SUPPLEMENTARY INFORMATION

Implications of early diagnosis of autosomal dominant polycystic kidney disease: A *post hoc* analysis of the TEMPO 3:4 trial

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Contents

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Supplementary Tables

Supplementary Table 1. TKV rate of growth (%/year) within the treatment period, age at diagnosis as a continuous variable (intention-to-treat subjects)

		Annualized % Growth Rate					Slope (%)			Treatment Effect (%)				
Treatment Group	**N**	**Mean**	**Median**	**SD**	**Min**	**Max**	**Slope**	**Lower**	**Upper**	**Difference**	**Lower**	**Upper**	***p*-value**	***p*-value for Interaction of Age at Diagnosis**
Tolvaptan	819	2.777	2.265	5.659	-23.129	64.270	2.752	2.410	3.094	-2.670	-3.23	-2.12	<0.0001	0.3026
Placebo	458	5.608	5.585	5.330	-20.634	43.948	5.495	4.926	6.067					

Supplementary Table 2. Rate of change in renal function, estimated by Chronic Kidney Disease-Epidemiology Collaboration equation (mL/min/1.73 m^2), within the treatment period, age at diagnosis as a continuous variable (subjects in CKD stages 2–3 only)

		Rate of Change Per Year					Slope (95% CI)			
Treatment Group	**N**	**Mean**	**Median**	**SD**	**Min**	**Max**	**Slope**	**Lower**	**Upper**	***p*-value for Interaction of Age at Diagnosis**
Tolvaptan	574	-1.622	-2.927	18.165	-157.01	245.754	-3.013	-3.263	-2.763	0.6603
Placebo	301	-4.346	-4.244	6.187	-81.283	17.903	-4.306	-4.686	-3.926	0.4437

Supplementary Table 3. Rate of change in renal function, estimated by Chronic Kidney Disease-Epidemiology Collaboration equation (mL/min/1.73 m^2), within the treatment period, age at diagnosis as a continuous variable (intention-to-treat subjects)

		Rate of Change Per Year					Slope (95% CI)			Absolute Treatment Effect (95% CI)				
Treatment Group	**N**	**Mean**	**Median**	**SD**	**Min**	**Max**	**Slope**	**Lower**	**Upper**	**Difference**	**Lower**	**Upper**	***p*-value**	***p*-value for Interaction of Age at Diagnosis**
Tolvaptan	863	-1.083	-2.511	25.905	-258.56	476.635	-2.270	-2.935	-2.506	0.980	0.600	1.360	<0.0001	0.3947
Placebo	465	-3.735	-3.481	5.757	-81.283	24.585	-3.700	-4.080	-3.321					

Supplementary Table 4. Sensitivity analysis: linear mixed model of eGFR, intention-to-treat subjects

	Linear Mixed Model (N=1381))		
Variable	**Coefficient**	**95% Confidence Interval**	***p*-value**
Intercept	12.0683	(8.5895, 15.5471)	<.0001
Time, yr	-3.5485	(-5.4151, -1.6819)	0.0002
Male	-0.2018	(-0.7584, 0.3548)	0.4773
Age, yr	-0.1671	(-0.2319, -0.1023)	<.0001
Mayo Class A	-2.0210	(-4.3876, 0.3456)	0.0942
Mayo Class B	2.1363	(0.6742, 3.5983)	0.0042
Mayo Class C	1.2829	(0.3815, 2.1843	0.0053
Mayo Class D	0.9099	(0.1048, 1.7150)	0.0268
Baseline eGFR	0.9161	(0.8985, 0.9338)	<.0001
Age at diagnosis ≤18 years	-0.2803	(-0.9755, 0.4149)	0.4293
Male x time	0.0962	(-0.2538, 0.4462)	0.5899
Age x time	-0.0453	(-0.0821, -0.0084)	0.0161
Mayo Class A x time	4.0204	(1.4437, 6.5972)	0.0022
Mayo Class B x time	2.7224	(1.9136, 3.5313)	<.0001
Mayo Class C x time	1.6828	(1.1004, 2.2652)	<.0001
Mayo Class D x time	1.0431	(0.5073, 1.5790)	<.0001
Baseline eGFR x time	0.0157	(0.0065, 0.0249)	0.0008
Age at diagnosis ≤18 years x time	0.7239	(0.2765, 1.1713)	0.0015

Linear mixed model with variables listed above, where intercept and time are random effects.
eGFR, estimated glomerular filtration rate.

Supplementary Table 5. Baseline characteristics of childhood diagnosis subjects by reason for diagnosis

	With Symptoms		Without Symptoms		
Parameter	**N**	**Value**	**N**	**Value**	***p*-value for Comparison**
Male, n (%)	93	46 (49)	201	101 (50)	0.9002
RAASi use, n (%)	93	75 (81)	201	124 (62)	0.0012
Hypertension, n (%)	93	82 (88)	201	156 (78)	0.0320
CKD Stage 1, n (%)	92	42 (46)	201	86 (43)	0.6462
CKD Stage 2, n (%)	92	36 (39)	201	89 (44)	0.4083
CKD Stage 3, n (%)	92	14 (15)	201	26 (13)	0.5975
Age (yr), mean (SD)	93	32.76 (8.85)	201	34.84 (7.62)	0.0400
eGFR (CKD-EPI, mL/min/1.73 m^2), mean (SD)	92	88.48 (26.17)	201	86.91 (22.82)	0.6033
TKV (mL), median (interquartile range)	93	1583 (1208,2419)	201	1453 (1067,2004)	0.0410

CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor.

Supplementary Table 6. Total kidney volume rate of growth (%/year) within the treatment period in childhood diagnosis subjects by reason for diagnosis

		Annualized % Growth Rate						Slope (%)			Treatment Effect (%)			
Subgroup	**Treatment Group**	**N**	**Mean**	**Median**	**SD**	**Min**	**Max**	**Slope**	**Lower**	**Upper**	**Difference**	**Lower**	**Upper**	***p*-value**
CD with symptoms	Tolvaptan	53	4.273	4.140	4.886	-6.504	16.839	4.062	2.774	5.367	-1.794	-4.01	0.370	0.1043
	Placebo	26	6.039	5.513	5.112	-3.484	16.551	5.929	3.677	8.230				
CD without symptoms	Tolvaptan	107	2.863	3.283	4.497	-9.083	13.079	2.940	2.119	3.767	-1.526	-3.05	-0.029	0.0457
	Placebo	62	4.574	5.195	5.531	-8.877	18.327	4.511	2.970	6.075				

CD, childhood diagnosis.

Supplementary Table 7. Rate of change in renal function, estimated by Chronic Kidney Disease-Epidemiology Collaboration equation (mL/min/1.73 m^2), within the treatment period in childhood diagnosis subjects by reason for diagnosis

			Rate of Change Per Year					Slope (95 CI%)			Absolute Treatment Effect (95% CI)				
Subgroup	**Treatment Group**	**N**	**Mean**	**Median**	**SD**	**Min**	**Max**	**Slope**	**Lower**	**Upper**	**Absolute Difference**	**Lower**	**Upper**	**Difference (%)**	***p*-value**
CD with symptoms	Tolvaptan	55	-1.043	-2.362	10.310	-15.463	63.709	-2.837	-3.794	-1.880	0.566	-0.871	2.002	16.62	0.4396
	Placebo	27	-3.111	-2.822	5.493	-21.535	14.929	-3.403	-4.839	-1.967					
CD without symptoms	Tolvaptan	118	3.397	-1.811	44.921	-32.102	476.635	-1.994	-2.603	-1.386	1.203	0.173	2.234	37.63	0.0221
	Placebo	65	-3.351	-2.953	5.294	-20.290	17.903	-3.197	-4.228	-2.167					

CD, childhood diagnosis.

Supplementary Table 8. Difference in observed and predicted eGFR within the treatment period in adulthood diagnosis and childhood diagnosis subjects matched by Mayo risk class and age at study inclusion

	Observed eGFR – Predicted eGFR (mL/min/1.73 m^2)						Paired T-test	
	N	**Mean**	**Median**	**SD**	**Min**	**Max**	**95% CI of Mean**	***p*-value**
Tolvaptan-treated								
CD	180	6.82	6.61	11.22	-18.95	48.03	(5.17. 8.47)	<0.0001
AD	180	5.43	5.36	10.41	-38.14	45.84	(3.90, 6.96)	<0.0001
Placebo-treated								
CD	87	1.83	1.72	10.51	-34.62	33.24	(-0.41, 4.07)	0.1080
AD	87	0.63	0.59	9.49	-26.74	27.51	(-1.40, 2.65)	0.5390

AD, adulthood diagnosis; CD, childhood diagnosis.

Supplementary Table 9. Difference in observed and predicted eGFR within the treatment period in adulthood diagnosis and childhood diagnosis subjects, excluding subjects at CKD stage 1 at baseline (i.e., baseline CKD stages 2–4)

	Observed eGFR – Predicted eGFR (mL/min/1.73 m²)						Paired T-test	
	N	**Mean**	**Median**	**SD**	**Min**	**Max**	**95% CI of Mean**	***p*-value**
Tolvaptan-treated								
CD	111	4.73	2.59	10.23	-16.59	38.49	(2.81, 6.66)	<0.0001
AD	495	2.99	2.53	9.20	-35.81	29.55	(2.17, 3.80)	<0.0001
Placebo-treated								
CD	50	-0.51	0.01	9.03	-23.97	23.65	(-3.08, 2.06)	0.6913
AD	255	-1.91	-1.92	9.59	-32.69	32.39	(-3.09, -0.72)	0.0017

AD, adulthood diagnosis; CD, childhood diagnosis.

Supplementary Table 10. Difference in observed and predicted eGFR within the treatment period in childhood diagnosis subjects by reason for diagnosis

	Observed eGFR – Predicted eGFR (mL/min/1.73 m²)						Paired T-test	
	N	**Mean**	**Median**	**SD**	**Min**	**Max**	**95% CI of Mean**	***p*-value**
Tolvaptan-treated								
CD with symptoms	59	7.92	7.45	12.07	-16.59	48.03	(4.77, 11.06)	<0.0001
CD without symptoms	125	6.30	5.15	10.66	-18.95	34.20	(4.41, 8.19)	<0.0001
Placebo-treated								
CD with symptoms	28	3.22	5.26	11.74	-34.62	19.19	(-1.33, 7.77)	0.1584
CD without symptoms	69	1.76	1.28	10.28	-22.31	33.24	(-0.72, 4.23)	0.1608

AD, adulthood diagnosis; CD, childhood diagnosis.

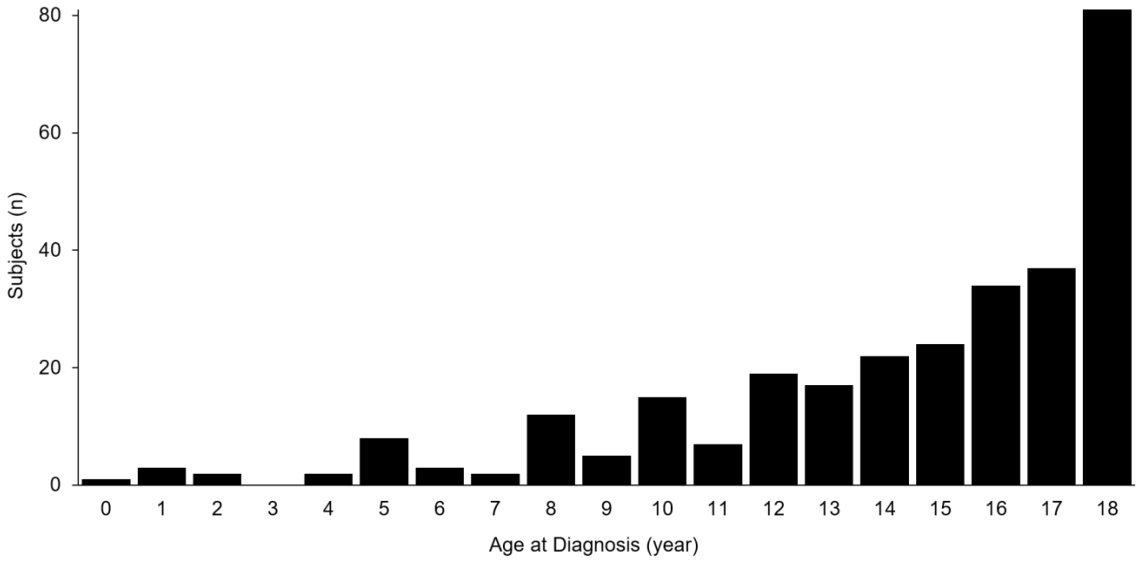
Supplementary Table 11. Sensitivity analysis: difference in observed and predicted eGFR within the treatment period in adulthood diagnosis and childhood diagnosis subjects, mixed polynomial eGFR prediction model

	Observed eGFR – Predicted eGFR (mL/min/1.73 m^2)						Paired T-test	
	N	**Mean**	**Median**	**SD**	**Min**	**Max**	**95% CI of Mean**	***p*-value**
Tolvaptan-treated								
CD	187	-1.51	-0.32	22.54	-47.61	84.61	(-4.76,1.74)	0.3618
AD	727	1.41	1.51	23.46	-74.58	98.12	(-0.29,3.12)	0.1044
Placebo-treated								
CD	97	-1.80	0.41	21.66	-58.43	51.61	(-6.17,2.56)	0.4148
AD	378	0.72	1.52	23.88	-67.83	73.98	(-1.70,3.13)	0.5588

The prediction equation is based on Yu et al, *Kidney Int* 2019;95:1253–1261;Supplementary Table S2: [2.40*age-0.04*(age^2)+60.79](if class A), [2.31*age-0.05*(age^2)+72.82](if class B), [0.38*age-0.04*(age^2)+121.58](if class C), [1.74*age-0.07*(age^2)+111.4](if class D), [2.87*age-0.11*(age^2)+98.06](if class E).
AD, adulthood diagnosis; CD, childhood diagnosis, eGFR, estimated glomerular filtration rate.

Supplementary Figure 1. Age at diagnosis in the childhood diagnosis (A) and adulthood diagnosis (B) groups in TEMPO 3:4

A



B