

SUPPLEMENTAL MATERIAL

Supplement I

TEE large # of bubbles (vs. not large #)									Cochran-Armitage test of trend	Generalized mixed model test of linear trend
Database	% with factor (overall and by point score group)									
	ALL	0-3	4	5	6	7	8	9-10		
ALL	64%	52%	58%	60%	70%	68%	66%	68%	0.0021	0.6415
CODICIA	74%	75%	91%	77%	82%	68%	61%	71%	0.0412	** Generalized mixed model test of linear trend over 7 ordered categories (site included as random effect) p-value =0.7239 if raw score is used OR=1.013 (95% CI 0.941, 1.091)
French PFO/ASA	82%		50%	82%	86%	86%	80%	76%	0.5115	
APRIS	23%	0%	20%	40%					0.188	
Bern	66%	80%	65%	61%	73%	66%	64%	50%	0.2956	
PICSS	40%	33%	33%	58%	45%	33%	38%	43%	0.8812	
Lausanne	47%	50%	50%	0%	100%	0%	50%	67%	0.5971	
Toronto										
Tufts	52%	43%	40%	47%	60%	60%	80%	40%	0.1218	
German	56%	41%	59%	54%	61%	57%	53%	74%	0.1646	

TEE characteristic of large # of bubbles (vs. not large #) across RoPE Score strata. Results are presented in aggregate and also by component database.

TEE shunt at rest (vs. no shunt)									Cochran-Armitage test of trend	Generalized mixed model test of linear trend
Database	% with factor (overall and by point score group)									
	ALL	0-3	4	5	6	7	8	9-10		
ALL	70%	77%	68%	74%	70%	70%	68%	62%	0.0987	p=.7678
CODICIA										** Generalized mixed model test of linear trend over 7 ordered categories (site included as random effect) p-value =0.8094 if raw score is used OR=1.012 (95% CI 0.916, 1.120)
French PFO/ASA	60%		50%	67%	55%	61%	64%	57%	0.9022	
APRIS	90%	100%	100%	80%					0.3448	
Bern	62%	56%	63%	54%	60%	71%	70%	50%	0.4574	
PICSS	74%	78%	67%	58%	84%	80%	77%	71%	0.5353	
Lausanne	47%	100%	100%	0%	0%	50%	75%	0%	0.1912	
Toronto										
Tufts	79%	78%	64%	82%	81%	94%	69%	80%	0.6142	
German	81%	81%	71%	92%	81%	79%	78%	100%	0.4766	

TEE characteristic of shunt at rest (vs. no shunt) across RoPE Score strata. Results are presented in aggregate and also by component database.

Hypermobile septum (vs. no hypermobile septum)									Cochran-Armitage test of trend	Generalized mixed model test of linear trend
Database	% with factor (overall and by point score group)									
	ALL	0-3	4	5	6	7	8	9-10		
ALL	25%	27%	27%	29%	26%	26%	21%	20%	0.0325	p=.0802
CODICIA	43%	56%	41%	37%	45%	53%	33%	35%	0.3955	** Generalized mixed model test of linear trend over 7 ordered categories (site included as random effect) p-value= 0.0420 if raw score is used OR=0.93 (95% CI 0.860, 0.997)
French PFO/ASA	19%		0%	15%	23%	20%	20%	16%	0.8678	
APRIS	13%	0%	17%	17%					0.5425	
Bern	21%	20%	29%	11%	23%	31%	14%	20%	0.9858	
PICSS	15%	11%	6%	42%	20%	7%	9%	14%	0.8154	
Lausanne	47%	0%	100%	60%	33%	100%	40%	14%	0.3597	
Toronto	24%	50%	38%	36%	29%	17%	19%	17%	0.0324	
Tufts	27%	33%	17%	33%	27%	7%	33%	40%	0.7912	
German	22%	19%	29%	31%	19%	21%	14%	21%	0.2287	

TEE characteristic of hypermobile septum (vs. no hypermobile septum) across RoPE Score strata. Results are presented in aggregate and also by component database.

TEE combination #1 – hypermobile septum AND large # of bubbles									Cochran-Armitage test of trend	Generalized mixed model test of linear trend
Database	% with factor (overall and by point score group)									
	ALL	0-3	4	5	6	7	8	9-10		
ALL	15%	16%	14%	13%	19%	17%	13%	12%	0.5207	** Generalized mixed model test of linear trend over 7 ordered categories (site included as random effect) p-value= 0.4229 if raw score is used OR=0.96 (95% CI 0.87, 1.06)
CODICIA	36%	50%	41%	27%	42%	39%	24%	35%	0.2642	
French PFO/ASA	16%	.	0%	0%	23%	19%	17%	9%	0.6301	
APRIS	13%	0%	17%	17%	0.5425	
Bern	17%	20%	24%	4%	20%	28%	14%	0%	0.6678	
PICSS	6%	0%	0%	25%	5%	0%	8%	14%	0.477	
Lausanne	4%	0%	50%	0%	0%	0%	0%	0%	0.2091	
Toronto	0%	0%	0%	0%	0%	0%	0%	0%		
Tufts	13%	24%	0%	11%	15%	0%	20%	20%	0.6738	
German	9%	0%	7%	15%	10%	8%	6%	16%	0.3424	

TEE composite of hypermobile septum AND large # of bubbles across RoPE Score strata. Results are presented in aggregate and also by component database.

TEE – VERY large # of bubbles (vs. not very large number or small #)									Cochran-Armitage test of trend	Generalized mixed model test of linear trend
Database	% with factor (overall and by point score group)									
	ALL	0-3	4	5	6	7	8	9-10		
ALL	44%	35%	38%	41%	51%	48%	44%	48%	0.0237	p=.6621
CODICIA	74%	75%	91%	77%	82%	68%	61%	71%	0.0412	** Generalized mixed model test of linear trend over 7 ordered categories (site included as random effect) p-value= 0.9067 if raw score is used OR=1.01 (95% CI 0.93, 1.08)
French PFO/ASA	52%	.	25%	45%	59%	57%	53%	42%	0.4184	
APRIS	15%	0%	20%	20%	0.489	
Bern	48%	60%	47%	43%	43%	45%	55%	50%	0.9167	
PICSS	29%	33%	11%	42%	35%	27%	23%	43%	0.5412	
Lausanne	20%	0%	50%	0%	100%	0%	25%	0%	0.7191	
Toronto		
Tufts	16%	19%	0%	6%	10%	20%	30%	40%	0.1296	
German	32%	17%	29%	31%	41%	35%	17%	53%	0.1858	

TEE characteristic of VERY large # of bubbles (vs. not very large number or small #) across RoPE Score strata. Results are presented in aggregate and also by component database.

TEE -Composite #3 small (not large) # bubbles AND hypermobile septum									Cochran-Armitage test of trend	Generalized mixed model test of linear trend
	% with factor (overall and by point score group)									
Database	ALL	0-3	4	5	6	7	8	9-10		
ALL	6%	9%	9%	10%	5%	6%	3%	3%	0.0009	p=.0753
CODICIA	7%	6%	0%	10%	3%	13%	9%	0%	0.6431	** Generalized mixed model test of linear trend over 7 ordered categories (site included as random effect) p-value= 0.0527 if raw score is used OR=0.88 (95% CI 0.77, 1.00)
French PFO/ASA	1%	.	0%	8%	0%	0%	1%	0%	0.2837	
APRIS	0%	0%	0%	0%		
Bern	5%	0%	6%	7%	3%	3%	0%	20%	0.4691	
PICSS	9%	11%	6%	17%	15%	7%	0%	0%	0.3228	
Lausanne	13%	0%	50%	33%	0%	100%	0%	0%	0.2566	
Toronto	0%	0%	0%	0%	0%	0%	0%	0%		
Tufts	9%	10%	17%	15%	0%	0%	0%	20%	0.317	
German	11%	16%	14%	11%	8%	13%	6%	5%	0.1232	

TEE composite of small (not large) # bubbles AND hypermobile septum across RoPE Score strata. Results are presented in aggregate and also by component database.

TEE -Composite #4 small /medium # bubbles (not very large) AND hypermobile septum									Cochran-Armitage test of trend	Generalized mixed model test of linear trend
Database	% with factor (overall and by point score group)									
	ALL	0-3	4	5	6	7	8	9-10		
ALL	9%	10%	12%	12%	8%	9%	5%	7%	0.0128	p=.3004
CODICIA	7%	6%	0%	10%	3%	13%	9%	0%	0.6431	** Generalized mixed model test of linear trend over 7 ordered categories (site included as random effect) p-value= 0.2556 if raw score is used OR=0.93 (95% CI 0.83, 1.04)
French PFO/ASA	4%	.	0%	8%	5%	3%	3%	8%	0.6772	
APRIS	7%	0%	0%	17%	0.2685	
Bern	9%	0%	18%	7%	13%	10%	0%	20%	0.8213	
PICSS	10%	11%	6%	25%	15%	7%	0%	0%	0.2693	
Lausanne	13%	0%	50%	33%	0%	100%	0%	0%	0.2566	
Toronto	0%	0%	0%	0%	0%	0%	0%	0%		
Tufts	15%	14%	17%	21%	15%	0%	20%	20%	0.8422	
German	14%	17%	20%	11%	10%	19%	8%	10%	0.3332	

TEE composite of small /medium # bubbles (not very large) AND hypermobile septum across RoPE Score strata. Results are presented in aggregate and also by component database.

Supplement II

	All PFO patients with at least some TEE data (n=1294)	RoPE Score > 6 (n=637)	RoPE Score ≤ 6 (n=657)	p-value **
TEE findings*				
Large # bubbles (vs. not large)	64.4% (695/1079)	67.4% (347/515)	61.7% (348/564)	0.5286
Shunt at rest (vs. no shunt)	69.6% (484/695)	67.6% (238/352)	71.7% (246/343)	0.4474
Hypermobile septum (vs. not)	25.3% (320/1265)	23.0% (144/626)	27.5% (176/639)	0.1063
Sensitivity analyses				
Combo #1: Large & Hyper (vs not)	15.1% (182/1206)	14.5% (86/595)	15.7% (96/611)	0.4661
Combo #2:	(n=1062)	(n=509)	(n=553)	0.2021
Not large AND Not hypermobile	28.7% (305)	27.7% (141)	29.7% (164)	
Large OR hypermobile	54.1% (575)	55.4% (282)	53.0% (293)	
VERY Large # bubbles (vs. rest)	44.4% (479/1079)	46.4% (239/515)	42.6% (240/564)	0.5793
Comb #3: Not large & hypermobile	6.0% (72/1209)	4.2% (25/597)	7.7% (47/612)	0.2373
Comb #4: Not Very large & hypermobile	8.6% (104/1204)	6.9% (41/597)	10.4% (63/607)	0.3210

Large represents size of shunt defined as > 10 bubbles. Very large represents an uncountable number of bubbles (too large). Hypermobile represents to ≥ 10 mm of excursion of the interatrial septum. *Repeated from Table 3, ** p-values from generalized mixed models (TEE Variables ONLY) adjusting for random site effect, with logit link for all binary TEE outcomes and cumulative logit for TEE combo #2 (ordered) 3-level variable.