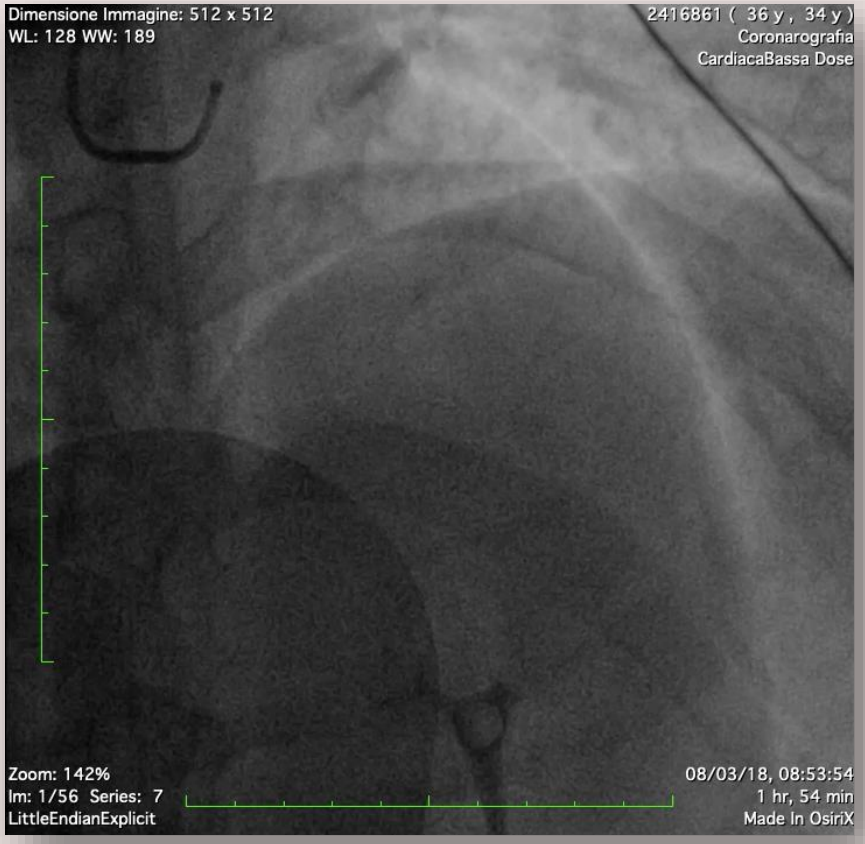
↑ Increased signal ↓ Decreased signal ↔ Iso-intense signal

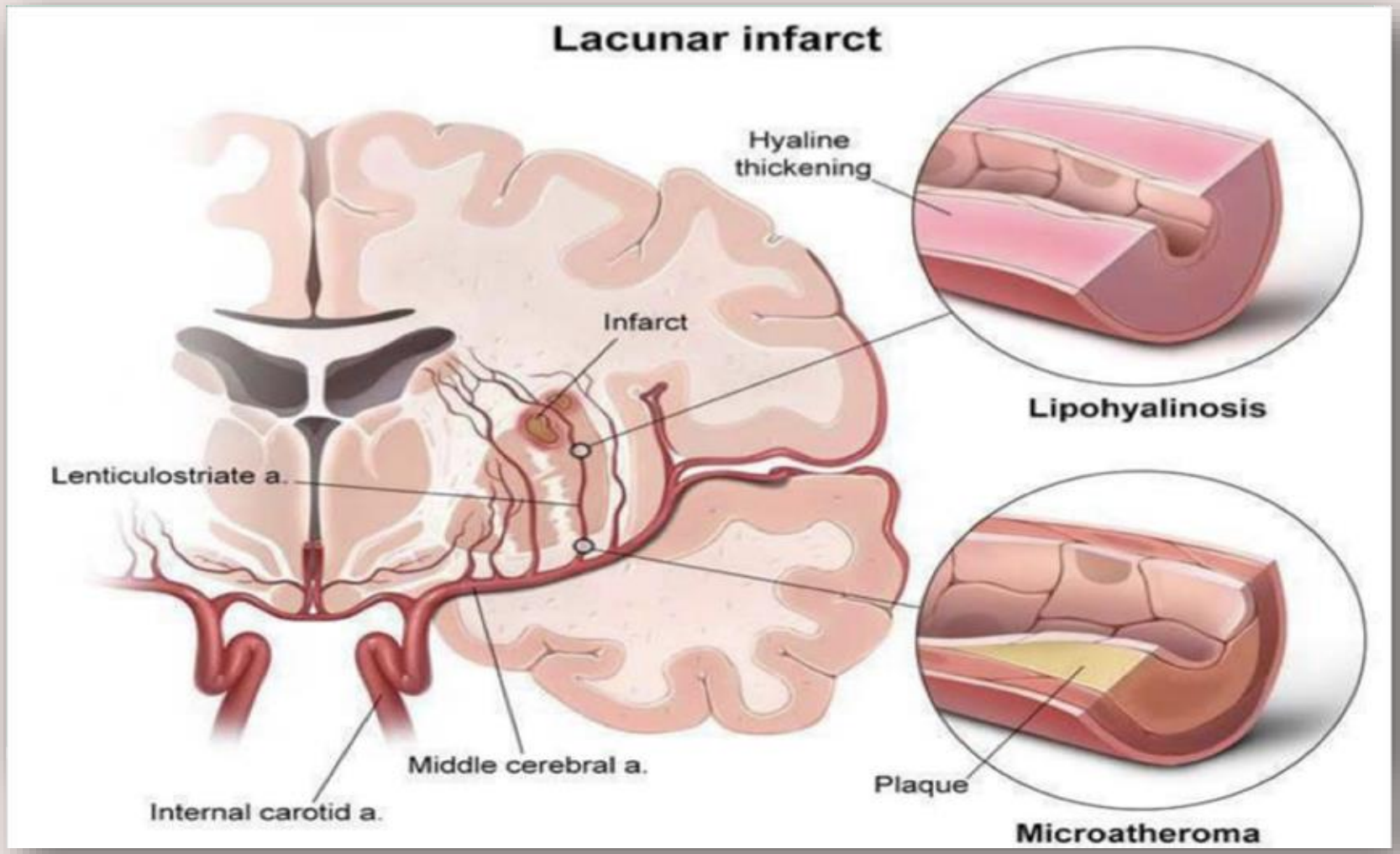


Joanna M. Wardlaw. Journal of the American Heart Association. What are White Matter Hyperintensities Made of?, Volume: 4, Issue: 6, DOI: (10.1161/JAHA.114.001140)

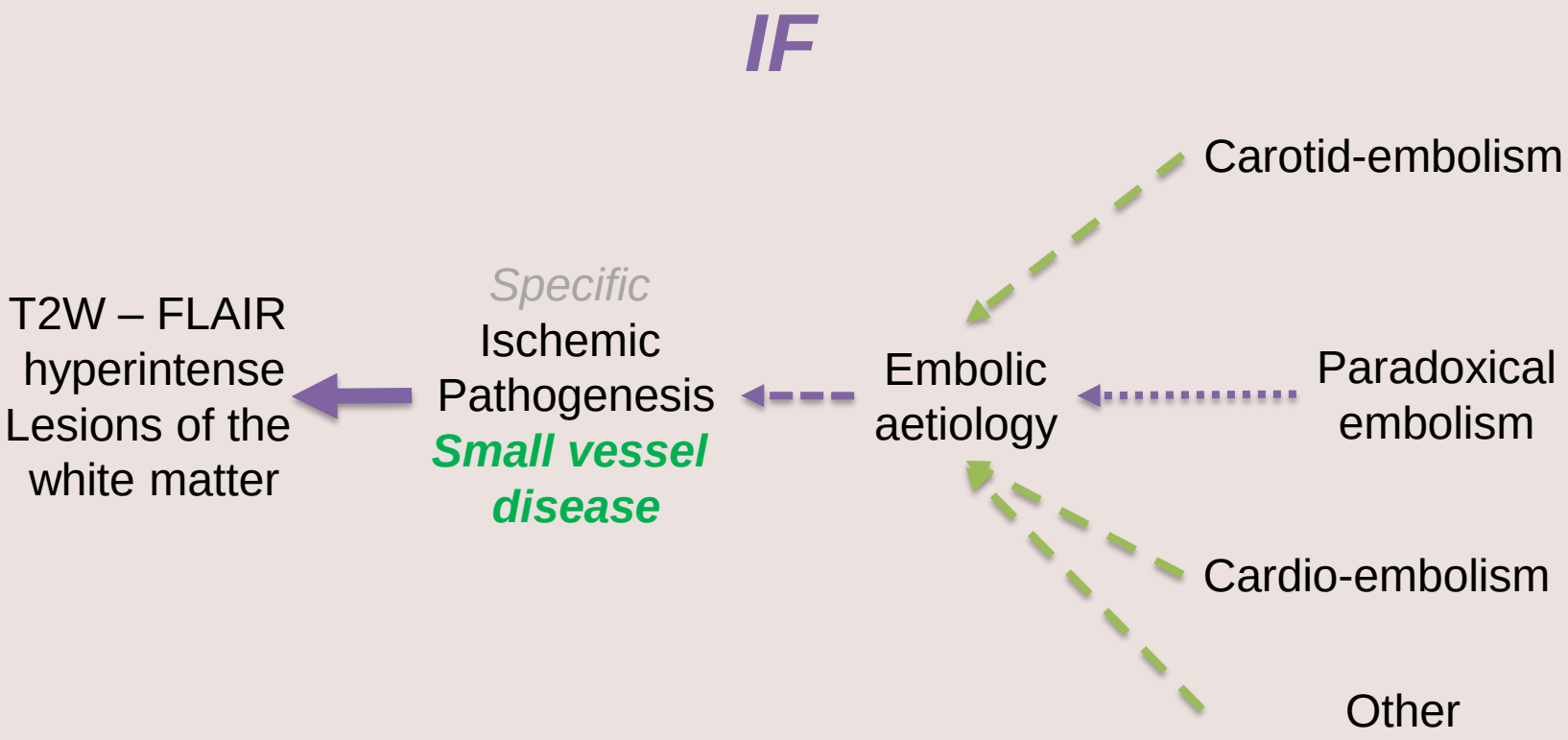
Lets make a poll!






Lacunar infarct
Hyaline thickening
Infarct
Lipohyalinosis
Lenticulostriate a.
Middle cerebral a.
Internal carotid a.
Plaque
Microatheroma

PFO closure would make sense



- There are **no solid randomized data** which support PFO closure in patients with **migraine** w/ or w/out aurea
- T2 hyperintensities, in the white matter are likely **small vessel disease** in a patient w/ hypertension
- There are **no high anatomical risk features** of the *fossa ovalis*

THE CHALLENGE

A patient with migraine, positive MR and PFO:

What to do?

*Let's wait, **control atherosclerosis risk factors** and follow the patient*