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REVIEW

Cardiovascular Manifestations and Management in ADPKD

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Cardiovascular disease (CVD) is the major cause of mortality in autosomal dominant polycystic kidney disease (ADPKD) and contributes to significant burden of disease. The manifestations are varied, including left ventricular hypertrophy (LVH), intracranial aneurysms (ICAs), valvular heart disease, and cardiomyopathies; however, the most common presentation and a major modifiable risk factor is hypertension. The aim of this review is to detail the complex pathogenesis of hypertension and other extrarenal cardiac and vascular conditions in ADPKD drawing on preclinical, clinical, and epidemiological evidence. The main drivers of disease are the renin-angiotensin-aldosterone system (RAAS) and polycystin-related endothelial cell dysfunction, with the sympathetic nervous system (SNS), nitric oxide (NO), endothelin-1 (ET-1), and asymmetric dimethylarginine (ADMA) likely playing key roles in different disease stages. The reported rates of some manifestations, such as LVH, have decreased likely due to the use of antihypertensive therapies; and others, such as ischemic cardiomyopathy, have been reported with increased prevalence likely due to longer survival and higher rates of chronic disease. ADPKD-specific screening and management guidelines exist for hypertension, LVH, and ICAs; and these are described in this review.

Kidney Int Rep (2023) **8,** 1924–1940; https://doi.org/10.1016/j.ekir.2023.07.017
KEYWORDS: autosomal dominant polycystic kidney disease; cardiovascular disease; endothelial dysfunction; hypertension; intracranial aneurysms; valvular heart disease

ADPKD is the fourth most common cause of kidney failure worldwide and the most common monogenic cause of kidney impairment.[1] ADPKD is caused by autosomal dominant inheritance of pathogenic mutations (or *de novo* mutations) in either *PKD1* (∼78% of cases) or *PKD2* (∼15% of cases), which results in impaired function of proteins polycystin-1 or polycystin-2 respectively, or rarely mutations in other genes (such as *ALG5, ALG9, DNAJB11, GANAB*, or *IFT140*) that have an effect on polycystin function.[2,3] Polycystins have particular functional importance in renal tubular epithelial cells where its dysfunction leads to the hallmark finding of numerous, enlarging, fluid-filled cysts in the kidneys.[1] Cystogenesis occurs sporadically and is hypothesized to be triggered by a reduction in total functional polycystin-1 below a certain "threshold" level (∼10%–30% below normal).[4,5] The reduction may be due to a somatic mutation in the unaffected polycystin allele, localized kidney injury, environmental factors, and/or stochastic factors[4,5]

Loss of function of polycystin proteins in other cell types leads to extrarenal manifestations in ADPKD.[1,6] In vascular endothelial cells, vascular smooth muscle cells (VSMCs), cardiomyocytes, and cardiac fibroblasts, the reduction in polycystin-1 contributes to early development of CVD.[1,6] CVD is the most common cause of mortality and is a major cause of morbidity in patients with ADPKD.[6–8] The cardiovascular manifestations present in the second and third decade of life, often prior to development of kidney impairment, and the subclinical manifestations such as endothelial dysfunction and arterial stiffness present earlier.[7,9,10] The driving factors of CVD in ADPKD are enlarging cysts stimulating the RAAS and SNS combined with inherited dysregulation of vasoactive molecules (NO, ADMA, ET-1).[6,7] In addition, ciliary-related abnormalities in cell development and cell-to-cell communication in vascular endothelial cells, smooth muscle cells and cardiomyocytes predispose to the development of

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Received 16 March 2023; revised 27 June 2023; accepted 24 July 2023; published online 4 August 2023

arterial aneurysms and cardiac valvular disease.[9,11] The development of vascular abnormalities are also hypothesized to be due to the "threshold" mechanism of disease; however, this level varies between different tissues and cell types, and is independent of kidney cystogenesis.[4,12] CVD is a significant chronic condition that has acute and detrimental consequences. Changing clinical characteristics, increased patient education, and evolving therapies have resulted in increased patient survival but with the ongoing burden of high CVD risk.[6] Clinicians and patients should be vigilant about screening and initiating management early to improve outcomes. This review discusses the epidemiological risk factors, pathogenesis, screening, and management of CVD in ADPKD. Hypertension is the most common manifestation, and its severity impacts other conditions; therefore, it will be discussed first, followed by cardiomyopathies (LVH, ischemic cardiomyopathy, and others), valvular heart disease (mitral valve prolapse [MVP] and mitral regurgitation [MR]), ICAs, and other vascular malformations.

HYPERTENSION

Epidemiology and Clinical Associations

Hypertension is the most common presenting symptom of ADPKD, has a mean onset at 27 years old and occurs in 50%–70% of patients prior to decline in kidney function.[6,7] Hypertension is also common in children with ADPKD, with a 2016 meta-analysis reporting a 20% prevalence (95% confidence interval 15%–27%).[13] Hypertension is a major modifiable risk factor for the development of CVD and a key contributor to the development of LVH and albuminuria.[14] For pregnant women with ADPKD, hypertension leads to a significantly greater risk of preeclampsia (54% vs. 8% in normotensive women with ADPKD, $P < 0.001$), maternal complications (~85% vs. ~30% in normotensive ADPKD, $P < 0.001$) and kidney function decline (0.8% of hypertensive ADPKD pregnancies progressed to kidney failure compared to 0% in the normotensive ADPKD and 0.0001% in the general population).[15,16] In addition, the presence of hypertension is linked with increased severity of cystic kidney disease in children and adults.[17] Cohort studies (including the large longitudinal CRISP cohort) of hypertensive patients with ADPKD have shown significantly greater kidney sizes, rates of kidney growth, decline in kidney function, and progression to kidney failure compared to normotensive patients with ADPKD.[10,12,18–22]. Together, these findings reflect the central role of hypertension in cardiovascular and kidney disease progression in ADPKD.

Pathogenesis of Hypertension

The pathogenesis of hypertension in ADPKD occurs through 2 main mechanisms: (i) hypertension driven by cystic growth and renal dysfunction and (ii) hypertension driven by vascular dysfunction due to abnormal polycystin function.[23,24] The key downstream mediators of hypertension are the RAAS, NO, ADMA, ET, and the SNS.

Cystic Growth and Kidney Dysfunction as Drivers of Hypertension

Kidney cyst expansion leads to nephron obstruction and intrarenal microvascular ischemia stimulating the RAAS and SNS, and driving systemic hypertension.[25] Cohort and histological studies have shown that both circulating and intrarenal renin, angiotensin II, and angiotensin-converting enzyme (ACE) levels are increased in ADPKD.[26,27] Renin, aldosterone, and ACE activity was increased compared to patients with chronic kidney disease (CKD) and essential hypertension, implying an ADPKD-specific process contributing to RAAS overactivity (than renal dysfunction alone, another driver of RAAS activation).[24,26,27] Similarly, RAAS overactivity is detected in hypertensive patients with ADPKD prior to the development of renal impairment.[27,28] Focal ischemia of the parenchyma or the juxtaglomerular apparatus directly, stimulates renin secretion and RAAS activation.[29] Graham *et al.*[30] found additional renin secreting cells lining intrarenal vessels of ADPKD kidneys, which likely contribute to unregulated renin release and increased RAAS activity, particularly in patients with early or mild cyst burden. Graham *et al.*[30] also found hyperplasia of juxtaglomerular apparatus in ADPKD kidneys, a feature also found in noncystic CKD, which likely plays a role in RAAS overactivity in late ADPKD when kidney dysfunction is established. RAAS is also a stimulator of angiogenesis and renal epithelial cell growth contributing further to cyst growth and the persistence of hypertension in vicious cycle (Figure 1).[24,29]

In addition, kidney cyst growth leads to stretching of the renal capsule and the release of neuromodulator signaling molecules from injured kidney tissue (such as bradykinin, neurokinin A, calcitonin gene-related peptide, substance P, and prostaglandins) leading to stimulation of surrounding renal sympathetic nerves and increased SNS activity.[31–33] Angiotensin II also directly increases vascular sympathetic tone, leading to raised peripheral vascular resistance and blood pressure (Figure 1).[32,33] This is reflected in the published literature, where measures of SNS activity in patients with ADPKD are significantly increased compared to noncystic CKD, essential hypertension, and healthy controls.[32,34] In patients with ADPKD who are on

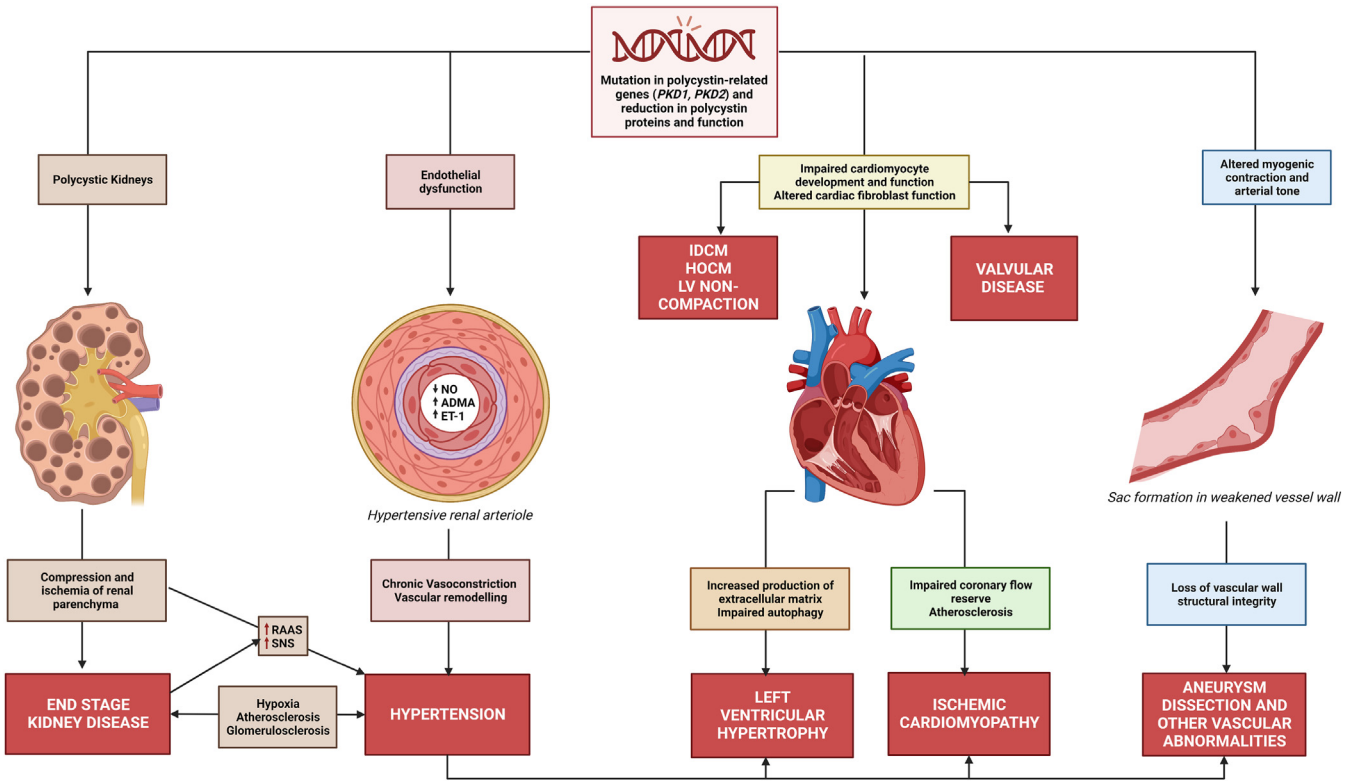

Figure 1. Pathogenesis of cardiovascular disease in ADPKD. Inherited abnormalities and reduction of functional polycystin-1 and polycystin-2 proteins impact multiple organ systems. Kidney cyst growth activates the RAAS and SNS, driving hypertension and other cardiovascular abnormalities. Endothelial dysfunction and chronic vasoconstriction lead to hypertension and vascular abnormalities, including arterial stiffness, thickening of vessel walls and atherosclerosis. These vascular changes also contribute to other arterial abnormalities such as intracranial aneurysms, dissections, and coronary artery disease. Hypertension is also a key risk factor for development of LVH and together contribute to the risk of coronary ischemia, likely predisposing patients to ischemic cardiomyopathy. Hypertensive arterial injury and development of cardiomyopathy leads to impaired end organ perfusion and atheroma development, which in turn, leads to renal injury with glomerulosclerosis and further RAAS activation in a pathogenic cycle. ADMA, asymmetric dimethylarginine; ADPKD, autosomal dominant polycystic kidney disease; ET-1, endothelin-1; HOCM, hypertrophic obstructive cardiomyopathy; IDCM, idiopathic dilated cardiomyopathy; LVH, left ventricular hypertrophy; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

dialysis, the morphological changes associated with SNS overactivity (increased renal nerve density and renal arterial sympathetic innervation) are significantly increased compared to non-ADPKD patients who are on dialysis, and these changes are thought to play a pivotal role in the persistence of hypertension in kidney failure.[33,35]

Chronic pain has an estimated prevalence of 50% to 60% in patients with ADPKD, and may contribute to SNS hyperactivity and hypertension.[36–38] Moreover, chronic pain is reported as a cause of sleep disturbance in 16.8%–20.8% of patients with ADPKD.[36,37] Pain may also contribute to poorer BP control through its potential role in loss of overnight decrease in BP and increase in early prewaking BP (a feature attributed to spikes in SNS overactivity) described in patients with ADPKD; however, the current evidence is circumstantial.[38] Further studies are required to evaluate the impact of chronic pain, SNS overactivity, and elevated BP in ADPKD. This may be of additional importance to other cardiovascular manifestations because SNS overactivity independently contributes to the development of LVH, arterial remodeling, arrhythmias, and heart failure.[39]

Vascular Dysfunction as a Driver of Hypertension and CVD

Endothelial dysfunction is pathogenic precursor to chronic CVD and has been detected in patients with ADPKD prior to the development of hypertension or LVH.[6] Endothelial dysfunction results in vascular abnormalities, including loss of flow-mediated dilation and increased arterial stiffness, which occur prior to hypertension, suggesting a role in its pathogenesis.[40,41]

Polycystins are expressed at high levels in the cilia of vascular endothelial cells where they sense fluid shear stress, detect minute changes to BP, and have a central role in flow-related endothelial response and performance.[42–45] In transgenic mice, endothelial PC-1 mediates Ca^{2+}-dependent hyperpolarization and vasodilation through the activation of nitric oxide synthase (NOS) and intermediate or small-conductance

K^+ channels.[46] PC-1 forms a complex with PC-2 which localizes to the plasma membrane of vascular endothelial cells.[46,47] The loss of either PC-1 and/or PC-2 reduces flow-mediated vasodilation and an increase in BP.[46–48] These conditional endothelial-specific knockout models provide evidence that CVD occurs prior to and independent of kidney impairment in ADPKD.[46–48]

However, as kidney impairment develops, mechanisms of hypertension common to other forms of CKD (such as increased RAAS activity and sodium retention) contribute to progression of CVD in ADPKD.[49] This was demonstrated by endothelial-*PKD1* knockout mice, where 5 of 6 nephrectomy exacerbated impaired flow-mediated dilation.[48]

Vascular endothelial cilia play a role in the regulation of cell division and endothelial-to-mesenchymal transition functions, which likely contributes to structural abnormalities such as vascular ectasias and MVP.[50] In VSMCs primary cilia, PC-1 and PC-2 play a role in cell-extracellular matrix interaction and responses to mechanical stimulation.[51] PC-2, localized to the plasma membrane on VSMCs, mediates sensing of intraluminal wall stretch, myocyte Ca^{2+} regulation, and modulation of myogenic tone.[52,53] Cell culture and animal models have demonstrated that the quantity of PC-1 and PC-2, and their relative balance, is important to modulate their action on myocyte constriction and myogenic tone.[45,54] The outcome of alterations of PC-2 in VSMCs in the current literature is conflicting. Studies of aortic arteries from $PKD2^{+/-}$ mice displayed exaggerated contraction to phenylephrine stimulus, whereas VSMC-specific *PKD2* knockout mice developed vasodilation and reduced BP in mesenteric and hindlimb arteries.[52,54] These differences may reflect variable expression between cell-specific and global constitutive knockout of *PKD2*.[45,52] Although the exact mechanisms require further elucidation, polycystin expression and function is variable between cell types and these changes are important in the pathogenesis of CVD. Due to these abnormalities in polycystin function, key mediators of endothelial function NO, ADMA, and ET-1 are dysregulated (through the mechanisms described below and contribute to hypertension and vascular complications, including aneurysm, dissection, and atherosclerosis (Figure 1).[50]

Reduced Nitric Oxide. NO is a potent driver of endothelial-mediated vasodilation and in normal conditions, PC-1 and PC-2 modulate flow-stimulated Ca^{2+}-dependent NOS activation, hyperpolarization, and relaxation in vascular endothelial cells.[46,47] The reduction or inhibition of this process leads to vasoconstriction and increased BP.[25,47] Zhang *et al*.[55] detected a >70% reduction in NO metabolites in 2 separate human ADPKD cell lines. Other clinical and preclinical studies have detected this decrease in NO levels and NOS activity in ADPKD.[55–58] This reduction has been detected prior to establishment of hypertension or kidney impairment, and has a negative linear correlation with BP in hypertensive patients.[56,59] Lorthioir *et al*.[58] demonstrated a reduction in NO release and heat-stimulated flow-mediated dilation in normotensive patients with ADPKD compared to healthy controls, which improved with infusion of dopamine (stimulation of endothelial dopamine receptors restores Ca^{2+} influx in polycystin-deficient cells). Although in contrast to other studies, baseline plasma nitrite was higher in the ADPKD group compared with controls in this study, nitrite levels did not increase in response to heating as they did in controls, demonstrating a deficiency in NO production.[58] These are supported by studies by Wang *et al*.,[59] who demonstrated a reduction in NO metabolites and maximal acetylcholine-induced vasodilation (in normal conditions acetylcholine increases NO by stimulating intracellular calcium and activating NOS) in normotensive patients with ADPKD. The effect could not be overcome or further suppressed by an NO substrate (L-arginine) or a NOS inhibitor (NG-nitro-L-arginine methyl ester, or L-NAME) implying an inherent inactivity of endothelial NOS in ADPKD.[57,59] Interestingly, ADPKD vessels responded to SIN-1, an exogenous NO-donor, to induce endothelial relaxation confirming that the endothelium in these normotensive patients were still able to respond to but unable to generate NO.[59] Although a reduction in NO is a pathological feature in diabetes and CKD-related hypertension, is it unclear if it occurs early in these diseases as it does in ADPKD.[59] Furthermore, there is persistence of NO deficiency until late stage ADPKD, with the development of characteristic sclerotic lesions in renal vessels (that are similar to those found in animals treated with NOS inhibitors), highlighting its pathogenic role in both early and late ADPKD.[60]

Increased ADMA and Oxidative Stress. ADMA is a potent NO-inhibitor and its levels are significantly increased in ADPKD compared to controls, including in patients with ADPKD with normal kidney function and BP.[25,60] ADMA suppresses endothelial NO stimulating vasoconstriction, increasing peripheral vascular resistance and promoting atherosclerosis.[25] ADMA is increased in all-cause CKD stage 3 onward, but is elevated early (CKD stage 1) in ADPKD.[60] Even modest increases in ADMA levels (as demonstrated in the study above) can inhibit vasodilation and further impair NO production.[60,61] Intravenous infusions of ADMA in healthy subjects significantly reduces renal blood flow

and vasodilatory responses; and in CKD rats, ADMA infusion resulted in glomerular capillary loss and vascular sclerosis.[62,63] Furthermore, elevated ADMA levels are a strong predictor of coronary vascular disease and mortality in patients with CKD.[64,65] Further studies are required to evaluate the long-term impacts of ADMA; however, given its role in vascular dysfunction and the documented elevated levels, it is likely an important mediator of CVD in ADPKD.

The cause of increased ADMA is not certain but has been linked to increased oxidative stress and decreased clearance early ADPKD.[25] Studies of patients with ADPKD with preserved kidney function demonstrated a significant increase in markers of oxidative stress (prostaglandin-2α, prostaglandin-D2, prostaglandin-E2, 8-isoprostane, and lipid peroxidation product 13-hydroxyoctadecadienoic acid), which are known to further decrease NO availability.[25,60,66,67] In addition, elevated oxidative stress is associated with vascular dysfunction (as measured by impaired flow-mediated dilation) further supporting the interaction of these pathways and their contribution to disease.[67]

Increased Endothelin-1. ET-1 is an endothelial-derived systemic and intraglomerular mediator of blood flow.[68] It acts as a vasoconstrictor in the renal cortex and a vasodilator in the renal medulla, and its actions are mediated by NO.[69] Focal ischemia, hypoxia, and increased angiotensin II caused by cyst growth are strong stimulators of ET-1.[69,70] It is speculated that ET-1 has a compensatory role in early ADPKD to maintain blood flow to medullary areas obstructed by cysts and to maintain sodium balance in the setting of tubular loss; however, this role becomes pathogenic as disease progresses, contributing to elevated BP and sodium retention, particularly in the setting of reduced NO mediation.[68–71]

The imbalances of these endothelial mediators, vascular dysfunction, and consequences of cyst growth lead to the development and persistence of hypertension, kidney impairment, and CVD in a pathogenic cycle (Figure 1).[63,72–74]

Management of Hypertension

Detailed screening and therapeutic recommendations, including lifestyle and pharmacological interventions are presented in Table 1. Briefly, all patients with ADPKD should be screened for hypertension at the time of diagnosis and during follow-up, and managed with standard lifestyle principles, which include low sodium diet (<100 mmol/d), regular exercise, weight loss (if overweight), and smoking cessation. Sodium intake in ADPKD can be assessed using the scored salt questionnaires and recommended dietary changes are similar to other types of CKD.[88–90] The first-line agents for antihypertensive therapy are ACE inhibitors (ACEi); or if not tolerated, angiotensin receptor blockers (ARB).[91] The effectiveness of ACEi/ARB was tested in the landmark HALT-PKD randomized controlled trials which used by a 2-by-2 factorial design to evaluate a lower BP target of 95/60 to 110/75 mm Hg (vs. standard BP targets of 120/70 to 130/80 mm Hg), and combination of ACEi-ARB (vs. ACEi) alone on annual percentage change in total kidney volume.[78] The results showed that lower BP targets were associated with slower kidney growth, lower left ventricular mass index and albuminuria.[78] These beneficial effects were greatest in participants with large kidneys (≥ 75th percentile total kidney volume) and under the age of 30 years, participants with total kidney volume greater than the median, and in male participants.[78] The combination therapy of ACEi-ARB did not alter the rate of annual total kidney volume increase or eGFR.

CARDIAC MANIFESTATIONS IN ADPKD

Left Ventricular Hypertrophy and Other Cardiomyopathies

Epidemiology and Risk Factors of LVH

LVH is a serious complication of ADPKD and its presence increases the risk of premature death and major cardiovascular events (including arrhythmias and heart failure), especially when LVH coexists with hypertension.[44,92] There is variability in the reported prevalence of LVH in ADPKD from 41% in a study in 1997 (Chapman *et al.*[93]), 21.4% in a 2019 study (Chen *et al.*[92]) and 3.9% in the HALT-PKD study (2006–2014).[44,78,92–94] Furthermore, a recent retrospective study in February 2023 (Arjune *et al.*[95]) reported a 65% incidence of LVH in patients with ADPKD compared with 55% in controls. A key difference between these studies is the imaging modality; HALT-PKD used cardiac magnetic resonance imaging (the current gold-standard to measure ventricular dimensions) and the other studies used ultrasound echocardiography (with variability from advances in echocardiogram technology in the 26 years between the 2 studies). The lower prevalence of LVH in more recent studies may also be due to altered diagnostic definitions; increased and earlier screening; and importantly, increased use of RAAS blockers (5% in the 1997 study, 63.5% in the 2019 study, and >80% before commencement of HALT-PKD).[78,92–94] Notably, when the same criteria for left ventricular mass in the HALT-PKD study was applied to the 2023 study, the incidence of LVH was found to be 5% (which is much more consistent with the HALT-PKD cohort).[94,95] The lower incidence of LVH seen in recent studies is likely due to more effective introduction of antihypertensive therapy.[92,94]

Table 1. Screening and management of cardiovascular manifestations in ADPKD

Hypertension
Screening
• Individuals with ADPKD or at-risk (family history or equivocal kidney ultrasound) should have annual BP measurement[75]
• ABPM and home BP recordings are recommended to diagnose early hypertension or masked hypertension
Targets
• BP ≤130/80.[76,77]
• A lower target 95–110 systolic and 60–75 mm Hg diastolic should be considered for selected patients in early disease stages (estimated glomerular filtration rate >60 ml/min per 1.73 m^2) and less likely to experience adverse effects. A lower target slowed rate of kidney growth and reduced left ventricular mass in the HALT-PKD studies but did not affect kidney function.[78]
• This target does not apply to patients with kidney failure. In these patients, higher BP was associated with better survival.[79]
• For children, consensus recommendation is to target blood pressure <75th percentile for their age.[80]
Non-pharmacological interventions
• Sodium restriction to <100 mmol/d (2.3 g sodium/d or 6 g salt/d).
• Smoking cessation, particularly because it is an independent risk factor for CVD and CKD.
• Maintenance of healthy weight (body mass index 20–25).
• Regular exercise for at least 30 minutes 5 days a week (as compatible with cardiovascular health).
Pharmacological interventions
• ACEi, or if not tolerated, ARB should be used as first-line agents for hypertension.
◦ Should be implemented with low-sodium diet to optimize effectiveness.[81]
◦ Dual RAAS blockade is not recommended.[78]
◦ Caution should be exercised with their use in child-bearing aged women due to their teratogenic risks.
• Choice of second-line agent is based on patient factors and comorbidities.
• Patients whose BP does not drop overnight (as evaluated by ABPM) may benefit from dosing antihypertensive at night.
• Other modifiable cardiovascular risk factors (such as hypercholesterolemia, smoking, and coronary artery disease) should be assessed and treated as per CKD guidelines.[82]
Left ventricular hypertrophy and other cardiomyopathies
Screening
• Diagnosis of cardiomyopathies are made by echocardiography.
• Screening is not recommended for LVH because management is currently focused on BP reduction.
• Patients with a family history of ventricular noncompaction or idiopathic dilated cardiomyopathy should have a screening echocardiogram.
Management
• Lifestyle interventions to reduce modifiable CVD risk factors as described for hypertension.
• Patients with LVH and hypertension should be treated with ACEi or ARB as first-line therapy.[76]
• Specific management of ischemic cardiomyopathy includes ACEi or ARB, beta-blockers, aspirin, statins, and revascularization where possible[83]
• Management of other cardiomyopathies should be individualized and include fluid management and optimization of cardiac function with ACEi/ARB, beta-blockers, diuretics, aldosterone antagonists, and digitalis, where indicated.
Valvular heart disease
Screening
• Adults and children with a heart murmur should be screened with an echocardiogram.
• Asymptomatic screening is not recommended.
Management
• Management is based on severity and patient comorbidities, and follows principles of heart failure management, which includes diuretic therapy, beta-blockers, and ACEi as needed.
• Patients with valvular disease have a higher risk of arrhythmias, and may require screening and treatment with anti-arrhythmics and anticoagulation.[84]
Intracranial aneurysms
Imaging should be done urgently for any patient with ADPKD and neurological symptoms (severe or atypical headache, history of transient ischemic attack, neurological deficits, cranial nerve palsy) because it may be due to an ICA or other intracranial vascular abnormality
Screening
• Screening is performed by computer tomographic angiogram or magnetic resonance angiogram (gold standard, "time of flight" MRI can be done without gadolinium)
• Screening is suggested for patients:
◦ With a family or personal of ICA or
◦ If in high-risk professions (e.g., commercial pilots) or
◦ Prior to major elective surgery (e.g., kidney transplant)
• Repeat screening scans every 5–10 years[85]
• Asymptomatic screening is controversial and consensus recommendations do not suggest screening due to low yield of significant ICAs and risk of undue patient anxiety[77,81]
Management
• Management is dependent on patient and aneurysm characteristics and should be made in consultation with neurosurgery.
• Small ICAs (<5 mm) may be monitored 6-monthly or 12-monthly and then possibly at longer intervals if they remain stable.
• Larger ICAs may require endovascular or surgical intervention.
• Ongoing risk factor modification with smoking cessation, rigorous blood pressure management to target BP <130/80 mm Hg and control of classic CVD risk factors.[85,86]
Abdominal Aortic Aneurysms
There are no ADPKD-specific guidelines for management of AAA and patients should be managed as per the general recommendations below.[87]
Screening
• Opportunistic screening during other investigations (e.g., ultrasound, CT, or MRI of the abdomen) is recommended by expert opinion.
• Single-episode ultrasonography screening is recommended for:
◦ Male patients aged >65 years old with a smoking history
◦ Patients aged >65 years old with an immediate family history of AAA
◦ Adult patients with personal or immediate family history of Marfan, Loeys-Dietz, or similar syndrome
◦ Patients with known thoracic or popliteal aortic aneurysms
Management
• is dependent on patient and aneurysm characteristics and should be made in consultation with vascular surgery.
• may involve active surveillance or intervention with either open repair or endovascular aneurysm repair.

AAA, abdominal aortic aneurysms; ABPM, ambulatory BP monitoring; ACEi, angiotensin-converting enzyme inhibitors; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin receptor blockers; BP, blood pressure; CT, computed tomography; CVD, cardiovascular disease; CKD, chronic kidney disease; ICA, intracranial aneurysm; IDCM, idiopathic dilated cardiomyopathy; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; PKD, polycystic kidney disease; RAAS, renin-angiotensin-aldosterone system.

Hypertension is a major risk factor in the development of LVH, and studies in ADPKD demonstrate a positive linear correlation with higher BPs and the presence of LVH.[96] In children with ADPKD, elevated or borderline (above the 75th percentile) BP led to significant higher rates of LVH compared with children with lower BP.[97,98] Particularly in "borderline" hypertensive patients, masked hypertension and loss of overnight decrease in systolic BP is a contributor to the development of LVH.[98,99] Although LVH is a well-known consequence of hypertension, multiple studies of normotensive children and young adults with ADPKD have also shown increased rates of LVH compared with non-ADPKD controls, including those with similar 24-hour BP readings.[24,92,93,100] Chen *et al*.[92] reported a similar prevalence of LVH in hypertensive (22.4%) and normotensive (17.9%) groups. Chapman *et al*.[93] reported a higher prevalence of LVH in normotensive ADPKD (23%) compared to healthy controls (16%); however, hypertensive ADPKD was significantly higher than both (48%). Therefore, hypertension is clearly a major driving factor for LVH in ADPKD; however, there are other predisposing mechanisms that lead to the increased prevalence of LVH in normotensive patients with ADPKD.

Kidney dysfunction and increased age are independent risk factors for the presence of LVH in ADPKD, similar to the non-ADPKD population.[38,93,94] Total kidney volume is also associated with LVH, independent of BP and kidney function.[92] Furthermore, high early morning or prewaking BP has been demonstrated in patients with ADPKD with LVH who did not have any other risk factors, suggesting that SNS overactivity may contribute to the development of LVH in ADPKD.[38]

Pathogenesis of LVH

The most commonly described trigger for LVH is an increase in volumetric burden on the left ventricle (usually due to hypertension or cardiac valvular disease) resulting in compensatory increase in myocardial hypertrophy leading to LVH. Over time, increased deposition of extracellular matrix and myocardial fibrosis results in ventricular stiffness and diastolic dysfunction.[101] Angiotensin II, a mediator of this process, is overactive in ADPKD.[24]

The dysfunction of polycystins in experimental knockout models of *PKD1* and *PKD2* show significant cardiac abnormalities, and this may explain the incidence of LVH in normotensive patients with ADPKD. Primary cilia, expressing PC-1 and PC-2, are present in cardiomyocytes (particularly endocardial-facing) during early fetal development and contribute to cardiac left–right axis development, valvulogenesis, and myocardial regeneration; however, these cilia are no longer expressed in adult animal models.[102,103] Instead, in adult rat cardiomyocytes, PC-1 localizes to the plasma membrane where it functions as a mechanosensor independently or in complex with PC-2.[104] Studies of cardiomyocytes in PC-1 knockout mice demonstrate reduced L-type calcium channels and intracellular signaling, increased cell proliferation leading to cardiac wall thickening, and reduced cardiac contractility compared to controls.[104,105] Primary cilia, which highly express PC-1 are also found in cardiac fibroblasts and these cells normally accumulate at the site of myocardial injury and regulate matrix deposition and fibrosis.[106] Impairment of fibroblastic cilia results in increased cardiac hypertrophy and fibrosis.[106] In the $PKD1^{RC/RC}$ mouse phenotype (which has a reduction but not complete loss of PC-1 expression), there is a dosage effect of PC-1 on the severity of the cardiac hypertrophy.[107]

PC-2 localizes to the sarcoplasmic reticulum and loss of PC-2 in murine cardiomyocytes leads to reduced cardiac shortening and cardiac dyssynchrony.[108,109] Furthermore, decreased PC-2 alters cardiomyocyte beta-adrenergic pathways in murine $PKD2^{+/-}$ without hypertension or cystic disease, and these changes may contribute to high incidence of atrial fibrillation reported in patients with ADPKD.[108,109] In addition, reduced PC-1 and PC-2 in ADPKD leads to dysregulation of mammalian target of rapamycin, an important regulator of autophagy, a process which maintains cardiomyocyte size, function, and structure.[110] PC-2 also has a role in inducing and regulating autophagy via its Ca^{2+-} conductance effects, independent of the mammalian target of rapamycin pathway.[111] Preclinical PKD studies show that reduced autophagy leads to left ventricular hypertrophy, dilation and contractile dysfunction.[44,110] These mechanisms together likely contribute to the development of LVH in ADPKD.

Management of LVH

Recommendations for management of LVH include rigorous BP control with use of a RAAS blocker as first-line therapy because ACEi and ARBs reverse the hypertrophic changes in the left ventricle (Table 1).[76] The current focus of treatment is based on BP reduction; however, it is not clear if this alters cardiac outcomes, particularly given that there is a subset of patients with LVH without hypertension.[92,93] In addition, in the large cohort HALT-PKD studies, the rate of serious cardiovascular events were unchanged despite a reduction in left ventricular mass index in the group with lower BP targets.[78] Further longitudinal studies with serial imaging are required to characterize the effects of treatment in patients with LVH and ADPKD.

It should be noted that LVH is a structural finding and does not accurately reflect cardiac function, particularly in those patients without other manifestations of CVD.[112] Therefore, the assessment of cardiac function should accompany investigations for LVH, including echocardiographic determination of ejection fraction and possible inclusion of newer methods to detect cardiac strain, such as 2-dimensional strain or global longitudinal strain.[112,113] Furthermore, there are studies reporting increased cardiac strain in patients with ADPKD (detected by increased left ventricular global longitudinal strain on echocardiography) with normal ejection fractions and preserved kidney function.[112,114] This subclinical sign of cardiac dysfunction is associated with decreased functional capacity (measured by 6-minute walk and timed up and go tests) and quality of life in CKD; however, further evaluation in ADPKD populations are required to determine its predictive long-term risk.[113,115]

Ischemic Cardiomyopathy

Ischemic heart disease is a major complication of CKD, but specific data in ADPKD is limited. Two large cohort studies, from China and Taiwan, reported a >2-fold higher incidence of myocardial infarction in patients with ADPKD, which was associated with increased severity of coronary disease and poorer cardiovascular outcomes compared with non-ADPKD controls.[116,117] In particular, Yang *et al.*[117] showed that those with ADPKD had a higher incidence of ST-elevation myocardial infarction (75% compared with 59%), sudden cardiac death (11.5% vs. 4.6%), need for coronary artery bypass grafting (7.7% vs. 5.4%) and higher overall mortality (13.5% vs. 6.2%). Most prior large ADPKD studies excluded patients with a history of ischemic heart disease and this may contribute to the relative paucity of data on ischemic cardiomyopathy in this group. However, clinical and preclinical studies show early vascular changes (as described above) lead to impairment of flow-mediated dilation and impaired coronary flow reserve in ADPKD.[118] The presence of hypertension and LVH contributes to these vascular changes leading to the premature development of arterial stiffness and cardiac dysfunction.[6,119] Increased levels of angiotensin II and ADMA also contribute to early atherosclerosis of coronary arteries.[50,119] Furthermore, in normotensive patients with ADPKD with normal kidney function, coronary artery velocity reserve was significantly decreased and carotid intima-media thickness was increased compared to non-ADPKD controls, suggesting changes to coronary vasculature that predispose to ischemia occur at an early stage.[119] Studies of human, mouse, and rat cardiac fibroblasts with loss of functional PC-1 demonstrate impaired myocardial healing from ischemic injury and alterations in scar architecture, increasing the risk of developing cardiomyopathy following myocardial infarction.[106] As with ischemic cardiomyopathy from other causes, the management principles in ADPKD include classic CVD risk factor modification, treatment with RAAS blockers, beta-blockers, aspirin, statin, and revascularization where possible.[83]

Other Cardiomyopathies

Other rare cardiomyopathies are reported in ADPKD, including idiopathic dilated cardiomyopathy, which is characterized by left ventricular dilatation and systolic dysfunction; and hypertrophic obstructive cardiomyopathy, which is characterized by asymmetrical LVH and diastolic dysfunction.[92] In a retrospective study of 667 patients with ADPKD who had echocardiographs, 58 had primary cardiomyopathy identified; idiopathic dilated cardiomyopathy was found in 5.8%, hypertrophic obstructive cardiomyopathy in 2.5%, and left ventricular noncompaction in 0.3%.[120] *PKD1* mutations were found in 100% ($n = 2$) of patients with noncompaction and those with *PKD2* mutations had twice the expected incidence of idiopathic dilated cardiomyopathy (36.8%, $n = 7$), suggesting that polycystin expression impacts the pathogenesis of these conditions.[120] Mutations in *PKD2* are linked with impaired intracellular calcium flux leading to decreased cardiac contractility, thin ventricular walls, and dilated cardiomyopathy; and (as described earlier in this review) mutations in *PKD1* can lead to cardiac hypertrophy and reduced myocyte fractional shortening, predisposing to the development of cardiomyopathies.[107,109,121]

Diastolic dysfunction is commonly reported in patients with ADPKD, usually in late disease stage with established kidney failure; however, it has also been reported in early disease prior to development of hypertension, LVH, and kidney impairment.[122–124] As with the LVH, polycystin-related dysfunction of cardiomyocytes and vascular cells (as described earlier in this review) are likely involved in the pathogenesis of diastolic dysfunction.[6] There is no specific ADPKD management guidelines for these cardiomyopathies and recommended therapy is described in Table 1.

Valvular Heart Disease

The patterns of cardiac valvular and structural heart disease vary as ADPKD progresses. In early disease, the most common valvular abnormality is MVP; and as disease progresses to kidney failure, mitral and aortic valve calcification and regurgitation are more common.[122] Identification of these conditions are important because their presence can lead to systolic and diastolic

dysfunction, heart failure, and (for MR in particular) arrhythmias.[125]

MVP is considered a classic extrarenal manifestation of ADPKD; however, recent reports of its prevalence vary between 0% and 26%.[125–131] In a study in 2001 (Lumiaho *et al.* [126]) of 109 patients with *PKD1* mutations, MVP was found in 26%, which was significantly higher than unaffected relatives (14%) and unrelated healthy controls (10%). In this study, MVP was present in greater portion in younger and normotensive groups with no association with gender or kidney function.[126] Hossack *et al.*[127] reported a similar prevalence of MVP (26%) in a study in 1988 in a cohort that predominantly had *PKD1* mutations detected by gene linkage. In a study in 1995 by Ivy *et al.*,[130] MVP was prevalent in 12% of children with ADPKD (compared to 3% non-ADPKD affected children from the same families) and its presence was associated with more severe renal phenotype (>10 cysts). However, a recent study in 2022 by Savis *et al.*[131] of 102 children and young adults with ADPKD, found 1 patient (0.98% prevalence) with MVP and 9 patients (8.8%) with changes that may represent early MVP changes or may be normal variation. Arjune *et al.*[95] found 6 out of 141 patients (4%) with MVP and another 2 studies in adults did not find any patients with MVP (Saggar-Malik *et al.*[128] and Miyamoto *et al.*[125]). Therefore, there is significant variability in the reported prevalence of MVP, and applicability of previous studies are limited by differences in genotype (greater portion of *PKD1* mutations), disease stage, presence of other comorbidities, changes in echocardiography technology, and diagnosis guidelines.[126,131,132] Further studies are needed to determine the true prevalence.

The presence of MVP in children, young adults, and normotensive patients suggests a connective tissue basis for its pathogenesis. Although the exact mechanism is still to be elucidated, likely mechanisms are: (i) polycystin-related ciliary dysfunction causing valvular cell growth abnormalities, altered valve geometry, myxomatous degeneration, and prolapse, or (ii) dysfunction of papillary muscle cell (which contain polycystin proteins) leading to abnormal valve biomechanics.[6,129,131]

MVP predisposes to MR because changes in the valve geometry can lead to separation of valve leaflets, particularly in the presence of increased left-sided preload as caused by hypertension and volume overload from kidney impairment and sodium retention.[129] In keeping with this, unlike MVP, the presence of other valvular abnormalities are associated with later disease stages when there is significant kidney dysfunction and progression of CVD.[133] Aortic valve calcification, mitral valve calcification, and MR were significantly more common findings in an ADPKD dialysis population (38%, 28%, and 8.6%, respectively) than MVP (4.3%).[133] Lumiaho *et al.*[126] also found a greater prevalence of grade 2 or 3 MR in *PKD1* patients (12.8% vs. 2.7%) and this was associated with age, systolic BP, and impaired kidney function, with no cases of MR in patients with normal kidney function. In a recent study of 65 patients with ADPKD of which approximately 30% had MR, Miyamoto *et al.*[125] found an increased prevalence of MR in those with *PKD1* mutations over *PKD2* or other ADPKD mutations (46.9% vs. 8.3% vs. 19.0%, respectively; $P = 0.02$); however, there were no other significant differences in prevalence of aortic regurgitation, mitral stenosis, or aortic stenosis between genotypes.[125] Arjune *et al.*[95] found a higher prevalence of 63% of MR in a study of 141 patients with ADPKD with CKD stages 1-4, although the authors have stipulated that most of these cases were of mild MR. Differences in diagnostic criteria may contribute to variability in the reported prevalence and uniform reporting guidelines in ADPKD would be beneficial in future research to evaluate the extent of these cardiac valvular manifestations.[134]

Current guidelines suggest echocardiographic evaluation of any cardiac murmur in ADPKD. Management of valvular abnormalities is based on the severity of patients' overall condition and follows the principals of heart failure management (Table 1).[84] There are no specific recommendations for ADPKD valvular disease.

VASCULAR MANIFESTATIONS

Intracranial Aneurysms

Epidemiology and Risk Factors for ICAs

Compared to the general population, ICAs are found in higher prevalence in the ADPKD population (9%–12% vs. 2%–3%) and present at a younger age (~40 years old vs. 51 years old).[85,86,135,136] Rupture of an ICA and resulting subarachnoid hemorrhage is catastrophic, and leads to death (in 30%–60%) or significant neurological deficits.[136–138] ICAs in patients with ADPKD are usually small (<5 mm in diameter) and found in the anterior circulation, with the exception of one large Finnish registry study where most ICAs were found in the middle cerebral artery, similar to the general population in Finland.[136,137,139,140]

The major known risk factor for the presence of ICAs in ADPKD is a positive personal or family history; and in this group, the prevalence of ICAs is reported as high as 22%.[135] The classic risk factors for ICAs such as the presence of hypertension, smoking and older age, also apply to the ADPKD population.[86] Furthermore, in studies from French and Japanese ADPKD cohorts,

females were significantly more likely to develop aneurysms than males.[136,139] In 2 Japanese studies, there was an association with more severe disease (reduced kidney function and larger kidney size) and the presence of ICAs.[141,142] Patients with *PKD1* mutations had a >2-fold increase in the risk of both ruptured and unruptured ICAs compared to those with *PKD2* mutations, with no significant influence from the type or location of the mutation.[136] These results from November 2022 are in contrast to with a previous case series from early 2003 that suggested that mutations in the 5′ region of *PKD1* correlated with increased risk of ICAs and rupture.[143]

Pathogenesis of ICAs

The increased incidence of ICAs in patients with ADPKD is due to inherited dysfunction of vascular endothelial and smooth muscle cells and is compounded by hypertension and CVD. Impaired ciliary function results in the vessels' inability to sense and react to fluid shear stress and loss of myogenic tone, leading to increased arterial wall stress, loss of structural integrity, sac formation, and expansion into an aneurysm (Figure 1).[85,123,136,144]

Management of ICAs

Given the high prevalence of ICAs in the ADPKD population, the decision to screen presymptomatic patients should be made in conjunction with the patient, taking into consideration their medical history and the potential for anxiety.[85,86,145] Screening is recommended for patients with family or personal history of ICAs.[85] Management should be decided in consultation with neurosurgery (Table 1).[85]

Other Vascular Malformations

The vessel wall abnormalities that lead to ICAs also predispose to the development of other vascular abnormalities. There have been case reports of dissections and aneurysms in most major vessels including aortic, coronary, carotid, cervicocephalic, and vertebral arteries.[132,144] Abdominal aortic aneurysms are reported as high as 5% to 10% in patients with ADPKD (vs. 2%–4% in the general population) with case reports of rupture resulting in devastating consequences.[138,146] Risk factors of hypertension, kidney dysfunction, age, and smoking predispose to abdominal aortic aneurysms formation and there are no specific recommendations for patients with ADPKD above the general guidelines (Table 1).[138] Dolichoectasias, which is the elongation and dilation of an arterial segment that can predispose to dissection or rupture, has been reported with increased incidence in a study of 178 patients with ADPKD (2%–2.5% in ADPKD vs. 0.06% in the general population).[147] Although these vascular malformations are a known feature of ADPKD, there have been no large registry, longitudinal, or systematic studies to determine the true burden of disease or provide specific screening guidelines. Expert opinion suggests that it is not unreasonable to extensively investigate patients with a strong personal or family history of vascular complications.[144] Management is specific to the vascular characteristics and organ involved, and treatment decisions should be made in conjunction with surgical or interventional teams.

CONCLUSIONS AND FUTURE DIRECTIONS

Longitudinal population studies in patients with ADPKD over the last decade have documented reduced rates of hypertension, LVH, and progression to kidney failure due to earlier diagnosis, engagement with healthcare professionals, and more rigorous CVD risk management.[17,148,149] Despite this, CVD remains the main cause of mortality, and patients with ADPKD experience more severe cardiovascular events than the general population and have risk factors that are not optimally controlled.[117,138,148] The pathogenesis of CVD is complex and evolves with progression of ADPKD during life. The clinical landscape of ADPKD therapies has changed with the introduction and increasing use of the vasopressin-2 receptor antagonist, tolvaptan, which is the first disease-modifying therapy that attenuates kidney cyst growth.[150] In addition, there are promising phase 3 trials with repurposed drugs (e.g., cystic fibrosis transmembrane conductance regulator modulator GLPG2737 [NCT04578548], and metformin [NCT04939935]) and evolving novel therapies (such as micro RNA inhibitors RGLS8429, which is currently undergoing a phase 1b trial) targeted at reducing cyst burden and maintaining kidney function.[151,152] It will be important to determine the impact of therapies that reduce cyst burden on CVD risk and outcomes, especially at different disease stages. The effect of statins to reduce oxidative stress and improve endothelial function have also been investigated in ADPKD.[153] Statin trials so far have had contradictory results, with a 3-year randomized controlled trial showing reduction in total kidney volume in children and young adults; however, other studies such as secondary analysis of the HALT-PKD study showed no effect. Nevertheless, a current trial (NCT03273413) is underway and further test its effects.[153–155]

Other research strategies in CVD and ADPKD should include further elucidation of the factors leading to endothelial dysfunction, particularly because much of

the research into some pathways, such as the role of ADMA, was published over a decade ago. In addition, because ADPKD-specific CVD can precede clinical kidney disease, development of therapies targeted at polycystin-related cardiovascular pathways are also required. Recently, dopamine receptor agonism was demonstrated to correct the reduction of Ca^{2+} influx, NO release, and flow-mediated vasodilation that occurs in ADPKD vascular endothelial cells and further research is required to determine its potential as a therapeutic target.[58,156] Other novel therapies could include approaches to attenuating early endothelial dysfunction by acting on the ADMA pathway, reducing SNS overactivity, and improving cardiomyocyte function.

Ongoing long-term longitudinal studies are required to determine the impact of any intervention on attenuating CVD in patients with ADPKD. To facilitate this, standardized outcome measures in ADPKD trials would be beneficial. Recent comprehensive reviews of the clinical ADPKD literature found significant variability study reporting, particularly in composite outcomes.[157,158] The 2020 international Delphi survey identified potential core outcome domains taking into account patient or care-giver and healthcare professionals' priorities, which may be considered in developing standardized outcomes.[159] Current therapeutic guidelines are appropriate and are based on general CVD and CKD recommendations; however, we await the release of the upcoming new version of the Kidney Disease: improving Global Outcomes ADPKD guidelines and determine the impact of recent trials on management recommendations.[157]

DISCLOSURE

The authors declare no competing interests.

ACKNOWLEDGMENTS

Funding

Funding provided by NHMRC (Project Grant 1164128), PKD Australia, and PS is supported by an ICPMR Jerry Koutts Scholarship for this work.

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