Safety and Efficacy of High Power Ablation for Atrial Fibrillation: A Systematic Review and Meta-Analysis

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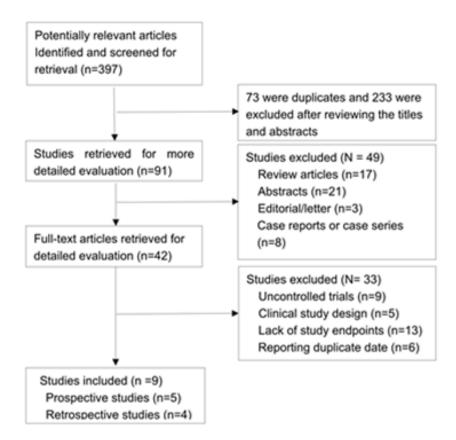
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Abstract

Background: Pulmonary veins reconnection due to insufficient lesions is an important cause of recurrence of atrial fibrillation (AF). High power ablation (HPA) with shorter duration or guided by Ablation index (AI) seen to increase efficacy and safety. This analysis aimed to evaluate the clinical benefits of HPA in patients with AF. Methods: The Medline, PubMed, Embase, and the Cochrane Library databases were searched for studies comparing HPA and conventional power ablation (CPA). Results: A total of nine trials with 2297 patients were included in the analysis. Pooled analyses demonstrated that HPA showed a benefit of first-pass pulmonary vein isolation (PVI) and acute PVs reconnection [risk ratio (RR): 1.27; 95% confidence interval (CI): 1.18–1.37, P < 0.001] and (RR: 0.52; 95% CI: 0.30–0.88, P = 0.01). HPA could reduce recurrence of atrial arrhythmias (RR: 0.71; 95% CI: 0.53–0.97, P = 0.03). Additionally, HPA was more beneficial in terms of procedural time [Weighted Mean Difference, (WMD): -41.19; 95% CI, -56.01 to -26.36, P < 0.001], ablation time (WMD: -19.45; 95% CI: -23.11 to -15.78, P < 0.001), and fluoroscopy time (WMD: -3.10; 95% CI: -5.52 to -0.68, P < 0.001) compared with the CPA approach. Moreover, HPA was associated with low complications (RR: 0.60; 95% CI: 0.36–0.99, P = 0.05). Conclusion: The HPA was a safe and effective approach for treating AF with clear advantages of procedural features. It was also associated with higher first-pass PVI, fewer acute PVs reconnection, recurrence of atrial arrhythmias and complications compared with the CPA approach.

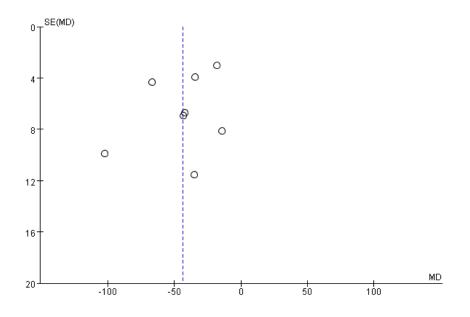
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		HPA	1	CPA	i		Risk Ratio		Risk Ratio	
Study or Subgroup		Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Berte B et al 2019		141	160	164	188	50.6%	1.01 [0.93, 1.09]		-	
Castrejón-Castrejón S et al 2	2020	54	94	39	89	13.5%	1.31 [0.98, 1.76]			
Dhillon G et al 2019		82	100	34	100	11.4%	2.41 [1.81, 3.22]		100 million (1997)	
Pambrun T et al 2019		92	100	73	100	24.5%	1.26 [1.10, 1.44]			
Total (95% CI)			454		477	100.0%	1.27 [1.18, 1.37]		•	
Total events		369		310						
Heterogeneity: Chi ² = 51.75, 0			001); l ² =	= 94%				0.5	0.7 1 1.5	2
Test for overall effect: Z = 6.1	1 (P < 0.	00001)						0.5	HPA CPA	-
		HP	A	CP	1		Risk Ratio		Risk Ratio	
Study or Subgroup		Events	Total	Events	Total	Weight	M-H, Random, 95%	CI	M-H, Random, 95% Cl	
Berte B et al 2019		10	75	18	82	29.5%	0.61 [0.30, 1.2	3]		
Castrejón-Castrejón S et al 2	2020	5	94	7	89	16.7%	0.68 [0.22, 2.0	5]		
Dhillon G et al 2019		22	100	36	100	42.7%	0.61 [0.39, 0.9	6]		
Pambrun T et al 2019		2	100	17	100	11.1%	0.12 (0.03, 0.5	0] +		
Total (95% CI)			369		371	100.0%	0.52 [0.30, 0.8	8]	•	
Total events		39		78						
Heterogeneity: Tau ² = 0.12; 0 Test for overall effect: Z = 2.4			3 (P = 0).16); I ² =	41%			0.05	0.2 1 HPA CPA	5
	HPA		CF	A			Risk Ratio		Risk Ratio	
Study or Subgroup E	Events	Total	Events	s Total	Weig	ht M-H	Random, 95% CI		M-H, Random, 95% CI	
Baher A et al 2018	241	574	41	6 113	22.7	%	1.03 [0.81, 1.31]		-	
Berte B et al 2019	14	80	11	6 94	11.9	196	1.03 [0.54, 1.97]			
Bunch TJ et al 2019	67	402	81	8 402	21.4	96	0.76 [0.57, 1.01]			
Dhillon G et al 2019	3	50	1	7 50	5.4	%	0.18 [0.06, 0.56]			
Kottmaier M et al 2020	14	97	3	2 100	13.8	%	0.45 [0.26, 0.79]	_		
Pambrun T et al 2019	5	50		6 50	5.7		0.83 [0.27, 2.55]	_		
Vassallo F et al 2019	7	41	1	1 35	8.8		0.54 [0.24, 1.25]	_		
Yazaki K et al 2020	9	32	1	1 32	10.4	%	0.82 [0.39, 1.70]			
Total (95% CI)		1326		876	100.0	0%	0.71 [0.53, 0.97]		•	
Total events	360		22	7						
Heterogeneity: Tau ² = 0.09;	Chi ² =	16.59	df = 7.0	P = 0.02	: P = 5	8%	-	0.2	0.5 1 2	<u> </u>

Study or Subgroup	HF Mean		Total	C Mean	PA SD 1	otal	Weight	Mean Difference IV, Random, 95% (n Difference andom, 95% Cl
Study of Subgroup Baher A et al 2018	<u>mean</u> 149	<u>65</u>	574	251	101	113		-102.00 [-121.37, -82.63			and the start of
Berte B et al 2019	82	18	80	100	22	94	12.0%	-18.00 [-23.94, -12.0			-
		63.6	402		59.2	402	11.8%	-66.50 [-74.99, -58.0		-	
Castrejón-Castrejón S et al 2020	106 156 3	33 33.7	48	120 199	45 35.9	47	10.7%	-14.00 [-29.90, 1.9			
Dhillon G et al 2019 Kottmaier M et al 2020		23.9	50 97		35.9 27.9	50 100	11.9%	-43.00 [-56.65, -29.3 -21.65 [-28.90, -14.4			•
Pambrun T et al 2019		18.2	50		21.2	50	11.8%	-34.30 [-42.04, -26.5]		+	.
Vassallo F et al 2019	106	23	41		33.6	35	11.1%	-42.00 [-55.17, -28.8		-	
Yazaki K et al 2020	115	32	32	150	57	32	9.5%	-35.00 [-57.65, -12.3	5]		-
Total (95% CI)			1374				100.0%	-41.19 [-56.01, -26.36	5]		·
Heterogeneity: Tau ² = 468.08; Chi ² = Test for overall effect: Z = 5.45 (P < 0.		df = 8	(P < 0.0	00001);1	*= 95%	•			-1		0 50 100
		IPA			CPA			Mean Difference			HPA CPA In Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight		3		andom, 95% Cl
Darier A et al 2016	37.9	13.9	342	55	19.2	87	12.9%				
Berte B et al 2019 Castrejón-Castrejón S et al 2020	23 17	5	80 48	36 34	11	94 47	14.7% 13.8%			-	
Dhillon G et al 2019		10.59	50	43.2	12.59	50					
Kottmaier M et al 2020	12.4	3.4	97	35.6	12.1	100	14.7%			-	
Pambrun T et al 2019	13	2.9	50	30.3	8.8	50	14.6%			-	
Vassallo F et al 2019 Yazaki K et al 2020	31.8 26	11.3 10	41 32	76 48	33.3 16	35 32	6.1% 10.5%	-44.20 [-55.76, -32.64 -22.00 [-28.54, -15.46		_	
										•	
Total (95% CI)	55 20 df	= 7 /P	740	0011-18-	070	495	100.0%	-19.45 [-23.11, -15.78	· +	•	
Heterogeneity: Tau ² = 22.19; Chi ² = 5 Test for overall effect: Z = 10.40 (P <			× 0.00	001), 1-=	: 87 %				-50	-25	0 25 50 HPA CPA
		HPA			PA			Mean Difference			n Difference
Study or Subgroup	Mean	SD	Total	Mean		Total	Weight	IV, Random, 95% C	I		ndom, 95% Cl
Berte B et al 2019	6	4	80	7	5	94	13.8%	-1.00 [-2.34, 0.34			-
Bunch TJ et al 2019 Castreión-Castreión S et al 2020	15	8.4 6	402 48	20.1 30	18.6 16	402 47	13.1% 9.1%	-5.10 [-7.10, -3.10]		. –	
Dhillon G et al 2019	7.7	ь 4.52	48 50	8.5	16 8.15	4/ 50	9.1%	-23.00 [-27.88, -18.12] -0.80 [-3.38, 1.78]			-
Kottmaier M et al 2020	6.3	3.9	97	6	3.8	100	14.0%	0.30 [-0.78, 1.38]		+
Pambrun T et al 2019	6	2.8	50	6.5	2.7	50	14.0%	-0.50 [-1.58, 0.58			1
Vassallo F et al 2019 Yazaki K et al 2020	8.8 12	6.6 9	41 32	8.52 13	3.5 6	35 32	12.7%	0.28 (-2.05, 2.61) -1.00 (-4.75, 2.75)			-+
	12	9		13	0						
Total (95% CI)			800				100.0%	-3.10 [-5.52, -0.68]	I		◆
Heterogeneity: Tau ² = 10.58; Chi ² = Test for overall effect: Z = 2.51 (P = 0		df = 7	(P < 0.	00001);	r = 939	6			-20		0 10 20
											IPA CPA
Study or Subgroup		HPA	Total	CP			inter 14	Risk Ratio			k Ratio
Baher A et al 2018	Eve	ents 16	<u>Total</u> 574	Events			<u>eight M</u> 3.3%	H, Fixed, 95% Cl 1.05 [0.31, 3.54]		M-H, FIX	ed, 95% Cl
Berte B et al 2019							7.3%				`
		1	80	3	3 9			0.3910.04.3.691	-		
Castrejón-Castrejón S et al 2020	0	1 0	80 48	6	-		7.5%	0.39 [0.04, 3.69]	•		
	0			6	i 4 5 5	7 17			•		,
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020	0	0 0 13	48 50 97	17	4 5 10	7 17 0 9 0 44	7.5% 9.3% 1.5%	0.08 [0.00, 1.30] 0.14 [0.01, 2.70] 0.79 [0.41, 1.53]			
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019	D	0	48 50	6	4 5 10	7 17 0 9 0 44	7.5% 9.3%	0.08 [0.00, 1.30] ← 0.14 [0.01, 2.70] ←			,
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019	0	0 0 13	48 50 97 50	17	4 5 10 5	7 17 0 9 0 44 0 8	7.5% 9.3% 4.5% 9.0%	0.08 [0.00, 1.30] 0.14 [0.01, 2.70] 0.79 [0.41, 1.53] 0.67 [0.12, 3.82] 	_		
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020	D	0 0 13	48 50 97	17	4 5 10 5 45	7 17 0 9 0 44	7.5% 9.3% 4.5% 9.0%	0.08 [0.00, 1.30] 0.14 [0.01, 2.70] 0.79 [0.41, 1.53]			
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^a = 4,57, df = 5	5 (P = 0.4	0 0 13 2 32 47); F	48 50 97 50 899	6 17 3	4 5 10 5 45	7 17 0 9 0 44 0 8	7.5% 9.3% 4.5% 9.0%	0.08 [0.00, 1.30] 0.14 [0.01, 2.70] 0.79 [0.41, 1.53] 0.67 [0.12, 3.82] 	0.5		- - 1 1.5 2
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events	5 (P = 0.4	0 0 13 2 32 47); F	48 50 97 50 899	6 17 3	4 5 10 5 45	7 17 0 9 0 44 0 8	7.5% 9.3% 4.5% 9.0%	0.08 [0.00, 1.30] 0.14 [0.01, 2.70] 0.79 [0.41, 1.53] 0.67 [0.12, 3.82] 	0.5		1 1.5 2
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^a = 4,57, df = 5	5 (P = 0.4	0 0 13 2 32 47); F	48 50 97 50 899	6 17 3	4 5 10 5 45	7 17 0 9 0 44 0 8	7.5% 9.3% 4.5% 9.0%	0.08 [0.00, 1.30] 0.14 [0.01, 2.70] 0.79 [0.41, 1.53] 0.67 [0.12, 3.82] 	0.5		
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^a = 4,57, df = 5	5 (P = 0.4	0 0 13 2 32 47); P	48 50 97 50 899	35	4 5 10 5 45	7 17 0 9 0 44 0 8	7.5% 9.3% 4.5% 9.0%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 [0.36, 0.99] −	0.5	HPA	A CPA
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^a = 4.57, df = 5 Test for overall effect: Z = 2.00 (P	5 (P = 0. 9 = 0.05)	0 0 13 2 32 47); P	48 50 97 50 899	35	45 10 45 45	7 17 0 9 0 44 0 8 4 10	7.5% 9.3% 4.5% 9.0%	0.08 [0.00, 1.30] 0.14 [0.01, 2.70] 0.79 [0.41, 1.53] 0.67 [0.12, 3.82] 	0.5	HPA Odds	
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^a = 4.57, df = 5 Test for overall effect: Z = 2.00 (P	5 (P = 0. 9 = 0.05)	0 0 13 2 32 47); P HPA ents	48 50 97 50 899 '= 0%	G G Evente	A S Tot:	7 177 0 § 0 444 0 § 4 100	7.5% 9.3% 9.5% 9.0% 0.0%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← 	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: ChI* = 4.57, df = 5 Test for overall effect: Z = 2.00 (P <u>Study or Subgroup</u> 6.1.1 Mild ETI Baher A et al 2018	5 (P = 0. - = 0.05) Ev	0 0 13 2 32 47); P HPA ents 120	48 50 97 50 899 '= 0% ' <u>Total</u> 574	6 3 17 3 3 3 5 CF Event 3	A S A A S A S A S A S A S A S A S A A S A A S A A A A A A A A A A A A A	7 177 0 § 0 44 0 8 4 100	7.5% 9.3% 9.5% 9.0% 0.0%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← Odds Ratio <u>Chr. Fixed, 95% CI</u> 0.67 (0.42, 1.06)	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^p = 4.57, df = 5 Test for overall effect Z = 2.00 (P Study or Subgroup 6.1,1 Mild ETI Baher A et al 2018 Castrejón-Castrejón S et al 202	5 (P = 0. - = 0.05) Ev	0 0 13 2 32 47); P HPA ents	48 50 97 50 899 *= 0% <u>Total</u> 574 48	6 3 17 3 3 3 5 CF Event 3	5 4 3 5 10 3 5 45 5 7 45 7 8 Tot 2 11 5 4	7 177 0 § 0 44 0 § 4 100	7.5% 9.3% 9.5% 9.0% 9.0% 9.0%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← 	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: ChI* = 4.57, df = 5 Test for overall effect: Z = 2.00 (P <u>Study or Subgroup</u> 6.1.1 Mild ETI Baher A et al 2018	5 (P = 0. - = 0.05) Ev	0 0 13 2 32 47); P HPA ents 120	48 50 97 50 899 '= 0% ' <u>Total</u> 574	6 3 17 3 3 3 5 CF Event 3	6 4 3 5 10 3 5 45 4	7 177 0 § 0 44 0 § 4 100	7.5% 9.3% 9.5% 9.0% 0.0%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← Odds Ratio <u>Chr. Fixed, 95% CI</u> 0.67 (0.42, 1.06)	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^P = 4.57, df = 5 Test for overall effect. Z = 2.00 (P <u>Study or Subgroup</u> 6.1.1 Mid ETI Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI) Total events Heterogeneity: Chi ^P = 0.46, df =	5 (P = 0. = 0.05) Ev 20 1 (P = 0	0 0 13 2 32 47); I ^a HPA tents 120 2 122 .50); I	48 50 97 50 899 *= 0% Total 574 48 622	6 3 3 3 5 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	6 4 3 5 10 3 5 45 4	7 177 0 § 0 44 0 § 4 100	7.5% 9.3% 9.5% 9.0% 9.0% 9.0%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← 	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^a = 4.57, df = 5 Test for overall effect. Z = 2.00 (P <u>Study or Subgroup</u> 6.1.1 Midd ET Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI) Total events	5 (P = 0. = 0.05) Ev 20 1 (P = 0	0 0 13 2 32 47); I ^a HPA tents 120 2 122 .50); I	48 50 97 50 899 *= 0% Total 574 48 622	6 3 3 3 5 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	6 4 3 5 10 3 5 45 4	7 177 0 § 0 44 0 § 4 100	7.5% 9.3% 9.5% 9.0% 9.0% 9.0%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← 	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi [®] = 4.57, df = 5 Test for overall effect: Z = 2.00 (P <u>6.11 Mild ETI</u> Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI) Total events Heterogeneity: Chi [®] = 0.46, df = Test for overall effect: Z = 2.01 (f	5 (P = 0. = 0.05) Ev 20 1 (P = 0	0 0 13 2 32 47); I ^a HPA tents 120 2 122 .50); I	48 50 97 50 899 *= 0% Total 574 48 622	6 3 3 3 5 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	6 4 3 5 10 3 5 45 4	7 177 0 § 0 44 0 § 4 100	7.5% 9.3% 9.5% 9.0% 9.0% 9.0%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← 	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^P = 4.57, df = 5 Test for overall effect. Z = 2.00 (P <u>Study or Subgroup</u> 6.1.1 Mid ETI Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI) Total events Heterogeneity: Chi ^P = 0.46, df =	5 (P = 0. = 0.05) Ev 20 1 (P = 0	0 0 13 2 32 47); I ^a HPA tents 120 2 122 .50); I	48 50 97 50 899 *= 0% Total 574 48 622	6 3 3 3 5 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	5 4 3 5 10 3 5 45 5 5 7 7	7 17 0 § 0 44 0 8 4 100 3 5: 7 1 0 5	7.5% 9.3% 9.5% 9.0% 9.0% 9.0%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← 	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^P = 4.57, df = 5 Test for overall effect. Z = 2.00 (P 6.1.1 Mid ETI Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI) Total events Heterogeneity: Chi ^P = 0.46, df = Test for overall effect. Z = 2.01 (f 6.1.2 Moderate ETI Baher A et al 2018 Castrejón-Castrejón S et al 202	5 (P = 0. = 0.05) Ev 20 1 (P = 0.04	0 0 13 2 32 47); I ² 120 2 122 .50); I	48 50 97 50 899 *= 0% Total 574 48 622 F = 0% 574 48	6 3 17 3 3 5 Cf Event 3 3 1	5 4 5 5 10 5 45 5 45 5 7 7 16 7 16 7 3 11 5 4	7 17 0 § 0 44 0 § 4 100 3 5; 7 (0 5 3 2; 7 (2.5% 1.3% 2.5% 0.0% 0.0% 0.0% 0.0% 3.1% 5.1% 9.2%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← 	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total events Heterogeneity: ChIP = 4.57, df = 5 Test for overall effect: Z = 2.00 (P 6.1.1 Mild ETI Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI) Total events Heterogeneity: ChIP = 0.46, df = Test for overall effect: Z = 2.01 (f 6.1.2 Moderate ETI Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI)	5 (P = 0. = 0.05) Ev 20 1 (P = 0.04	0 0 13 2 32 47); I ^a HPA tents 120 2 122 2.50); I) 66 2	48 50 97 50 899 *= 0% <u>Total</u> 574 48 622 F= 0%	6 3 17 3 3 3 5 CI Event 3 3 3 1	3 4 3 5 10 3 5 45 5 7 7 3 11 5 4 16 7 10 10 10 10 10 10 10 10 10 10	7 17 0 § 0 44 0 § 4 100 3 5; 7 (0 5 3 2; 7 (2.5% 3.3% 5.5% 0.0% 0.0% 0.0% 0.0% 0.0% 0.0% 0.1% 9.2%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← 0.60 (0.36, 0.99) ← 0.60 (0.36, 0.99) ← 0.67 (0.42, 1.06) 0.37 (0.07, 1.98) 0.64 (0.41, 0.99) ← 1.00 (0.53, 1.88)	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: Chi ^P = 4.57, df = 5 Test for overall effect: Z = 2.00 (P 5.11 Mid ETI Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI) Total events Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI) Total events	5 (P = 0. = 0.05) Ev 20 1 (P = 0.04	0 0 13 2 32 47); I ² HPA eents 120 2 122 2.50); I) 666 2 68	48 50 97 50 899 2 = 0% 1 Total 48 622 574 48 622	CI Event 3 3 1 1	3 4 3 5 10 3 5 45 5 7 7 3 11 5 4 16 7 10 10 10 10 10 10 10 10 10 10	7 17 0 § 0 44 0 § 4 100 3 5; 7 (0 5 3 2; 7 (2.5% 1.3% 2.5% 0.0% 0.0% 0.0% 0.0% 3.1% 5.1% 9.2%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← 	0.5	HPA Odds	Ratio
Castrejón-Castrejón S et al 2020 Dhillon G et al 2019 Kottmaier M et al 2020 Pambrun T et al 2019 Total (95% CI) Total events Heterogeneity: ChIP = 4.57, df = 5 Test for overall effect: Z = 2.00 (P Study or Subgroup 6.1.1 Mild ETI Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI) Total events Heterogeneity: ChIP = 0.46, df = Test for overall effect: Z = 2.01 (f 6.1.2 Moderate ETI Baher A et al 2018 Castrejón-Castrejón S et al 202 Subtotal (95% CI) Total events Heterogeneity: ChIP = 0.46, df = Total events Heterogeneity: ChIP = 1.19, df =	5 (P = 0.05) = 0.05) Ev 20 1 (P = 0 P = 0.04 20 1 (P = 0	0 0 13 2 32 47); I ² 120 2 122 50); I 2 66 2 68 8.27); I	48 50 97 50 899 2 = 0% 1 Total 48 622 574 48 622	CI Event 3 3 1 1	3 4 3 5 10 3 5 45 5 7 7 3 11 5 4 16 7 10 10 10 10 10 10 10 10 10 10	7 17 0 § 0 44 0 § 4 100 3 5; 7 (0 5 3 2; 7 (2.5% 1.3% 2.5% 0.0% 0.0% 0.0% 0.0% 3.1% 5.1% 9.2%	0.08 (0.00, 1.30) ← 0.14 (0.01, 2.70) ← 0.79 (0.41, 1.53) 0.67 (0.12, 3.82) ← 0.60 (0.36, 0.99) ← 	0.5	HPA Odds	Ratio
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