Long-acting somatostatin analogue treatments in Autosomal Dominant Polycystic Kidney Disease and Polycystic Liver Disease: A systematic review and meta-analysis

- Supplementary figures

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Supplementary Table 1: Electronic search strategy

Supplementary Figure 1. Funnel plots for primary outcomes

Supplementary Figure 2. Somatostatin treatment reduces change from baseline TKV

Supplementary Figure 3. Somatostatin treatment has no effect on diastolic and systolic blood pressure or progression to ESRF

Database	Terms
PUBMED	ADPKD
	PKD
	Polycystic kidney disease
	PLD
	Polycystic liver disease
	+
	Somatostatin
	Octreotide
	Lanreotide
Clinicaltrials.gov	ADPKD
	PKD
	Polycystic kidney disease
	PLD
	Polycystic liver disease
	+
	Somatostatin
	Octreotide
	Lanreotide
Cochrane Central Register of Controlled Trials	ADPKD
	PKD
	Polycystic kidney disease
	PLD
	Polycystic liver disease
	+
	Somatostatin
	Octreotide
	Lanreotide

Supplementary Table 1: electronic search strategy



 $\label{eq:supplementary Figure 1. Funnel plots for primary outcomes; eGFR (a), TKV (b) and TLV (c).$

a.

	Somatos	tatin Anal	Analogue Control					Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.5.1 Ocreotide										
Ruggenenti	54	23.6	12	57.7	25.7	12	1.4%	-3.70 [-23.44, 16.04]	2005	
Hogan	64.6	25.66	21	65.7	26.4	9	1.3%	-1.10 [-21.54, 19.34]	2010	
ALADIN	76.33	27.96	36	64.64	36.25	31	2.1%	11.69 [-4.00, 27.38]	2013	
ALADIN 2	19.6	6.3	35	19.9	9.2	35	38.6%	-0.30 [-3.99, 3.39]	2019	
Subtotal (95% CI)			104			87	43.4%	0.16 [-3.32, 3.65]		•
Heterogeneity: Tau ² = (0.00; Chi ² =	: 2.29, df=	3 (P = 0	.51); I² =	:0%					
Test for overall effect: 2	(P = 0.09 (P =	= 0.93)								
1.5.2 Lanreotide										
DIPAK-1	42.6	12.8	146	43.2	13.7	144	56.6%	-0.60 [-3.65, 2.45]	2018	
Subtotal (95% CI)			146			144	56.6%	-0.60 [-3.65, 2.45]		+
Heterogeneity: Not app	licable									
Test for overall effect: 2	C= 0.39 (P =	= 0.70)								
Total (95% CI)			250			231	100.0%	-0.27 [-2.57, 2.03]		+
Heterogeneity: Tau ² = (0.00; Chi² =	2.40, df=	4 (P = 0	.66); l² =	:0%				-	
Test for overall effect: Z	I = 0.23 (P =	= 0.82)								Eavours Control Eavours Somatostatin
Test for subgroup diffe	rences: Ch	ii ² = 0.10, (df = 1 (P	= 0.75),	² = 0%					

b.

	Som	atostat	tin	0	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
2.5.1 Ocreotide										
Ruggenenti	2.622	1.111	12	2.623	1.021	12	9.9%	-0.00 [-0.85, 0.85]	2005	
Hogan	1.128	0.796	21	0.873	0.306	8	23.8%	0.25 [-0.15, 0.66]	2010	
ALADIN	1.672	1.195	35	2.621	1.603	35	14.1%	-0.95 [-1.61, -0.29]	2013	-
ALADIN 2	3.043	2.32	35	3.613	1.69	35	8.3%	-0.57 [-1.52, 0.38]	2019	
Subtotal (95% CI)			103			90	56.1%	-0.28 [-0.91, 0.35]		
Heterogeneity: Tau ² =	: 0.28; C	hi² = 10.	.31, df=	= 3 (P =	0.02); l ^a	= 71%				
Test for overall effect:	Z = 0.87	(P = 0.)	38)							
2.5.2 Lanreotide LOCKCYST DIPAK-1 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect:	0.983 0.118 0.00; C Z = 5.18	1.173 0.227 hi² = 0.0 i (P ≤ 0.1	12 134 146 10, df = 00001)	1.17 0.272 1 (P = 0	2.66 0.265 .96); I² =	20 138 158 = 0%	4.7% 39.2% 43.9 %	-0.19 [-1.53, 1.15] -0.15 [-0.21, -0.10] -0.15 [-0.21, -0.10]	2009 2018	•
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	: 0.06; C Z = 1.20 ferences	hi² = 10. ⊢(P = 0.: ∶ Chi² =	249 .39, df: 23) 0.15, c	= 5 (P = lf = 1 (P	0.07); Iª = 0.70),	248 = 52% ² = 0%	100.0%	-0.19 [-0.50, 0.12]		-1 -0.5 0 0.5 1 Favours Somatostatin Favours Control

c.

	Som	atostati	n		Control			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
2.6.1 Ocreotide										
Caroli	1.524	0.453	12	1.58	0.48	12	8.9%	-0.06 [-0.43, 0.32]	2010	
Hogan	5.557	2.659	28	5.36	3.33	14	0.3%	0.20 [-1.81, 2.20]	2010	· · · · · · · · · · · · · · · · · · ·
Pisani	1.479	0.47	14	1.837	0.748	14	5.8%	-0.36 [-0.82, 0.10]	2016	
Subtotal (95% CI)			54			40	14.9%	-0.17 [-0.46, 0.12]		-
Heterogeneity: Tau ² =	0.00; Ch	i ^z = 1.12,	df = 2	(P = 0.5	7); I ^z = 04	%				
Test for overall effect:	Z = 1.14	(P = 0.25	i)							
2.6.2 Lanreotide										
LOCKCYST	4.471	10.417	27	4.896	10.804	26	0.0%	-0.42 [-6.14, 5.29]	2009	· · · · · · · · · · · · · · · · · · ·
Van Aerts	-0.052	0.388	83	0.089	0.382	74	85.0%	-0.14 [-0.26, -0.02]	2019	
Subtotal (95% CI)			110			100	85.1%	-0.14 [-0.26, -0.02]		\bullet
Heterogeneity: Tau ² =	0.00; Ch	i ^z = 0.01,	df = 1	(P = 0.9	2); I ² = 04	%				
Test for overall effect:	Z = 2.29	(P = 0.02)	9							
										•
Total (95% CI)			164			140	100.0%	-0.15 [-0.26, -0.03]		\bullet
Heterogeneity: Tau ² =	0.00; Ch	i² = 1.16,	df = 4	(P = 0.8	9); I² = 0°	%				
Test for overall effect:	Z = 2.56	(P = 0.01)							Favours Somatostatin Favours Control
Test for subaroup diff	erences:	$Chi^2 = 0.$	03. df =	= 1 (P =	0.87), I ² =	= 0%				

Supplementary Figure 2. Lanreotide treatment significantly reduced TKV and TLV but not eGFR. Ocreotide treatment does not improve TKV, TLV or eGFR. Forest plots depicting the effects of somatostatin analogues on eGFR (a), TKV (b) and TLV (c) with trials that used Ocreotide separated from trials which used Lanreotide. Horizontal lines represent the 95% Confidence intervals the studies with mean difference or risk ratio indicated by coloured square. The Diamond represented pooled mean difference or risk ratio RR analysis with a 95% confidence interval.

	Son	natosta	tin	0	Control			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Ruggenenti	71	107	12	162	114	12	55.3%	-91.00 [-179.46, -2.54]	2005	
LOCKCYST	-17	188.6	12	50	335	20	13.1%	-67.00 [-248.50, 114.50]	2009	
Hogan	-14	586.7	21	71	206	8	5.2%	-85.00 [-373.69, 203.69]	2010	
ALADIN	220	289	35	454	472	35	12.9%	-234.00 [-417.35, -50.65]	2013	
DIPAK-1	118	898	134	272	1,061	138	7.9%	-154.00 [-387.35, 79.35]	2018	
ALADIN 2	604	597	35	939	595	35	5.5%	-335.00 [-614.24, -55.76]	2019	
Total (95% CI)			249			248	100.0%	-124.49 [-190.28, -58.71]		◆
Heterogeneity: Tau² =	0.00; C	hi² = 4.8	i2, df=	5 (P = 0	.46); l² :	= 0%				
Test for overall effect:	Z = 3.71	(P = 0.	0002)							Favours Somatostatin Favours Control

Supplementary Figure 3. Somatostatin treatment reduces change from baseline TKV. Forest plots depicting the effects of Somatostatin analogue vs controls on TKV when change from baseline means are used to correct for heterogeneity and variability in initial TKV's. Horizontal lines represent the 95% confidence intervals the studies with mean difference indicated by coloured square. The Diamond represented pooled mean difference analysis with a 95% confidence interval.

а.

	Som	atosta	itin	С	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Ruggenenti	143	13	12	143	9	12	5.3%	0.00 [-8.95, 8.95]	2005	
ALADIN	123.8	9	40	122.9	11.7	39	20.1%	0.90 [-3.71, 5.51]	2013	
DIPAK-1	132	8.8	133	131	15.2	142	50.4%	1.00 [-1.91, 3.91]	2018	
ALADIN 2	132.6	13.6	51	130.3	6.9	49	24.2%	2.30 [-1.90, 6.50]	2019	
Total (95% CI)			236			242	100.0%	1.24 [-0.83, 3.31]		•
Heterogeneity: Tau ² = Test for overall effect:	0.00; CI Z = 1.18	ni² = 0. (P = 0	.37, df=).24)	= 3 (P =	0.95);	I ² = 0%				-20 -10 0 10 20 Favours Somatostatin Favours Control

b.

	Soma	itosta	tin	Co	ontro	I		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Ruggenenti	94	14	12	91	9	12	2.3%	3.00 [-6.42, 12.42]	2005	
ALADIN	77.3	7.2	40	77.9	8.2	39	17.9%	-0.60 [-4.01, 2.81]	2013	
DIPAK-1	81.7	8.5	133	80.5	8.2	142	53.2%	1.20 [-0.78, 3.18]	2018	-+ B
ALADIN 2	82.4	6.1	51	82.9	8	49	26.6%	-0.50 [-3.30, 2.30]	2019	
Total (95% CI)			236			242	100.0%	0.47 [-0.97, 1.91]		◆
Heterogeneity: Tau ² = Test for overall effect:	0.00; Ch 7 = 0.64	ί² = 1. (Ρ = Γ	.64, df= 1.52)	= 3 (P =	0.65)	; I² = 09	%			
	_ 0.01	v – c	/							Favours Somatostatin Favours Control

c.

	Somatos	statin	Contr	ol		Risk Ratio		Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl				
DIPAK-1	3	153	2	152	40.0%	1.49 [0.25, 8.79]	2018					
ALADIN 2	3	51	8	49	60.0%	0.36 [0.10, 1.28]	2019					
Total (95% CI)		204		201	100.0%	0.64 [0.16, 2.49]						
Total events	6		10									
Heterogeneity: Tau ² = Test for overall effect:	= 0.39; Chi : Z = 0.65 (F	= 1.63, P = 0.52;	df = 1 (P)	= 0.20)	; I² = 39%)		0.01 0.1 1 10 100 Favours Somatostatin Favours Control				

Supplementary Figure 4. Somatostatin treatment has no effect on diastolic and systolic blood pressure or progression to ESRF. Forest plots depicting the effects of Somatostatin analogue vs controls on Systolic blood pressure (a), Diastolic blood pressure (b) and progression to ESRF (c). Horizontal lines represent the 95% Confidence intervals the studies with mean difference or risk ratio indicated by coloured square. The Diamond represented pooled mean difference or risk ratio RR analysis with a 95% confidence interval.