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Range and variability of outcomes reported in randomized trials conducted in patients with polycystic kidney disease: a systematic review

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Abstract

Rationale & objective: Trials in autosomal dominant polycystic kidney disease (ADPKD) have increased, but their impact on decision-making has been limited. Since heterogeneity in reported outcomes may be responsible, we assessed their range and variability in ADPKD trials.

Study Design: Systematic review.

Setting and Study Population: Adult participants in clinical trials in ADPKD.

Selection Criteria for Studies: We included trials that studied adults and were published in English. For trials that enrolled patients without ADPKD, only those enrolling ≥50% of participants with ADPKD were included.

Data extraction: We extracted information on all discrete outcome measures, grouped them into 97 domains, and classified them into clinical, surrogate, and patient-reported categories. For each category, we choose 3 most frequently reported domains and performed a detailed analysis of outcome measures.

Analytical approach: Frequencies and characteristics of outcome measures were described.

Results: Among 68 trials, 1413 different outcomes measures were reported. Ninety-seven domains were identified, 41 (42%) were surrogate, 30 (31%) clinical and 26 (27%) patient-reported. The 3 most frequently reported domains were in the surrogate category: kidney function (54, 79% trials; using 46 measures), kidney and cyst volumes (43, 63%; 52 measures), blood pressure (27, 40 %, 30 measures); in clinical category: infection (10, 15%; 21 measures), cardiovascular events (9, 13%; 6 measures), end-stage kidney disease (8, 12%; 5 measures); in the patient-reported category: pain related to ADPKD (16, 24%; 26 measures), pain for other reasons (11, 16%; 11 measures), diarrhea/constipation/gas (10, 15%; 9 measures).

Limitations: Outcomes measures were assessed for only the top 3 domains in each category.

Conclusions: The outcomes in ADPKD trials are broad in scope and highly variable. Surrogate outcomes were most frequently reported. Patient-reported outcomes were uncommon. A consensus-based set of core outcomes meaningful to patients and clinicians is needed for future ADPKD trials.

Key words: Autosomal dominant polycystic kidney disease, systematic review, outcomes, nephrology, epidemiology.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the leading cause of genetic kidney disease, which can be life-threatening[1]. Patients with ADPKD face a progressive disease course that often culminates in end-stage kidney disease (ESKD), which necessitates dialysis or kidney transplantation. Approximately 70% of patients with ADPKD require kidney replacement therapy by the age of 65 years[2]. ADPKD and its related complications including, cardiovascular, hepatic, digestive and neurological disease, and symptoms such as pain, can severely impair psychosocial well-being and lifestyle[3].

The past two decades have seen an increase in the number of randomized trials in patients with ADPKD. Since patients with ADPKD can experience a lengthy natural history of disease, the choice of outcomes in trials is challenging. Some events, such as the need for kidney replacement therapy, are unlikely to occur during the standard follow up time of a clinical trial. Therefore, trials in ADPKD have often focused on surrogate outcomes such as kidney volume and function[6-9]. Systematic reviews of pharmacological interventions in patients on ADPKD confirm absence of clinical outcomes like ESKD from many trial reports and demonstrate insufficient reporting on patient-reported outcomes such as pain[10]. Inconsistent reporting of outcomes of direct importance to patients and clinicians can limit decision-making and the ability to make reliable estimates of effect of interventions across trials. [4,5].

Detailed empiric evidence of outcome reporting in trials is not available in the context of ADPKD. The aim of this study was to assess the range and variability of outcome domains and measures reported in trials in ADPKD. This will inform the development of core outcomes sets that are important to patients with ADPKD, their families, and clinicians, for more consistent reporting of relevant outcomes to support decision-making.

Methods

Selection criteria

We searched MEDLINE, Embase, the Cochrane Kidney and Transplant Specialized Register, Australian and New Zealand Clinical Trials Registry (ANZCTR; www.anzctr.org.au), the European clinical trials register (www.clinicaltrialsregister.eu) and ClinicalTrials.gov to identify all randomized controlled trials (RCT) and protocols of RCT involving patients with ADPKD, up to 1 October 2019 (the search strategy is available in the supplementary appendix Table S1). We excluded trials that did not include adults (aged 18 years or over), and those published in languages other than English. For trials that also enrolled patients without ADPKD, only trials with at least 50% of patients with ADPKD were included.

Data extraction

For each trial, we extracted the following trial characteristics: first author, year of publication, participating countries, sample size, mean age of participants, study duration, intervention type, primary outcome, and all discrete outcome measures. A discrete outcome measure was defined as any measurement or event reported separately for all trial arms. All levels of specification of the outcome measures were extracted if reported, domain (e.g. kidney function), specific measurement (e.g. estimation of glomerular filtration rate [eGFR] by the modification of the diet in renal disease [MDRD] formula), method of aggregation (percentage change), specific metric (between the start and the end of the study period), and time point of measure from trial commencement[15,16].

Analysis

The discrete outcome measures from all included trials were classified into outcome domains by one reviewer (BS). The list of outcome domains was reviewed by two reviewers independently (AT

and YC) and any discrepancies were discussed to reach agreement about the classification (AT, BS and YC). These outcome domains were further grouped into three categories: surrogate (biochemical or physiological outcomes that may or may not be validated as a substitute for a clinical outcome e.g. hemoglobin), clinical (medical event or comorbidity diagnosed by the clinician e.g. cardiovascular disease), and patient-reported (outcomes reported directly by patients regarding how they feel or function), using standard definitions[17-21]. The classification was determined by the same three authors. The number of trials that reported each outcome domain was calculated. For each category (clinical, patient reported and surrogate outcome domain), we choose the three more frequently reported outcome domains and performed a detailed analysis of outcome measures to explore their heterogeneity. We performed descriptive analyses using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org/)

Results

Trial characteristics

We identified and included 68 trials involving 10750 participants (Figure 1). Thirty-six (53%) trials were published, one (1%) was protocol, and 31 (46%) were registered trials (unpublished). The year of publication/registration ranged from 2001 to 2019. The median (interquartile range [IQR]) duration of trials was 18 (6 to 24) months. The median (IQR) sample size of trials were 50 (29 to 100) participants. Fifty-nine (86%) trials assessed a pharmacological intervention, three (5%) evaluated a surgical intervention, and six (9%) assessed a dietary intervention. The trial characteristics are provided in Table 1.

Outcome measures and domains

Across the 68 trials, 1413 outcomes measures were reported. The median (IQR) number of outcome measures (defined as a different measurement, aggregation, metric and time point) was 11 (6 to 30) per trial. The median (IQR) number of outcome measures exclusive of time points was 7 (5 to 19) per trial. The 1413 outcome measures were classified into 97 outcome domains, of which 41 (42%) were surrogate, 30 (31%) were clinical, 26 (27%) were patient-reported outcomes. The top six most frequently reported outcome domains were kidney function (54, 79% trials), kidney and cyst volumes (43, 63%), blood pressure (27, 42%), proteinuria and albuminuria (22, 32%), unspecified adverse events (20, 29%) and pain (kidney, abdominal, epigastric (16, 24%]). Ninety outcome domains (93%) were reported in less than 20 % of trials. The proportion of trials reporting each outcome domain is provided in Figure 2. Mortality and ESKD were reported in 6 (9%) and 8 (12%) trials, respectively.

The number of unique outcomes measures and time points for nine outcomes domains (the top three outcome domains for each category– surrogate, clinical, patient-reported outcomes) are shown in Figure 3. The three most frequent surrogate outcomes were “kidney function” (54, 79% trials), which had 46 outcome measures (131 including time points), “kidney and cyst volumes” (43, 63% trials) which had 52 (88 including time points) outcome measures, and “blood pressure” (28, 41% trials) which had 30 (65 including time points) outcome measures (Figure 4 a-c).The specific measurement used for the three most frequent surrogate outcomes are detailed in Table S2 (supplementary appendix).The three most frequently reported clinical outcomes were “infection” (10, 15% trials), which had 21 (33 including time points) measures, “cardiovascular event” (9, 13% trials) which had 6 different outcome measures (14 including different time points), and “ESKD” (8, 12% trials) which had 5 (17 including time points) outcome measures (Figure 4 d-f). The three most frequent patient-reported outcomes were “pain (kidney, abdominal, epigastric)” (16, 24% trials), which had 26 outcome measures (42 including time points), “pain (other)” (11, 16% trials) which had 11 (18 including time points) outcome measures, and “diarrhea/constipation/gas/bloating

(10, 15% trials) which had 9 (16 including time points) outcome measures (Figure 4 g-i). The specific tools used to measure pain are detailed in Table S3 (supplementary appendix).
We performed a sensitivity analysis by category of outcome over time and assessed the proportion of trials that reported at least one outcome domain per category (clinical, patient reported and surrogate outcome domain) per time period. The results indicate a trend toward increasing frequency in clinical and patient reported outcome, but this was not significant (supplementary appendix Figure S1).

Characteristics of primary outcomes

Across the 68 trials, a primary outcome was specified in 56 (82%) trials; 47 (69%) trials specified a single primary outcome; and 9 (13%) specified multiple primary outcomes. The 47 studies reporting a single primary outcome were primarily surrogate (45, 66% trial) and less commonly clinical (1, 2% trial), and patient-reported outcomes (1, 2% trial). Among the 47 single primary outcomes, the two most frequently reported were kidney and cyst volumes (17, 27% trials) and kidney function (13, 19% trials).

Discussion

The outcomes reported in ADPKD trials are very broad in scope (97 outcome domains) and inconsistently reported across trials with 93% of these outcome domains reported in less than 20% of trials. Most (73%) outcome domains were either surrogate or clinical outcomes. The most frequently reported outcome domains were surrogate endpoints such as kidney function, kidney and cyst volumes, blood pressure and proteinuria/albuminuria. The most frequently reported clinical outcomes were infection, cardiovascular events and ESKD, which were reported in 16, 14 and 13% of trials, respectively. Mortality was reported in 9% of trials. Pain related to kidney cyst was the

most frequently reported patient-reported outcome, and it appeared in 24% of trials. There was also a large range and variability at the level of outcome measures, with 1413 different outcome measures reported across trials.

Studies have shown that patients are concerned about the need for dialysis or kidney transplantation and this clinical outcome has been consistently identified to be of highest priority among patients with ADPKD and health professionals[28-30]. However, because ADPKD is a slowly progressive disease, trials with clinical endpoints in ADPKD may not be feasible. For example, the HALT-PKD trial had a follow up of up to 7 years, yet only 10% of the participants required kidney replacement therapy[27]. Not surprisingly, ESKD has been reported in 13% of trials in ADPKD.

Instead, trials in ADPKD frequently report the outcomes kidney function and kidney and cyst volumes[7-9]. Although recent updates made by the US Food and Drug Administration and European Medicines Agency[22,23] recognize assessment of kidney function with eGFR as an appropriate intermediate endpoint for CKD, and total kidney volume is qualified by the Food and Drug Administration and the European Medicines Agency as a prognostic biomarker for selecting patients at high risk for a progressive decline in kidney function[24], the evidence to support the validity and applicability of these surrogate endpoints remain uncertain. We have shown that current outcome measures for kidney function and kidney volume reported in trials vary widely with 38 measures for kidney function and 55 measures for kidney and cyst volumes. Such variability in outcome measures limits reliable estimates of the effects of interventions across trials. Indeed, we demonstrate that 95% (92/97) of the outcome domains were reported in less than 30% of trials. This finding shows the potential for serious outcome reporting bias in meta-analysis of trials in ADPKD[37,38].

Patients with ADPKD suffer of very specific pains and troubles which are not found in other patients with CKD. Patients have described ADPKD as a "painful inheritance"[31]and the intense and unpredictable pain may be underrecognized by health professionals. Quality of life (QoL) in ADPKD is also known to be impaired in patients with ADPKD[32], and a recent systematic review found that QoL was lower in patient with ADPKD compared to the general population and was not associated with kidney function and kidney volume[33]. Our findings show that patient-reported outcomes were infrequently reported across trials in ADPKD. Despite being the most frequently reported patient-reported outcome, pain appeared in 16% of trials. Among other patient-reported outcomes reported in the ADPKD trials were side effects caused by the medications. Outcomes that have been highly prioritized by patients and caregivers with ADPKD include ability to work, mobility/physical function, and fatigue, which were reported in 2%, 9% and 11% trials, respectively[35].

The omission of patient-important outcomes in trials has also been noted in dialysis, kidney transplantation, and pediatric kidney disease[11,12,36]. This may be explained by the lack of patient-reported outcome measures (PROMs) that have been validated in this population. There are efforts to develop tools to measure and report patient-reported outcomes, such as the ADPKD Impact Scale (ADPKD-IS)[34], which was developed with input from patients and clinicians. The ADPKD-IS addresses three conceptual domains: physical, emotional and fatigue, and health related QoL and specific disease burden in ADPKD patients. It is important to obtain a consensus on which patient-reported outcome matter to all stakeholders in order to validate a specific measure in ADPKD trials. We suggest that further work is needed to establish feasible and validated PROMs to support consistent assessment and reporting of symptoms and life impact outcomes across trials.

This study provides detailed evidence of the heterogeneity of outcomes reported in trials in people with ADPKD. However, there are potential limitations. We only assessed outcomes reported in

trials and could not ascertain outcomes that were actually measured, recognizing that some outcomes may have been measured but not reported in the trial. Non-English trials were excluded but we expected that this could have underestimated the range and heterogeneity of outcomes. We did not analyze all the measures reported because of resource constraints and because additional evidence of further heterogeneity was unlikely to be more informative, instead we analyzed the outcomes measures for the top three most frequently reported outcomes domains for each category (surrogate, clinical, and patient-reported).

These results highlight the need for consensus on critically important outcomes to be measured and reported consistently in all trials involving patients with ADPKD, to ensure that trials address the shared priorities of patients, caregivers and health professionals, and thereby support better care and outcomes in ADPKD. As part of the global Standardized Outcome in Nephrology (SONG) initiative[14], SONG-PKD was recently launched to establish core outcomes with the involvement of patients, caregivers and health professionals.

The outcomes reported in ADPKD trials are varied, heterogeneous and focused on surrogate outcomes related to progression to ESKD. Clinical and patient-reported outcomes such as ESKD and pain are seldom reported. The development of a core outcome set for ADPKD will improve outcome reporting which will be of relevance and of importance to all stakeholders in clinical trials, and ultimately will strengthen trial-based evidence to inform decision-making in ADPKD based upon the outcomes that matter to patients, caregivers and health professionals.

Supplementary Material

Figure S1: Difference in the proportion of trials that reported at least 1 clinical, patient-reported, and surrogate outcome over time.
Table S1: Search strategy
Table S2. Specific measurements used for kidney function, kidney and cyst volume and blood Pressure
Table S3. Specific questionnaire used for pain

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Authors' contributions: Research design: all authors; Data collection: BS, YC, JCC, AT; Data analysis: all authors. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Table 1. Characteristics of included trials (n=68)

Trial characteristic	Number of trials (%)
Year of publication	
2001-2005	6 (9)
2006-2010	18 (26)
2011-2015	19 (28)
2016-2019	25 (37)
Duration of trial (months)	
< 6	10 (15)
6 – 11	8 (12)
12 – 23	16 (23)
24 – 35	20 (29)
≥ 36	14 (21)
Sample size (n)	
1 to 50	32 (47)
51 to 100	16 (24)
101 to 200	9 (13)
>200	11 (16)
Location	
United States of America	23 (34)
Europe	27 (40)
Asia	11 (16)
Oceania	2 (3)
Multinational studies	5 (7)
Intervention type	
Pharmacological	59 (87)
Dietary	6 (9)
Surgical	3 (4)

Figure 1. Search results

Figure 2. Frequency of outcomes domains reported in trials in autosomal dominant polycystic kidney disease.

Figure 3. Number of outcome measures and time points used for selected outcome domains.

Figure 4a-i. Outcome measures and time points reported for selected outcome domains.