

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Walz G, Budde K, Mannaa M, et al. Everolimus in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2010;363:830-40. DOI: 10.1056/NEJMoa1003491.

Supplementary Appendix

Table 1. Changes in eGFR from Baseline. Changes in eGFR were calculated, using the MDRD formular. Nearly identical results were obtained using the CKD-EPI formula.

Change from baseline in eGFR	Everolimus (N = 213)	Placebo (N = 216)	Difference	P value
Week 1	2.03	-0.89	2.92	<0.001
Week 2	1.73	-0.87	2.60	<0.001
Week 4	0.57	-1.22	1.79	0.005
Month 3	-0.48	-1.17	0.69	0.356
Month 6	-2.29	-2.19	-0.10	0.890
Month 9	-4.58	-2.42	-2.16	0.004
Month 12	-5.42	-3.22	-2.20	0.004
Month 18	-7.71	-5.54	-2.17	0.008
Month 24	-8.91	-7.68	-1.23	0.145

Table 2. Antihypertensives after Study

	Everolimus (N = 213)	Placebo (N = 216)	Difference (p value)
Total N (%)	198 (93.0%)	198 (91.7%)	0.7178
Agents acting on RAS, N (%)	191 (89.7%)	188 (87.0%)	0.4528
Beta blocking agents, N (%)	101 (47.4%)	94 (43.5%)	0.4388
Calcium Channel blocker, N (%)	71 (33.3%)	70 (32.4%)	0.9182
Diuretics, N (%)	66 (31.0%)	54 (25.0%)	0.1967

Table 3A. Lipid profile – Values at Baseline and after 24 Months

	Everolimus (N = 214)	Placebo (N = 217)	Difference (p values, t- test)
Total Cholesterol (mmol/L)			
Baseline	5.3 ± 1.0	5.1 ± 1.0	0.046
Month 12	6.0 ± 1.2	5.1 ± 0.9	<0.001
Month 24	5.9 ± 1.0	5.1 ± 0.9	<0.001
Triglycerides (mmol/L)			
Baseline	1.5 ± 0.9	1.5 ± 0.9	0.896
Month 12	2.2 ± 1.2	1.6 ± 1.0	<0.001
Month 24	2.3 ± 1.5	1.7 ± 1.2	<0.001
LDL (mmol/L)			
Baseline	1.5 ± 0.4	1.5 ± 0.4	0.728
Month 12	1.4 ± 0.4	1.4 ± 0.4	0.678
Month 24	1.4 ± 0.4	1.4 ± 0.4	0.871
HDL (mmol/L)			
Baseline	3.3 ± 0.9	3.0 ± 0.8	0.135
Month 12	3.7 ± 0.9	3.1 ± 0.9	<0.001
Month 24	3.6 ± 0.8	3.1 ± 0.7	<0.001

Table 3B. Lipid Lowering Agents

Before Study Initiation	Everolimus (N = 213)	Placebo (N = 216)	Difference (p value)
Total N (%)	29 (13.6%)	29 (13.4%)	>0.999
Statins	22 (10.3%)	26 (12.0%)	0.647
Other Lipid-Lowering Agents	7 (3.3%)	4 (1.9%)	0.379

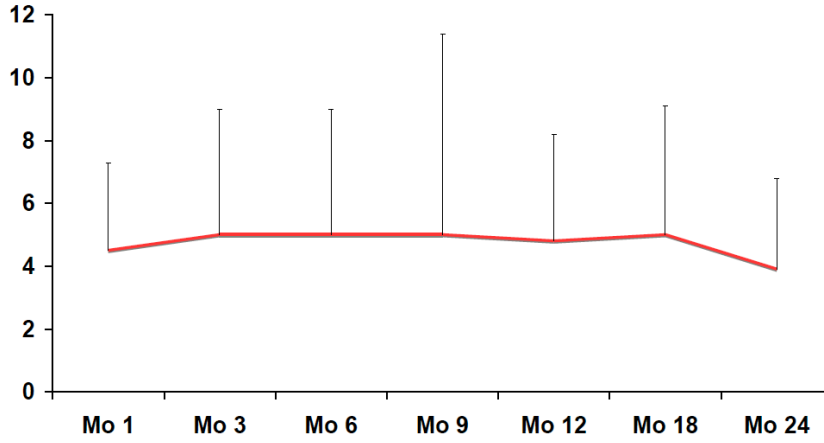
After Study Initiation	Everolimus (N = 213)	Placebo (N = 216)	Difference (p value)
Total N (%)	85 (39.9%)	46 (21.3%)	<0.001
Statins	76 (35.7%)	42 (19.4%)	<0.001
Other Lipid-Lowering Agents	12 (5.6%)	8 (3.7%)	0.369

Table 4. Major Protocol Violations. Major protocol violations were determined before unblinding the database and resulted in exclusion of patients from the per-protocol population. Note that several patients had more than one major protocol violation.

	Everolimus (N= 214)	Placebo (N=217)
Patients without major protol violations	91 (42.5%)	123 (56.7%)
Patients with major protocol violations	123 (57.5%)	94 (43.3%)
Missing MRI at month 12 and/or 24	96 (44.9%)	68 (31.3%)
Deviation from standard MRI procedure	27 (17%)	
Incomplete kidney coverage	18 (11%)	
Incomplete separation from liver cysts	40 (24%)	
Artifacts due to strong patient motion	8 (5%)	
Other	71 (43%)	
Missing baseline MRI	45 (21.0%)	42 (19.6%)
Deviation from standard MRI procedure	27 (31%)	
Incomplete kidney coverage	30 (35%)	
Incomplete separation from liver cysts	19 (22%)	
Artifact due to strong patient motion	5 (6%)	
Other	6 (7%)	
Missing MRI at month 12 and 24	50 (23.4%)	35 (17.1%)
Missing MRI only at month 12	4 (1.9%)	7 (3.2%)
Missing MRI only at month 24	42 (24.3%)	26 (12.0%)
Valid baseline MRI and missing MRI at month 12 and/or 24	64 (29.9%)	42 (19.4%)
Missing MRI at month 12 and 24	23 (10.7%)	13 (6.0%)
Missing MRI only at month 12	4 (1.9%)	(2.8%)
Missing MRI only at month 24	37 (17.3%)	23 (10.6%)
Study drug interruption for more than 28 consecutive days or more than 56 days combined	26 (12.1%)	14 (6.5%)
GFR < 30 mL/min/1.73m ²	17 (7.9%)	10 (4.6%)
Code broken without emergency reason	4 (1.9%)	-
No post baseline visit	1 (0.5%)	1 (0.5%)
Unresolved history or current drug or alcohol abuse	1 (0.5%)	-
History of malignancy during the last five years	1 (0.5%)	1 (0.5%)
Pregnancy	1 (0.5%)	-

Everolimus in ADPKD

A



B

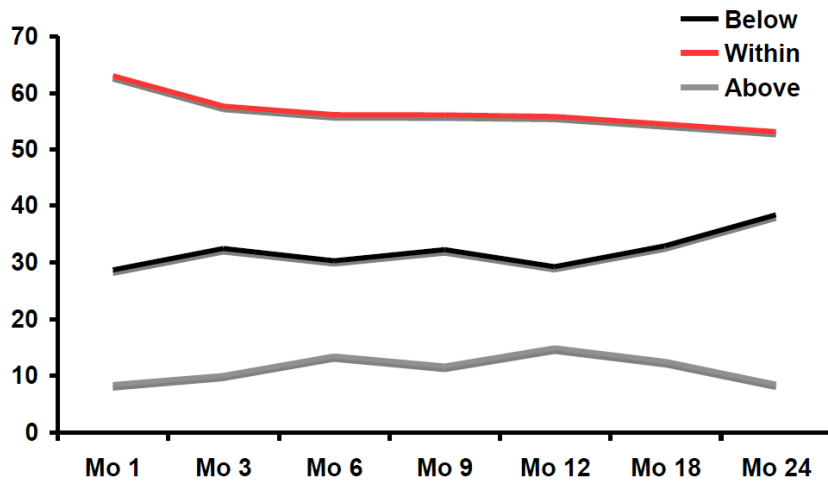


Figure 1. Everolimus trough levels.

A. Depicted are the mean everolimus trough levels with standard deviation.

B. Depicted is the percentage of patients within (red), below (black) or above (grey) the desired everolimus concentration between 3 and 8 ng/mL.

Everolimus in ADPKD

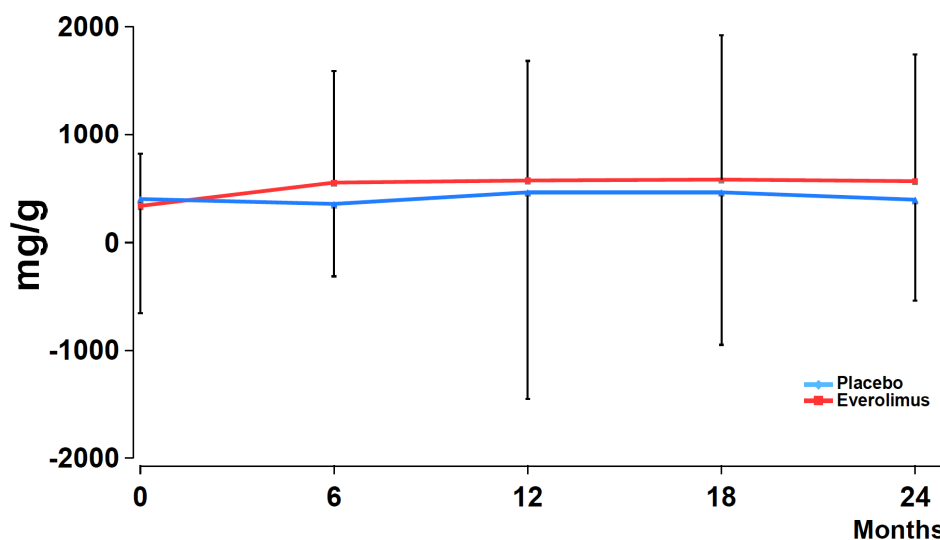


Figure 2. Proteinuria.

Proteinuria, estimated as urinary protein/creatinine ratio (mg/g), is depicted with standard deviations over the 2-year treatment period. After two years the difference between the everolimus and placebo group was 296 mg/g ($p=0.008$).

Information. MRI Protocol

All measurements were carried out on 1.5T MR scanners. A phased-array surface coil was positioned with its center over the inferior costal margin. An initial scout scan was performed to localize the kidneys. Breath-hold coronal T2-weighted images (FSE/HASTE) with fat saturation, followed by T1 weighted in- and out-of-phase gradient echo images (Flash/GE) without fat suppression were obtained. All three sequence were acquired with coronal orientation, FOV = 400mm, 256x256 matrix and with slice packages covering the entire volume of interest including kidneys and kidney cysts. TE and TR were 200ms/652ms for the T2-weighted sequence, and (2,38ms/4,76ms)/150ms for the opus and in-phase gradient echo sequences, respectively. Total kidney volumes were measured from T1-weighted images using region of interest drawing. Renal cyst volumes were determined using T2-weighted images and region-based thresholds, utilizing an interactive selection of a threshold by an analyst using T2-weighted images. Cysts were brighter than the renal parenchyma in T2-weighted images and were segmented from voxels with intensity values higher than the threshold. Total kidney and cyst volumes were calculated from sets of contiguous images by summing the products of the area measurements and the slice thickness. The percentage of the cyst volume was determined from the ratio of cyst volume to total kidney volume.