

# Arterial stiffness may predict renal and cardiovascular prognosis in autosomal-dominant polycystic kidney disease

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**Background and aims:** Autosomal-dominant polycystic kidney disease (ADPKD) is one of the most common causes of end-stage renal disease (ESRD). The most important cause of death among ADPKD patients is cardiovascular (CV). The aim of this study was to examine the prognostic significance of arterial stiffness on CV and renal outcomes in ADPKD. **Methods:** A total of 55 patients with ADPKD were examined. Pulse wave velocity was determined and stiffness index ( $SI_{DVP}$ ) was calculated. Combined primary endpoints (CV and renal) were major CV events (myocardial infarction, stroke, and CV intervention) as CV endpoints, and attaining of ESRD or start of renal replacement therapy as renal endpoints. Secondary endpoints were CV or renal endpoints separately. **Results:** The mean age of those 55 ADPKD patients was  $45 \pm 12$  years, 21 patients were male. The average value of the  $SI_{DVP}$  was  $11.11 \pm 2.22$  m/s. The patients were divided into two groups by the cutoff value of 11 m/s of  $SI_{DVP}$  and then outcomes were analyzed. In the higher arterial stiffness group ( $SI_{DVP} > 11$  m/s), occurrence of combined primary endpoint (CV and renal) was significantly higher than in the group with more elastic arteries ( $p = 0.033$ ). A statistically significant difference was found in the renal endpoints ( $p = 0.018$ ), but not in the CV endpoints ( $p = 0.952$ ) between the two groups. **Conclusions:** Increased arterial stiffness predicts the onset of ESRD in ADPKD. Assessment of  $SI_{DVP}$  appears to be a useful method for estimating the renal and CV prognosis in ADPKD.

**Keywords:** arterial stiffness, chronic kidney disease, autosomal-dominant polycystic kidney disease, renal function, renal prognosis

## Introduction

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common hereditary chronic kidney disease (CKD) with the prevalence of 1/400–1,000 live births (45). The majority of cases show autosomal-dominant inheritance. Mutations of two genes, polycystin 1 (PC1) and polycystin 2 (PC2), are responsible for development of the disease; however, the precise pathogenic mechanism remains unknown (20). The mutant PC1 and PC2 proteins modify the function of renal tubular cells. As a result, epithelial cell proliferation segmentally develops in the renal tubuli, and the tubulointerstitial matrix may be disorganized leading to the formation of growing cysts of various sizes. The clinical picture of ADPKD is

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characterized by the slow enlargement of the renal cysts, which gradually compress the normal kidney parenchyma, and thus the disease slowly progresses into end-stage renal disease (ESRD). The formation and enlargement of kidney cysts usually coexist with extrarenal CV manifestations, including intra- and extracranial aneurysms, heart valvular defects, and increased carotid intima-media thickness (11, 12, 23).

It is widely accepted that vascular dysfunction is common in ADPKD and CV complications are mostly responsible for the increased mortality of ADPKD patients (14, 41). More than 80% of CV complications are associated with dysfunction and disorders of the arteries (15) and one of the greatest contributors to CV dysfunction is stiffening of the large elastic arteries (25).

The aim of this study was to determine vascular function and to evaluate the prognostic significance of arterial stiffness on renal function and CV events in ADPKD patients. We examined whether increased arterial stiffness could be an independent predictor of major CV events (myocardial infarction, stroke, revascularization, and cardiac death) or ESRD. We also purposed to determine the prognostic cutoff arterial stiffness value by photoplethysmography. Such data are lacking in the literature as arterial stiffness has not yet been assessed with photoplethysmography in renal patients.

## Methods

### *Participants*

This study was started between April 2007 and December 2008 at the 2nd Department of Internal Medicine and Nephrological Centre, University of Pécs with 60 patients who had ADPKD. Local ethics committee approved the clinical study protocol (no. 3170/2008) and written informed consents were obtained from all participants. The diagnosis of ADPKD was made on the basis of clinical picture, physical examination, and the typical abdominal ultrasound morphology. Exclusion criteria were severe clinical conditions (NYHA III-IV heart failure, stroke and myocardial infarction within 3 months, uncontrolled cardiac arrhythmia, malignant disease requiring active treatment, and ongoing infection with fever). Patients with ESRD (CKD stage 5), renal replacement therapy, or kidney transplant were also excluded from the study.

### *Clinical assessment*

The modification of diet in renal disease formula was used to determine renal function [estimated glomerular filtration rate (eGFR): ml/min/1.73 m<sup>2</sup>]. The classical CV risk factors, such as hypertension, carbohydrate metabolism disorders (diabetes mellitus, impaired glucose tolerance, and elevated fasting glucose level), obesity, lipid abnormalities, and smoking, were also assessed at the first visit. The World Health Organization criteria were used for the definition of the metabolic syndrome. All enrolled patients were regularly examined at 3- to 6-month intervals (or more often if necessary). At visits, any adverse events since the last visit were interviewed, physical status was determined, and detailed laboratory tests were performed. Blood pressure was calculated as the average of three measurements after 10 min resting. Complete CV examinations (echocardiography, ergometry, coronarography, etc.) were carried out when it seemed to be necessary based on the patients' complaints. Abdominal ultrasound was performed on all patients every 2 years.

On follow-up, five patients did not attend the check-ups, thus their data were not analyzed.

### *Determination of vascular stiffness*

We used the finger photoplethysmography method by the Pulse Trace System (Micro Medical Ltd., Rochester, UK) to assess pulse wave velocity (PWV) as described earlier (21, 22). This method allows the determination of the stiffness index (SI), which can be derived from the digital volume pulse (DVP), and is reflected as  $SI_{DVP}$ . Briefly, DVP includes two distinct waves during the cardiac cycle: an early systolic one that originates from the pressure wave at the time of the left ventricular ejection, which could be measured in the finger artery, followed by a second peak due to a reflected wave from more peripheral segments, which usually form the aortic bifurcation. The SI is derived from body height relative to the time difference between the forward and reflected pulse waves:  $SI_{DVP} \text{ (m/s)} = \text{height}/\Delta t$ . The recorded pulse curve profile is principally determined by the PWV of the large arteries (8, 18). Based on literature data, the results of the method used here correlate with those of other methods, such as the central aortic PWV (34). Higher  $SI_{DVP}$  values indicate increased vascular stiffness (2, 6, 33).

Patients were allowed to take their regular medications. The participants were asked not to smoke and not to drink coffee on the day of the examination. All subjects were examined in supine position after at least 10 min of resting. Single waveform was obtained by averaging the DVP profiles for 30 s. To enhance the accuracy of the  $SI_{DVP}$  measurements, five period samples were taken and the upper and lower values of DVP were deleted. The remaining three values were averaged and used for further analysis, including the variability test. All measurements were performed in the morning hours between 9 and 11 a.m., thereby eliminating confounding effects of the circadian variability.

The data analyser was unaware of clinical information of the patients.

### *Statistical analysis*

All results are expressed as mean  $\pm$  SD for variables with normal distribution unless otherwise specified. Survival was examined by Mantel–Cox log-rank test. Cox regression analysis was used to evaluate the effects of factors on survival. Receiver operating characteristic (ROC) analysis was performed to determine the SI value that separates the two groups most appropriately for the outcome. Multivariate analysis was used to explore the factors that influence CV events and impaired renal function.

On the basis of the average SI value, the patients were divided into two groups at the cutoff point of 11 m/s, and the outcome of the two groups was analyzed and compared. The combined primary endpoint was the combination of myocardial infarction, stroke, or CV intervention as the CV endpoints or ESRD (CKD stage 5) and start of renal replacement therapy as the renal endpoints. Subsequently, CV and renal endpoints were analyzed separately as secondary endpoints.

Statistical analysis was performed using the SPSS software version 22.0, and  $p$  value of  $<0.05$  was considered as statistically significant.

## **Results**

A total of 55 ADPKD patients (21 males, mean age:  $45 \pm 12$  years) were analyzed. Patients were followed up for an average of  $63 \pm 32$  months. The clinical characteristics and occurrence of CV risk factors are summarized in Table I. The mean  $SI_{DVP}$  value was  $11.11 \pm 2.22$  m/s and the patients were divided into two groups at this cutoff value. Table I

Table I. Baseline characteristics of ADPKD patients

	ADPKD patients (n = 55)	SI ≤ 11 m/s (n = 27)	SI > 11 m/s (n = 28)	p value
Male/female (n)	21/34	8/19	13/15	0.103
Age (year)	45 ± 12	41 ± 10*	49 ± 11*	0.002
Follow-up time (month)	63 ± 32	67 ± 31	58 ± 33	0.156
Duration of ADPKD (year)	13.2 ± 9.2	12.8 ± 8.5	13.7 ± 9.7	0.364
eGFR (ml/min/1.73 m <sup>2</sup> )	72 ± 36	82 ± 37**	61 ± 31**	0.013
Stiffness index (m/s)	11.11 ± 2.22	9.44 ± 1.41***	12.71 ± 1.56***	0.001
<i>Metabolic syndrome components</i>				
Obesity [n (%)]	22 (40)	11 (37)	11 (39)	0.457
BMI (kg/m <sup>2</sup> )	28.5	28.4	28.5	0.453
Carbohydrate metabolic disorders [n (%)]	13 (24)	5 (18)	8 (28)	0.194
Dyslipidemia [n (%)]	26 (47)	13 (48)	13 (46)	0.450
Hypertension [n (%)]	46 (84)	21 (78)	25 (89)	0.128
Metabolic syndrome [n (%)]	13 (24)	5 (18)	8 (28)	0.194
Smoking [n (%)]	20 (36)	9 (33)	11 (39)	0.326
ACEI/ARB therapy [n (%)]	46 (84)	21 (78)	25 (89)	0.128

SI<sub>DVP</sub>: stiffness index; ADPKD: autosomal-dominant polycystic kidney disease; eGFR: estimated glomerular filtration rate; BMI: body mass index; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocking agent.

\* $p = 0.002$ .

\*\* $p = 0.013$ .

\*\*\* $p = 0.001$

shows the characteristic features of all patients and in the two subgroups. Patients with increased SI<sub>DVP</sub> (SI<sub>DVP</sub> > 11 m/s) were significantly older ( $p = 0.002$ ) and their renal function was significantly worse ( $p = 0.013$ ).

The occurrence of primary combined and secondary endpoints in the two subgroups are shown in Table II and Fig. 1A and B. Figure 1A shows that probability of the combined primary endpoint (CV and renal) was significantly higher in the subgroup with increased stiffness (SI<sub>DVP</sub> > 11 m/s) compared to the group with more elastic arteries (SI<sub>DVP</sub> ≤ 11 m/s), ( $\chi^2$ : 4.571;  $p = 0.033$ ). For the CV endpoint, there was no significant difference in the outcome between the two subgroups ( $\chi^2$ : 0.004;  $p = 0.952$ ) (data not shown). In contrast, probability of the renal endpoint was significantly higher with increased arterial stiffness ( $\chi^2$ : 5.591;  $p = 0.018$ ) (Fig. 1B).

We performed ROC analysis to determine the SI value obtained through the method finger photoplethysmography, which most appropriately separates the two subgroups for any outcome, and this SI<sub>DVP</sub> value was 10.66 m/s.

The Cox regression model showed that every 1 m/s increase of the SI increased the probability of the cumulative endpoint by 18.7% [odds ratio: 1.187 (CI: 1.001–1.408);  $p = 0.048$ ].

Table II. Occurrence of primary and secondary end points in the ADPKD patients

	Patients number ( <i>n</i> )	Primary, combined end points [ <i>n</i> (%)]	Secondary end points	
			Renal [ <i>n</i> (%)]	Cardiovascular [ <i>n</i> (%)]
SI <sub>DVP</sub> ≤ 11 m/s	27	12 (44)	9 (33)	3 (11)
SI <sub>DVP</sub> > 11 m/s	28	18 (64)	12 (43)	6 (21)
Total events [ <i>n</i> (%)]		30 (53)	21 (38)	9 (16)

SI<sub>DVP</sub>: stiffness index; ADPKD: autosomal dominant polycystic kidney disease

Multivariate analysis of variance was used to explore those factors that could predict CV events and renal functional decline, independently of other parameters; in this model, only baseline renal function (eGFR) has proved to be an independent prognostic factor for the combined CV and renal outcomes (Table III;  $p < 0.001$ ).

There were significantly more CV events in the group of patients with metabolic syndrome than in the group of patients without it ( $\chi^2$ : 6.246;  $p = 0.012$ ) (Fig. 2). SI<sub>DVP</sub> of the patients with metabolic syndrome was significantly higher than those of patients without it ( $12.1 \pm 2.3$  m/s vs.  $10.8 \pm 2.1$  m/s;  $p = 0.036$ ). Cox regression analysis showed that metabolic syndrome was an independent predictor for CV endpoints ( $p = 0.022$ ), but not for the combined primary and secondary renal endpoints (Table IV).

## Discussion

We have found that increased arterial stiffness was an independent prognostic factor for the combined CV and renal outcomes in ADPKD patients. Arterial stiffness measured by Pulse Trace System appears as a useful and applicable method for estimating the renal and CV prognosis in ADPKD.

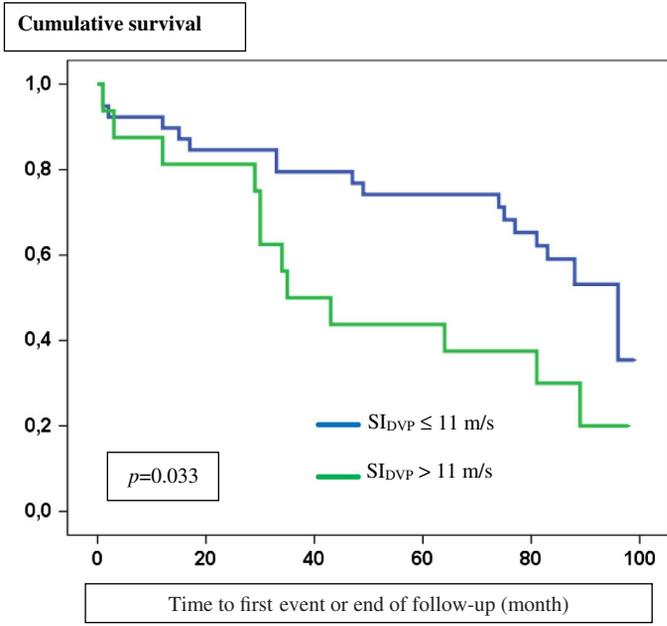
### *Increased arterial stiffness in CKD*

It was demonstrated several years ago that arterial stiffness is markedly increased in ESRD (9, 13, 17, 28, 29, 44). Recent data indicated that arterial stiffening is increased in CKD, even in patients with mild to moderate loss of renal function or in the presence of microalbuminuria (7, 46, 47, 50).

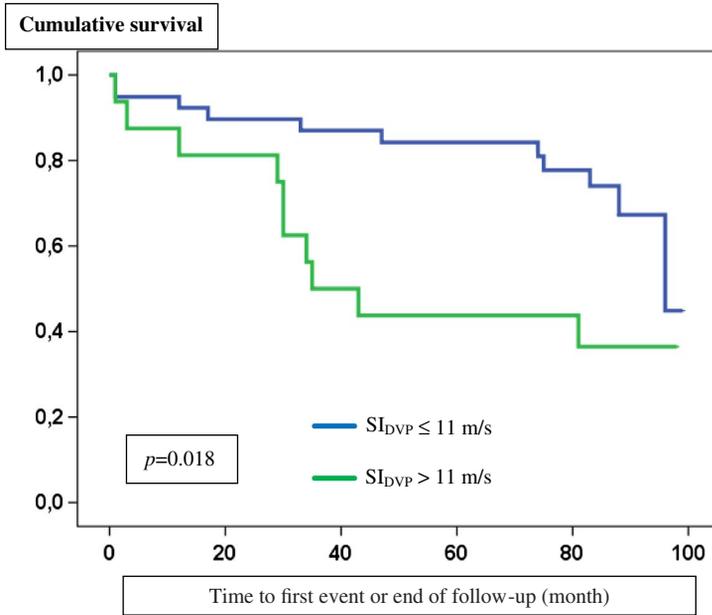
The pathophysiological mechanism of increased arterial stiffness observed in CKD is not entirely defined. Several putative mechanisms have been implicated, including chronic hypervolemia, chronic microinflammation, lipid peroxidation, suppression of the nitric oxide system, excessive sympathetic activity, activation of the renin–angiotensin–aldosterone system (RAAS), as well as increased mechanical stress due to either hypertension or the arterial wall calcification (19, 30).

### *Increased arterial stiffness and ADPKD*

ADPKD patients exhibit vascular dysfunction as increased arterial stiffness and this stiffness is evident very early in the course of ADPKD even in patients with normal renal function (5, 40). In a previous cross-sectional study, we showed that arterial stiffness is increased as the renal function declined in a homogeneous group of CKD patients with IgAN (22).



(a)



(b)

Fig. 1. (A) Primary, combined endpoints in ADPKD patients with  $SI_{DVP} > 11 \text{ m/s}$  versus  $SI_{DVP} \leq 11 \text{ m/s}$ . (B) Secondary renal endpoints in ADPKD patients with  $SI_{DVP} > 11 \text{ m/s}$  versus  $SI_{DVP} \leq 11 \text{ m/s}$

Moreover, we concluded that the etiology of CKD may also affect the degree of arterial stiffness by comparing IgAN and ADPKD patients, as our findings have shown that arterial stiffness develops earlier and the progression is more rapid in ADPKD than in IgAN patients with comparable renal function (22).

Table III. The prognostic role of each parameter in association with combined primary endpoints (multivariate analysis)

	<i>B</i>	SE	Wald	<i>df</i>	<i>p</i>	Exp ( <i>B</i> )
SI <sub>DVP</sub>	-0.049	0.114	0.182	1	0.670	0.952
Age	-0.017	0.022	0.603	1	0.437	0.983
eGFR	-0.055	0.010	28.208	1	<0.001	0.946
Gender	-0.884	0.455	3.786	1	0.052	0.413
Hypertension	-0.924	0.896	1.063	1	0.303	0.397
Carbohydrate metabolic disorder	0.016	0.507	0.001	1	0.975	1.016
Dyslipidemia	0.810	0.528	2.350	1	0.125	2.247
Obesity	-0.686	0.550	1.558	1	0.212	0.504

*B*: beta coefficient; SE: standard error; eGFR: estimated glomerular filtration rate

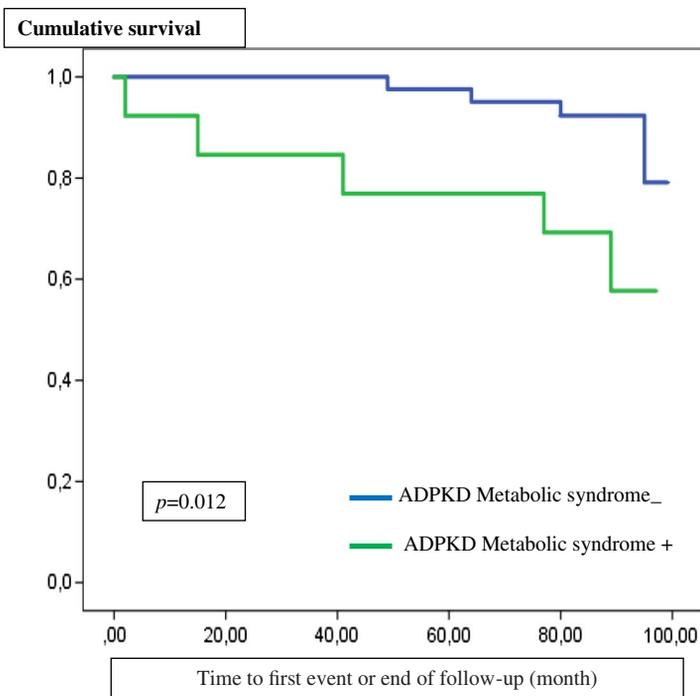


Fig. 2. Secondary cardiovascular endpoints in ADPKD patients with metabolic syndrome versus without metabolic syndrome

#### *The pathomechanism of the vascular lesions in ADPKD*

The pathomechanism of the premature CV lesions in ADPKD is not fully understood; however, several factors could be involved in the development of CV abnormalities in ADPKD. Nauli et al. (37) implied that vascular dysfunction in ADPKD may be a

Table IV. The prognostic role of metabolic syndrome in association with primary and secondary endpoints in ADPKD (Cox regression analysis)

	Hazard ratio	95% CI		Coefficient	SE	Z-statistic	p value
Primary, combined endpoints	2.046	0.949	4.410	0.716	0.391	1.827	0.067
Cardiovascular endpoints	4.676	1.239	17.641	1.542	0.677	2.277	0.022*
Renal endpoints	1.065	0.389	2.916	0.063	0.513	0.123	0.902

CI: confidence interval; SE: standard error; ADPKD: autosomal-dominant polycystic kidney disease.

\* $p = 0.022$

consequence of an inherited disorder of endothelial cilia. The disorder of the primary cilium, which covers the internal surface of endothelial cells of the blood vessels, may trigger a biochemical cascade mechanism leading to decreased nitric monoxide (NO) availability and endothelial dysfunction (1, 37). As a result, vascular remodeling by the cilium dysgenesis may develop due to impaired cell differentiation and altered connective tissue structure, thus leading to increased vascular rigidity. Consistently, the plasma concentration of NO was lower in ADPKD (16, 48, 49).

In another hypothesis, the cause of vascular complications in ADPKD could be explained by the polycystic kidney itself. Briefly, enlarged kidney cysts causing structural damage of the nephrons and distortion of the normal kidney structure lead to intrarenal ischemia that activates the RAAS system, which has important roles in CV remodeling. Activation of RAAS occurs very early in ADPKD patients, in both adults and children, often preceding the onset hypertension and renal failure (36, 39, 45). Hyperplasia of the renin-producing cells in the juxtaglomerular apparatus could be observed in the removed kidneys of ADPKD patients, referring to the involvement of RAAS activity (45). The vast majority of our ADPKD patients were treated with RAAS inhibitors, and thus we have no data to draw any conclusion on this.

Kocyyigit et al. (24) showed relationship between early arterial stiffness and inflammatory biomarkers in normotensive ADPKD patients by showing that arterial stiffness was increased prior to the onset of hypertension or renal function decline, and interleukin-6, tumor necrosis factor- $\alpha$ , and C-reactive protein levels were all significant predictors of PWV. This finding indicates the presence of low-grade, systemic inflammatory processes that contribute to early arterial damage and thus to the resultant arterial stiffness in ADPKD (24).

#### *Renal and CV outcome and increased vascular stiffness*

Epidemiologic longitudinal studies have clearly demonstrated that arterial stiffness has an independent predictive value of CV outcomes in different populations (10, 26, 27, 51). Blacher et al. (4) found that every 1 m/s elevation of PWV increased the CV and total mortality by 14% in ESRD. Recently, Nowak et al. (40) reported that impaired endothelium-dependent vasodilation and enhanced arterial stiffness were independent predictors of CV events and mortality in children and young adults with ADPKD having preserved renal function.

### *Metabolic abnormalities in ADPKD*

Mao et al. (32) described in a review that a wide range of metabolic abnormalities have been reported as part of the clinical spectrum of ADPKD. Pietrzak-Nowacka et al. (42) showed several components of metabolic syndrome, such as hypertension, abdominal obesity, and higher fasting blood glucose level in ADPKD. However, there remains uncertainty as to the consistency of these findings in different populations and the precise underlying molecular mechanisms that link them to the genetic defects in ADPKD (32).

In his reviews (11, 12), Ecker also calls attention to the early occurrence of CV complications in ADPKD and recommends multifactorial risk-reduction (hypertension, obesity, dyslipidemia, and smoking). Particularly, the most important is early detection of hypertension to prevent vascular complications and the use of angiotensin-converting enzyme inhibitor (ACEI) treatment to reduce CV events (11, 12, 35, 36). In this study, 84% of ADPKD patients take ACEI or angiotensin-receptor blocking agent to treat their hypertension, which could positively alter the  $SI_{DVP}$  and the CV outcome of the patients (31).

### *Methods for measurement of arterial stiffness*

Arterial stiffness can be measured by several methods (38). In this follow-up study, we applied finger photoplethysmography method using the Pulse Trace System to measure  $SI_{DVP}$ .  $SI_{DVP}$  is a composite parameter influenced by flexibility of the large central arteries as well as by reflective properties of the peripheral arteries. The usefulness of the  $SI_{DVP}$  was already successfully tested in healthy individuals and in patients with hypertension, diabetes mellitus, coronary arterial disease, and ESRD (3, 21). Furthermore,  $SI_{DVP}$  helped in risk stratification of both hypertensive and apparently healthy people with different CV risk factors (8, 18). However, the method was not used before our previous (22) and present studies for the stiffness measurement of ADPKD patients.

### *Study limitations*

The results of this study demonstrated that arterial stiffness measured by finger photoplethysmography has a prognostic value, although occasionally there are difficulties in registering the digital pulse volume. It may be problematic in some cases, mostly in elder patients to confidently separate systolic and reflective waves, and thus assess the SI. Atrial fibrillation and frequent atrial and ventricular ectopic activities could also limit the detection of correct pulse curves. We estimated and not measured the renal function; however, the use of eGFR is widely accepted throughout the literature. The study may be weakened by the low number of our cases. It is conceivable that study follow-up period was rather short to be sufficient to prove the difference in the occurrence of CV events and renal failure.

## **Conclusions**

We conclude that increased arterial stiffness predicts the occurrence of ESRD and CV endpoints in ADPKD, particularly, in patients with multiple CV risk factors; hence, early measurement of arterial stiffness can be recommended. Further studies are required with DVP (arterial SI) measurements using the Pulse Trace System to get this method widely accepted for predicting the renal progression and CV events in CKD.

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