KDIGO 2025 ADPKD GUIDELINE DATA SUPPLEMENT

Appendix A. Search strategies

Supplementary Table S1. Search strategies for systematic review topics

Search dates: Inception through October 10, 2023

Database	Search strategy
PubMed	("Polycystic Kidney Diseases"[mesh] OR "Polycystic Kidney, Autosomal Dominant"[mesh] OR (("autosomal dominant" OR autosomal-dominant) AND polycystic kidney disease*) OR ADPKD OR "Polycystic liver disease" [Supplementary Concept] OR (("autosomal dominant" OR autosomal-dominant) AND polycystic liver disease*) OR ADPLD) NOT ("address"[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case reports"[pt] OR "comment"[pt] OR "congress"[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "government publication"[pt] OR "historical article"[pt] OR "interview"[pt] OR "lecture"[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "comment"[ti] OR "Editorial" [Publication Type] OR "ephemera"[pt] OR "in vitro techniques"[mh] OR "introductory journal article"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR rat[tw] OR cow[tw] OR cows[tw] OR chicken*[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murinae[tw] OR cats[tw] OR cat[tw] OR dog[tw] OR dogs[tw] OR rodent[tw])
Embase	#1 'autosomal-dominant polycystic kidney disease' #2 'autosomal-dominant polycystic liver disease' #3 adpkd #4 adpld #5 OR/#1-4 #6 #5 AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [letter]/lim) AND [humans]/lim
Cochrane CENTRAL	#1 MeSH descriptor: [Polycystic Kidney Diseases] explode all trees #2 (("autosomal dominant" OR autosomal-dominant) AND polycystic AND (kidney OR liver) AND disease*) #3 ADPKD #4 ADPLD #5 OR #2 OR #3 OR #4

Appendix B. Concurrence with Institute of Medicine (IOM) standards for guideline development and Appraisal of Guidelines, Research and Evaluation (AGREE) reporting checklist

Supplementary Table S2. Guideline development checklist - IOM standards for development of trustworthy clinical practice guidelines (1)

IOM Standard	Description	Addressed in 2020 KDIGO BP in CKD guideline
Establishing transparency	Clear description on the process of guideline development.	See *Methods for Guideline Development*
Management of conflicts of interests	Disclosure of a comprehensive conflict of interests of the Work Group against a set-criteria and a clear strategy to manage conflicts of interest	See *Work Group Financial Disclosures*
Guideline group composition and guideline development	Appropriate clinical and methodological expertise in the Work Group The processes of guideline development are transparent and allow for involvement of all Work Group Members	For guideline group composition – see *Work Group Membership* For guideline development process see *Methods for Guideline Development*
Establishing evidence foundations for rating strength of recommendations	Rationale is provided for the rating the strength of the recommendation and the transparency for the rating the quality of the evidence.	See *Methods for Guideline Development*
Articulation of recommendations	Clear and standardized wording of recommendations	All recommendations were written to standards of GRADE and were actionable statements. Please see *Methods for Guideline Development*
External review	An external review of relevant experts and stakeholders was conducted. All comments received from external review are considered for finalization of the guideline.	An external public review was undertaken in October 2023
Updating	An update for the guidelines is planned, with a provisional timeframe provided.	The KDIGO clinical practice guideline will be updated. However, no set timeframe has been provided.

Abbreviations: BP: blood pressure; CKD: chronic kidney disease; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; IOM: Institute of Medicine; KDIGO: Kidney Disease Improving Global Outcomes

Supplementary Table S3. Adapted systematic review reporting standards checklist - IOM standards for systematic reviews (2)

Appropriate IOM systematic review standards	Addressed in 2020 KDIGO diabetes in CKD guideline
Methods	
Include a research protocol with appropriate eligibility criteria (PICO format)	See *Table 16 clinical question and systematic review topics in PICO format*
Include a search strategy	See *Appendix A*
Include a study selection and data extraction process	See guideline development process see *Methods for Guideline Development – Literature searching and article selection, data extraction*
Methods on critical appraisal	See *Methods for Guideline Development – Critical appraisal of studies*
Methods of synthesize of the evidence	See *Methods for Guideline Development – Evidence synthesis and meta-analysis*
Results	
Study selection processes	See *Methods for Guideline Development – Figure 57 – Search yield and study flow diagram*
Appraisal of individual studies quality	The summary of findings tables in Appendix C & D provide an assessment of risk of bias for all studies in a comparison between intervention and comparator.
Meta-analysis results	See *Appendix C & D* for summary of findings tables for meta-analysis results for all critical and important outcomes
Table and figures	See *Appendix C & D* for summary of findings tables

Abbreviations: CKD: chronic kidney disease; IOM: Institute of Medicine; KDIGO: Kidney Disease Improving Global Outcomes; PICO: population, intervention, comparator, outcome

Supplementary Table S4. AGREE checklist (3)

Checklist Item and Description	Reporting Criteria	Location
Domain 1: Scope and Purpose		
1. Objectives Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.	☐Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☐ Expected benefit(s) or outcome(s) ☐ Target(s) (e.g., patient population, society)	See *Methods for Guideline Development – Aim*
2. Questions Report the health question(s) covered by the guideline, particularly for the key recommendations	☐ Target population ☐ Intervention(s) or exposure(s) ☐ Comparisons (if appropriate) ☐ Outcome(s) ☐ Health care setting or context	See *Methods for Guideline Development – Table 16*
3. Population Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply	☐ Target population, sex, and age ☐ Clinical condition (if relevant) ☐ Severity/stage of disease (if relevant) ☐ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	See *Methods for Guideline Development – Table 16*
Domain 2: Stakeholder Involvement		
4. Group Membership Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence, and individuals involved in formulating the final recommendations.	☐ Name of participant ☐ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☐ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☐ A description of the member's role in the guideline development group	See *Work Group Membership*
5. Target Population Preferences and Views Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.	☐ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ☐ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	See *Methods for Guideline Development – Patient preferences and values*

Checklist Item and Description	Reporting Criteria	Location
6.Target Users Report the target (or intended) users of the guideline.	☐ The intended guideline audience (e.g., specialists, family physicians, patients, clinical or institutional leaders/administrators) ☐ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	See *Methods for Guideline Development – Aim*
Domain 3: Rigor of Development		
7. Search Methods Report details of the strategy used to search for evidence	☐ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☐ Time periods searched (e.g., January 1, 2004, to March 31, 2008) ☐ Search terms used (e.g., text words, indexing terms, subheadings) ☐ Full search strategy included (e.g., possibly located in appendix)	See *Methods for Guideline Development – Literature searching and article selection* See *Appendix A*
8. Evidence Selection Criteria Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale where appropriate.	☐ Target population (patient, public, etc.) ☐ Study design ☐ Comparisons (if relevant) ☐ Outcomes ☐ Language (if relevant) ☐ Context (if relevant)	*Methods for Guideline Development – Literature searching and article selection; Table 16*
9. Strengths & Limitations of the Evidence Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept	☐ Study design(s) included in body of evidence ☐ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☐ Appropriateness/relevance of primary and secondary outcomes considered ☐ Consistency of results across studies ☐ Direction of results across studies ☐ Magnitude of benefit versus magnitude of harm ☐ Applicability to practice context	See *Methods for Guideline Development – Critical appraisal of studies; See Table 16 and Appendixes C and D*

Checklist Item and Description	Reporting Criteria	Location
10. Formulation of Recommendations Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.	☐ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☐ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☐ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations, and the final vote)	See *Methods for Guideline Development – Developing the recommendations*
11. Considerations of Benefits and Harms Report the health benefits, side effects, and risks that were considered when formulating the recommendations.	☐ Supporting data and report of benefits ☐ Supporting data and report of harms/side effects/risks ☐ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☐ Recommendations reflect considerations of both benefits and harms/side effects/risks	See *Methods for Guideline Development – Balance of benefits and harms*
12. Link Between Recommendations and Evidence Describe the explicit link between the recommendations and the evidence on which they are based.	☐ How the guideline development group linked and used the evidence to inform recommendations ☐ Link between each recommendation and key evidence (text description and/or reference list) ☐ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	See *Methods for Guideline Development – Developing the recommendations; Grading the strength of the recommendations; The overall quality of evidence*

Checklist Item and Description	Reporting Criteria	Location
13. External Review Report the methodology used to conduct the external review.	☐ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☐ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☐ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☐ Outcomes/information gathered from the external review (e.g., summary of key findings) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	An external public review was undertaken in October 2023.
14. Updating Procedure Describe the procedure for updating the guideline.	☐ A statement that the guideline will be updated ☐ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☐ Methodology for the updating procedure	The KDIGO clinical practice guideline will be updated. However, no set timeframe has been determined.
Domain 4: Clarity of Presentation		
15.Specific and Unambiguous Recommendations Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.	☐ A statement of the recommended action ☐ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☐ Relevant population (e.g., patients, public) ☐ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☐ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	See *Guidelines*
16. Management of Options Describe the different options for managing the condition or health issue.	☐ Description of management options ☐ Population or clinical situation most appropriate to each option	See *Guidelines*

Checklist Item and Description	Reporting Criteria	Location
17. Identifiable Key Recommendations Present the key recommendations so that they are easy to identify.	☐ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☐ Specific recommendations grouped together in one section	See *Guidelines*
Domain 5: Applicability		
18. Facilitators and Barriers to Application Describe the facilitators and barriers to the guideline's application.	☐ Types of facilitators and barriers that were considered ☐ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☐ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☐ How the information influenced the guideline development process and/or formation of the recommendations	See *Guidelines*
19. Implementation Advice/Tools Provide advice and/or tools on how the recommendations can be applied in practice.	☐ Additional materials to support the implementation of the guideline in practice. For example: ☐ Guideline summary documents ☐ Links to check lists, algorithms ☐ Links to how-to manuals ☐ Solutions linked to barrier analysis (see Item 18) ☐ Tools to capitalize on guideline facilitators (see Item 18) ☐ Outcome of pilot test and lessons learned	See *Guidelines*

Checklist Item and Description	Reporting Criteria	Location
20. Resource Implications Describe any potential resource implications of applying the recommendations.	☐ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☐ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☐ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	See *Guidelines*
21. Monitoring/Auditing Criteria Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.	☐ Criteria to assess guideline implementation or adherence to recommendations ☐ Criteria for assessing impact of implementing the recommendations ☐ Advice on the frequency and interval of measurement ☐ Operational definitions of how the criteria should be measured	See *Guidelines*
Domain 6: Editorial Independence		
22. Funding Body Report the funding body's influence on the content of the guideline.	☐ The name of the funding body or source of funding (or explicit statement of no funding) ☐ A statement that the funding body did not influence the content of the guideline	See *Work Group Financial Disclosures*
23. Competing Interests Provide an explicit statement that all group members have declared whether they have any competing interests.	☐ Types of competing interests considered ☐ Methods by which potential competing interests were sought ☐ A description of the competing interests ☐ How the competing interests influenced the guideline process and development of recommendations	See *Work Group Financial Disclosures*

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Appendix C. Data supplement - Summary tables and evidence profiles cited in the guideline text

Supplementary Table S5. National/regional prevalence of ADPKD

Criteria: National or regional database of general populations

Study PMID (Reference)	Country / Region	Years	Data Source(s)	Sample Description	ADPKD Identification	Analysis Method	Prevalence (n/N) Incidence	Comment
Lanktree 2018 30135240 (1)	International (implied)*	Accessed 2017	Gnomad and BRAVO genomic sequencing databases	Unclear	Genomic sequencing	Simple (not model)	**PKD 1 mutations:** 6.8 (95% CI 5.0, 8.6) per 10,000 **PKD 2 mutations:** 2.6 (95% CI 1.4, 3.7) per 10,000 **PKD mutations (total):** 9.3 (95% CI 7.2, 11.5) per 10,000	Reported here are high-confidence mutations. Paper also reports likely PKD mutations.
Willey 2017 27325254 (2)	EU/EEA†	2012‡	EKFS–ADPKD UK GPRD ERA–EDTA	Population registry, national EMR, EU-wide registry	Based on registry data identification	Extrapolation from data sources across each other	**Minimum prevalence:** 3.29 per 10,000 (N=407,428,518) **Screening prevalence§:** 3.96 per 10,000 (N=407,428,518)	Based on prior epidemiologic studies of prevalence.
Neumann 2013 23300259 (3)	Germany, Southwest¶	2009-10	EKFS ADPKD Registry	Population-based registry	Entry in registry	Simple (not model)	**Overall prevalence:** 3.27 per 10,000 (891/2,727,351)	Some variability in point estimates per decade of age, but no information whether these differences were significant.
Yersin 1997 9351067 (4)	Seychelles	1993-95	All physicians and family members of k nown cases	All Seychelles inhabitants	Physician survey and investigation of family members	Simple (not model)	**3-yr prevalence:** 5.7 per 10,000 (42/74,331)	Primarily (possibly exclusively) among descendants of European ancestors. Much less prevalent among African and Asian ethnic groups.
Aung 2021 35419536 (5)	US	2002-18	Kaiser Permanente Southern California (KPSC) health system	Members of the KPSC health system, reflective of general population of Southern California	ICD-9, ICD-10	Simple (not model)	**Overall crude prevalence:** 4.26 per 10,000 (3868/9,071,375) **Overall age- and sex-standardized prevalence:** 4.15 per 10,000	Some variability in overall crude prevalence by race/ethnicity

Study PMID (Reference)	**Country / Region**	**Years**	**Data Source(s)**	**Sample Description**	**ADPKD Identification**	**Analysis Method**	**Prevalence (n/N) Incidence**	**Comment**
Suwabe 2020 31791998 (6)	US	1980-2016	Rochester Epidemiology Project and radiology databases of Mayo Clinic and Olmsted Medical Center	Patients at all medical facilities in Olmsted County, Minnesota	Medical record diagnostic codes and/or CT	Simple (not model)	**Prevalence of definite ADPKD on January 1, 2010** 4.7 (95% CI 3.5-5.9) per 10,000 **Prevalence of definite or likely ADPKD on January 1, 2010** 6.8 (95% CI 5.4-8.2) per 10,000 **Prevalence of definite, likely, or possible ADPKD on January 1, 2010** 12.4 (95% CI 10.5-14.3) per 10,000 **Annual incidence of definite ADPKD** 179 (95% CI 1.40-2.17) per 100,000 **Annual incidence of definite or likely ADPKD** 3.06 (95% CI 2.52-3.60) per 100,000 **Annual incidence of definite, likely, or possible ADPKD** 9.44 (95% CI 8.45-10.44) per 100,000	Some variability in annual incidence by age. Not nationally representative sample.
Willey 2019 31019924 (7)	US	2013-15	Truven Health MarketScan; National Ambulatory Medical Care Survey; USRDS	Insured[#]	ICD-9, ICD-10, and medical claims	Simple (not model) Prevalence is age-adjusted	**Commercial and Medicare Database** **Annual (1-yr, 2013) prevalence:** 1.74 per 10,000 (N=34,235,044) **Annual (1-yr, 2014) prevalence:** 1.97 per 10,000 (N=35,809,429) **Annual (1-yr, 2015) prevalence:** 2.10 per 10,000 (N=22,323,496) **Managed Medicaid Database** **Annual (1-yr, 2013) prevalence:** 2.26 per 10,000 (N= 4,721,746) **Annual (1-yr, 2014) prevalence:** 2.40 per 10,000 (N= 7,067,028) **Annual (1-yr, 2015) prevalence:** 2.20 per 10,000 (N= 7,688,020)	Age and gender differences found

Study PMID (Reference)	Country / Region	Years	Data Source(s)	Sample Description	ADPKD Identification	Analysis Method	Prevalence (n/N) Incidence	Comment
Willey 2021 33970726 (8)	US**	2016-17	IBM Marketscan Medicare	Commercially insured††	Diagnosis identified in database	Simple (not model)	**Annual (1-yr, 2017) prevalence**: 2.34 per 10,000 (4536/19,377,241) **2-yr prevalence**: 3.61 per 10,000 (5373/14,892,914)	Some regional and State-level variability existed

* "Multiple ethnicities including European, Finnish, African, South Asian, and Latino." Gnomad was "developed by an international coalition of investigators." BRAVO unclear. † Austria, Belgium, Croatia, Denmark, Estonia, Finland, France, Greece, Latvia, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the UK. ‡ Estimated for 2012 based on EKFS–ADPKD data from 2009-12, UK GPRD data from 1991-2008, and ERA-EDTA data from 2012. § Assuming intensive screening implemented in all countries. ¶ 11 administrative counties along the southern French and Swiss borders. # Excluding uninsured, but a sensitivity analysis comparing with a physician survey found similar estimates. ** Sampled by geographic regions, with oversampling from South. This oversampling does not appear to have been accounted for in the national estimates. †† Including those with Medicare Supplemental (retirees), but excluding uninsured and government-insured (Medicare non-Supplemental, Medicaid).
Abbreviations: ADPKD: autosomal-dominant polycystic kidney disease; CI: confidence interval; EU: European union; ICD: International Classification of Diseases; PKD: polycystic kidney disease

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Supplementary Table S6. Predictors for progression of kidney function in adults with ADPKD: Summary of consistency and direction of associations across multivariable analyses

Criteria: Multivariable analysis, ≥1 year follow-up

Factor	Strong + Assn (Higher Risk)	Weak* + Assn (Higher Risk)	Weak* − Assn (Lower Risk)	Strong − Assn (Lower Risk)	NS	No. Studies	Consistency	Association	Quality
Imaging: (ht)TKV		11			1	12	Consistent	Higher	Adequate
Lab: Kidney function, worse	**3**	12	1		7	23	Mostly	Higher, likely	Adequate
Genetics (PKD 1, trunc or non-trunc)	**3 (trunc)** **1 (PKD 1)**	2 (PKD 1) 1 (non-trunc)			3	10	Mostly	Higher, likely	Adequate
Tool: Mayo Imaging Classification		5			1	6	Mostly	Higher, likely	Adequate
Lab: Copeptin		3			1	4	Mostly	Higher, likely	Adequate
Dem: Age, older		9.5†	3.5†		10	23	Inconsistent	Unclear	Mixed
Early diagnosis	**2**			**1**	0	3	Inconsistent	Unclear	Mixed
Clinic: BP/HTN	**2**	7			8	17	Inconsistent	Unclear	Adequate
Early-onset HTN	**1**				1	2	Inconsistent	Unclear	Mixed
Lab: Uric acid	**2**	1			5	8	Inconsistent	Unclear	Adequate
Hx: Dyslipidemia	**1**				2	3	Inconsistent	Unclear	Adequate
Hx: Cardiovascular disease	**1**				2	3	Inconsistent	Unclear	Mixed
Hx: Diabetes				**1**	5	6	Consistent	NS	Adequate
Hx: Smoking					3	3	Consistent	NS	Mixed
Lab: Serum albumin					3	3	Consistent	NS	Adequate
Lab: Hemoglobin					3	3	Consistent	NS	Adequate
Dem: Sex (Female)			3	**2**	17	22	Mostly	NS, likely	Adequate
Clinic: Body size (e.g., BMI)		2			7	9	Mostly	NS, likely	Adequate
Urine: Proteinuria/Albuminuria		1			5	6	Mostly	NS, likely	Mixed

Includes only factors with data from at least 3 underlying studies.

* Or significant association of a continuous factor (e.g., per year of age). † One cohort had inconsistent results when analyzed by different researchers.

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; Assn: association; BMI: body mass index; BP: blood pressure; Dem: demographic, Ht: height; HTN: hypertension; Hx: history; No: number; NS: not significant; PKD: polycystic kidney disease; TKV: total kidney volume; Trunc: truncating.

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Supplementary Table S7. Comparison of different blood pressure targets (with antihypertensive treatment) in adults and children with ADPKD

Criteria: RCT, ≥1 year follow-up

Outcome	Population	# of Studies* (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
								Certainty of Evidence	Description of Findings	Importance of Outcome
Blood pressure	Pediatric	1 (1)	85	Serious limitations	N/A	Direct	Sparse	Very Low	SBP −6 (−15, 2) **DBP −6 (−11, −2)**	Critical
CKD: Kidney function	Adult	2 (2,3)	>557†	Some limitations	Consistent	Direct	Different measures used	Low	GFR‡ MD −0.3 (−1.1, 0.4) ml/min/1.73 m^2 per year	Critical
	Pediatric	1 (1)	85	Serious limitations	N/A	Direct	Sparse	Very Low	CrCl MD 1 (−21, 7) ml/min/1.73 m	
CKD: Kidney failure	Adult	1 (4)	75	Serious limitations	N/A	Direct	Sparse	Very Low	OR 1.44 (0.32, 6.50) RD (event rate 9%) 34 (−105, 172) per 1000	Critical
Ruptured ICA	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Mortality	Adult	1 (3)	558	No limitations	N/A	Direct	Highly imprecise	Very Low	OR 0.26 (0.01, 5.73) RD (event rate 0.7%) −7 (−17, 3.) per 1000	Critical
AEs, serious	Adult	1 (3)	558	No limitations	N/A	Direct	Sparse	Very Low	OR 0.87 (0.60, 1.27) RD (event rate 28%) −26 (−100, 47) per 1000	Critical
LVH	Adult	1 (3)	542	No limitations	N/A	Direct	Sparse	Low	**LVMI rate −0.60 (−0.93, −0.27) per year**	Important
	Pediatric	1 (1)	75	Serious limitations	N/A	Direct	Sparse	Very low	LVMI −2 (−10, 6)	
CKD: TKV	Adult	1 (3)	553	No limitations	N/A	Direct	Sparse	Low	**MD −1.0% (−1.6, −0.3) per year**	Important
	Pediatric	1 (1)	75	Serious limitations	N/A	Direct	Sparse	Very low	NS in 3 comparisons in different subpopulations	
Balance of Potential Benefits and Harms: ***Adults*** Possible lack of difference in effect on kidney function but better reduction in LVMI with lower BP target. Insufficient evidence for other outcomes, including harms								**Certainty of Overall Evidence:** ***Adults*** Low		
Children Insufficient evidence								***Children*** Very Low		

Outcomes without a row for pediatric (or adult) studies were not reported by the study conducted in children (or adults). * Treats the subanalyses in Cadnapaphornchai 2009 and MDRD (Klahr 1995) as all one study each. † The number of people analyzed for this outcome was not reported by Klahr 1995. ‡ Schrier 2014 (HALT PKD A) (3) reported estimated GFR. Klahr 1995 (MDRD) (2) reported measured GFR.

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AEs: adverse events; BP: blood pressure; CrCl: creatinine clearance; CKD: chronic kidney disease; DBP: diastolic blood pressure; GFR: glomerular filtration rate; ICA: intracranial aneurysm; LVH: left ventricular hypertrophy; LVMI: left ventricular mass index; MD: mean difference; N: number; N/A: not applicable; NS: statistically nonsignificant; OR: odds ratio; RD: risk difference; SBP: systolic blood pressure; TKV: total kidney volume.

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Supplementary Table S8. Comparison of RASi versus other antihypertensives in adults with ADPKD

Criteria: RCT, ≥1 year follow-up

Outcome	Comparison	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
								Certainty of Evidence	Description of Findings	Importance of Outcome
Blood pressure	RASi vs. non-RASi	3 (1,2,3)	102	Some limitations	Consistent	Direct	Various comparisons†	Moderate	**Sum SBP −1.8 (−3.0, −0.6)** **Sum DBP −2.8 (−4.6, −1.0)**	Critical
CKD Progression (Δ eGFR)	RASi vs. non-RASi	3 (1,2,3)	102	Some limitations	Inconsistent	Direct	Various comparisons	Low	Sum eGFR −0.5 (−8.7, 7.7)	Critical
Ruptured ICA	RASi vs. no RASi	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Mortality	RASi vs. no RASi	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Adverse event, serious	RASi vs. no RASi	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
LVH	RASi vs. no RASi	1 (3)	37	Some limitations	N/A	Direct	Single small study	Very Low	LVMI −0.3 (−4.0, 3.4)	Important
CKD Progression (Δ TKV)	RASi vs. no RASi	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Balance of Potential Benefits and Harms: RASi probably better control BP than other antihypertensives, but choice of RASi versus other antihypertensive may not impact CKD progression								**Certainty of Overall Evidence:** Low		

Abbreviations: Δ: change, ACEi: angiotensin converting enzyme inhibitor; ADPKD: autosomal dominant polycystic kidney disease; ARB: angiotensin receptor blocker; BB: beta blocker; CCB: calcium channel blocker; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; ICA: intracranial aneurysm; LVH: left ventricular hypertrophy; LVMI: left ventricular mass index; N: number; N/A: not applicable; OR: odds ratio; RASi: renin–angiotensin–aldosterone system inhibitor; RD: risk difference; SBP: systolic blood pressure; SCr: serum creatinine; Sum: summary (by meta-analysis).

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Supplementary Table S9. Comparison of nephrectomy versus no nephrectomy in adults with ADPKD

Criteria: Comparison of nephrectomy vs. no nephrectomy, related to transplant

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Graft loss	5 (2,3,5,6,10)	2002 vs. 868	Serious limitation*	Consistent	Direct	None	Low	Sum OR 1.02 (0.77, 1.34) Sum RD (sum event rate 11%) 2 (−24, 36) per 1000	Critical
Allograft function (eGFR)	1 (4)	27 vs. 60	Serious limitation †	N/A	Direct	Sparse, incomplete data	Very Low	Difference 0.2 ml/min (no SD reported)	Critical
Quality of life (various)	2 (2, 11)	164 vs. 230	Serious limitations	Consistent	Direct	Sparse per measure	Low	No differences	Critical
Functional outcomes	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Native kidney symptoms:							(none)	(none)	
RCC	1 (1)	51 vs. 0	Serious limitations	N/A	Indirect ‡	Sparse	Very Low	9.8% (histopathology)	Critical
Cyst Infection	1 (9)	31 vs. 32	Serious limitations †	N/A	Direct	Sparse	Very Low	**OR 0.15 (0.03, 0.76)**	Important
Death, ≥1 year	6 (3,5,6,8,9,10)	1067 vs. 844	Serious limitations*	Consistent	Direct	None	Low	Sum ES 0.80 (0.57, 1.13) Sum RD (sum event rate 14%) −29 (−62, 19) per 1000	Critical
Surgical complications:									
CD ≥IV	4 (1,2,5,10)	370 vs 532	Serious limitations	Consistent	Direct	Imprecise	Very Low	Sum OR 0.66 (0.14, 3.25)	Important
CD ≥III	4 (1,2,5,10)	370 vs 532	Serious limitations	Some inconsistency	Direct	Imprecise	Very Low	Sum OR 1.22 (0.38, 3.85)	Important
Transfusion	1 (7)	1677 vs 17,624	Some limitations	N/A	Direct	Sparse	Low	**adjOR 2.06 (1.44, 2.95)**	Important
Delayed graft function	4 (4,6,9,10)	235 vs. 249	Serious limitations †	Consistent	Direct	None	Low	Sum OR 1.04 (0.67, 1.60) Sum RD (sum event rate 19%) 8 (−64, 116) per 1000	Important
Balance of Potential Benefits and Harms: No evidence of a difference in critical outcomes of graft loss or post-transplantation death. Possible increased risk of post-surgical blood transfusion. A suggestion of lower risk of native kidney cyst infections. No evidence of a difference in delayed graft function. Unclear evidence regarding relative complication rates. No evidence of difference in long-term quality of life.							**Certainty of Overall Evidence:** Low		

* Most analyses were crude (unadjusted). † All analyses were crude (unadjusted). ‡ No study addressed question of difference in rates of clinical renal cell carcinoma.

Abbreviations: adjOR: adjusted odds ratio; ADPKD: autosomal dominant polycystic kidney disease; CD: Clavien Dindo classification; eGFR: estimated glomerular filtration rate; ES: effect size; N/A: not applicable; OR: odds ratio; RCC: renal cell carcinoma; RD: risk difference; Sum: summary.

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Supplementary Table S10. Comparison of bilateral versus unilateral nephrectomy in adults with ADPKD

Criteria: Comparison of bilateral vs. unilateral nephrectomy, related to transplant

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Graft loss	0						(none)		Critical
Allograft function (eGFR)	0						(none)		Critical
Quality of life (SF-36)	1 (2)	97	Serious limitations	N/A	Direct	Sparse	Very Low	Better SF-36 PCS after bilateral nephrectomy in long-term follow-up. No difference in QoL measures.	Critical
Functional outcomes	0						(none)		Critical
Psychosocial	0						(none)		Critical
Native kidney symptoms: Cyst Infection	0						(none)		Critical
Renal cell carcinoma	0						(none)		Important
Death, ≥1 year	0						(none)		Critical
Surgical complications	1 (1)	30	Serious limitations	N/A	Direct	Highly imprecise	Very Low	Total: OR 2.79 (0.58, 13.3)	Important
Delayed graft function	0						(none)		Important
Balance of Potential Benefits and Harms: Insufficient evidence							**Certainty of Overall Evidence:** Very Low		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; eGFR: estimated glomerular filtration rate; N: number; N/A: not applicable; OR: odds ratio; PCS: physical component summary; QoL: quality of life.

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Supplementary Table S11. Comparison of different timing of nephrectomy (in relation to time of transplant surgery) for receiving a kidney transplant in adults with ADPKD

Criteria: Comparison of pre-, simultaneous, and post-transplant nephrectomy

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Graft loss	5 (1-4,7)	248 vs 316	Serious limitations*	Consistent	Direct	Imprecise	Very Low	Pre vs. post/with: Sum OR 1.17 (0.63, 2.15) Sum RD (sum event rate 13%) 21 (−47, 148) per 1000	Critical
Allograft function (SCr or GFR)	3 (1,6,8)	149 vs 78	Serious limitations	Unclear	Indirect	Limited data	Very Low	Pre vs. with: No evident difference in SCr or GFR at follow-up	Critical
Quality of life (SF-36)	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Functional outcomes	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Native kidney symptoms:	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Death, ≥1 year	6 (1-5,8)	339 vs 348	Serious limitations*	Consistent	Direct	None	Low	Pre vs. post/with: **Sum OR 1.85 (1.03, 3.32)** Sum RD (sum event rate 8.0%) 68 (2, 186) per 1000	Critical
Surgical complications:	0	0	N/A	N/A	N/A	N/A	(none)	(none)	N/A
CD V	2 (4,6)	2186 vs. 303	Some limitations	Consistent	Direct	Sparse †	Low	Pre vs. post/with: **Sum OR 6.61 (1.25, 34.9)**	Critical
CD ≥IV	5 (1,3,5,6,8)	286 vs 288	Serious limitations	Consistent	Direct	Very imprecise ‡	Very Low	Pre vs. post/with: Sum OR 1.45 (0.50, 4.23)	Important
CD ≥III	5 (1,3,5,6,8)	286 vs 288	Serious limitations	Consistent	Direct	Imprecise	Low	Pre vs. post/with: Sum OR 2.02 (0.82, 4.98)	Important
Transfusion	3 (1,6,7)	2242 vs 326	Some limitations	Consistent	Direct	Imprecise	Low	Sum OR 0.62 (0.22, 1.72)	Important
Delayed graft function	3 (1,6,8)	146 vs 78	Serious limitations*	Inconsistent	Direct	Very imprecise	Very Low	Pre vs. with: OR 4.07 (0.55, 30.35)	Important
Balance of Potential Benefits and Harms: Possible increased risk of all-cause mortality and of in-hospital mortality (CD V) after transplantation in those who had pre-transplantation nephrectomy compared with post-transplant or simultaneous nephrectomy. No evidence of difference in graft loss or risk of transfusion at the time of transplantation in those who had pre-transplantation nephrectomy. Unclear if risk of other surgical complications differs.							**Certainty of Overall Evidence:** Low		

* Most analyses were crude (unadjusted). † One of two studies was small and highly imprecise. ‡ Two studies had zero events.

Abbreviations: adjOR: adjusted odds ratio; ADPKD: autosomal dominant polycystic kidney disease; CD: Clavien Dindo classification; GFR: glomerular filtration rate; N: number; N/A: not applicable; OR: odds ratio; RD: risk difference; SCr: serum creatinine; Sum: summary.

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Supplementary Table S12. Comparison of different surgical approaches for nephrectomy (HALN vs. open surgery) in adults with ADPKD

Criteria: Comparison of different surgical approaches

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Graft loss	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Allograft function (eGFR)	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Quality of life (SF-36)	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Functional outcomes	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Native kidney symptoms:	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Death, ≥1 year	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Surgical complications: CD V (Death)	3 (1,3,4)	133 vs. 49	Serious limitations	Consistent	Direct	Very imprecise*	Very Low	Sum OR 0.61 (0.14, 2.70)	Critical
CD ≥IV	2 (1,3)	75 vs. 36	Serious limitations	Consistent	Direct	Very imprecise	Very Low	Sum OR 1.30 (0.16, 10.5)	Important
CD ≥III	3 (1,3,5)	87 vs. 48	Serious limitations	Consistent	Direct	Imprecise	Low	Sum OR 1.89 (0.63, 5.66)	Important
Any	3 (1-3)	127 vs. 68	Serious limitations	Inconsistent	Direct	Very imprecise	Very Low	Sum OR 0.70 (0.17, 2.90)	Important
Transfusion	2 (1,3)	75 vs. 36	Serious limitations	Consistent	Direct	None	Low	**Sum OR 0.32 (0.12, 0.82)**	Important
Delayed graft function	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Balance of Potential Benefits and Harms: No evidence on benefits, but possible lower risk of transfusion with HALN than open surgery, but no evidence of differences in overall surgical complications							**Certainty of Overall Evidence:** Very Low		

* One study with 0 events.

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; CD: Clavien Dindo classification; eGFR: estimated glomerular filtration rate; HALN: Hand-assisted laparoscopic nephrectomy; N: number; OR: odds ratio; Sum: summary.

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Supplementary Table S13. Comparison of peritoneal dialysis versus hemodialysis in adults with ADPKD

Criteria: Direct comparison of PD vs. HD in ADPKD, ≥1 year follow-up

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Quality of life	N/A	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Functional	N/A	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	N/A	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Harms: Peritonitis	1 (4)	122 vs. 244	No limitations	N/A	Direct	Sparse, but precise	Low	**adjOR 1.72 (1.11, 2.68)** RD (event rate 45%) 322 (49, 750) per 1000	Critical
Pain	N/A	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Bulk symptoms	N/A	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Mortality	3 (1,2,4)	764 vs. 4930	Some limitations	Consistent	Direct	Some imprecision	Low	Sum ES 0.95 (0.58, 1.56) Sum RD (sum event rate 14%) −7 (−59, 78) per 1000	Critical
Residual kidney function	N/A	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Tolerability	3 (1,2,3)	712	Serious limitations	Consistent	Indirect	Incomplete reporting, large "effect size"	Low	Switch to HD vs. to PD: 21-27% vs. 1.4-6%	Important
Dialysis efficiency	N/A	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
BP control	N/A	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Harms: Hernia	1 (4)	122 vs. 244	No limitations	N/A	Direct	Sparse	Very Low	adjOR 1.64 (0.63, 4.27) RD (event rate 6.6%) 25 (−26, 75) per 1000	Important
Balance of Potential Benefits and Harms: No evidence of difference in mortality on PD vs. HD, with sparse evidence that about 21-27% switch from PD to HD. Possible increased risk of peritonitis with PD, but no evidence of increased risk of hernia.							**Certainty of Overall Evidence:** Low		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; adjOR: adjusted odds ratio; BP: blood pressure; CKD: chronic kidney disease; ES: effect size; HD: hemodialysis; ICA: intracranial aneurysm; LVH: left ventricular hypertrophy; N: number; N/A: not applicable; PD: peritoneal dialysis; RD: risk difference; Sum: summary.

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Supplementary Table S14. Comparison of peritoneal dialysis in adults with ADPKD versus adults with other forms of CKD

Criteria: Comparison of PD in ADPKD vs. General population, ≥1 year follow-up

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Quality of life	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Functional	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Harms: Peritonitis	10 (1-8,11,12)	867 vs. 5295	Some limitations	Consistent	Direct	None	Moderate	Sum OR 1.00 (0.77, 1.29) Sum RD (sum CR 31%) 0 (−71, 90) per 1000	Critical
Pain	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Bulk symptoms (e.g., cramping, breathlessness)	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
All-cause mortality	11(1-8,10-12)	1597 vs. 17,547	Some limitations	Inconsistent	Direct	None	Low	Sum OR 0.67 (0.34, 1.36) Sum RD (Sum CR 20%) −66 (−132, 72) Time to death: Median 6.0 vs. 5.6 yr, P=0.02 [1 study]	Critical
Residual kidney function	1 (1)	106 vs. 212	Serious limitations	N/A	Direct	Single study	Very Low	Net diff −0.8 (−1.7, 0.1)	Critical
Tolerability	8 (1,2,4,7,8,11)	741 vs. 5366	Some limitations	Consistent	Direct	None	Moderate	Switch to HD: Sum OR 1.01 (0.82, 1.25) Sum RD (Sum CR 23%) 0.5 (−44, 56) per 1000 Technique failure Sum OR 0.91 (0.76, 1.10) Sum RD (Sum CR 22%) −19 (−53, 21) per 1000 Time to failure: Median 6.2 vs. 6.5 yr, P=0.26 [1 study]	Important
Dialysis efficiency	3 (1,2,11)	242 vs. 1848	Serious limitations	Some inconsistency	Direct	None	Low	Sum Diff Kt/V −0.03 (−0.13, 0.07) Diff CrCl (total) 2.8 (−17.2, 22.8) [1 study] Weekly Kt/V >1.8 OR 2.26 (1.00, 5.08) (reported P=0.06) RD (control rate 84%) 80 (10, 150) per 1000 [1 study]	Important
BP control	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Harms: abdominal wall hernia	4 (1,3,4,6)	138 vs. 883	Serious limitations	Consistent	Direct	None	Low	**Sum OR 3.49 (1.67, 7.30) Sum RD (Sum CR 15%) 369 (99, 932) per 1000**	Important
Balance of Potential Benefits and Harms: No evidence of difference in mortality, dialysis/kidney outcomes or tolerability of PD between ADPKD and nonADPKD patients, but increased risk of abdominal wall hernia on PD (but not peritonitis) among patients with ADPKD							**Certainty of Overall Evidence:** Low		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; BP: blood pressure; CKD: chronic kidney disease; CR: capability ratio; CrCl: creatinine clearance; Diff: difference; HD: hemodialysis; ICA: intracranial aneurysm; LVH: left ventricular hypertrophy; N: number; N/A: not applicable; OR: odds ratio; PD: peritoneal dialysis; RD: risk difference; sum: summary; yr: year.

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Supplementary Table S15. Comparison of tolvaptan versus no tolvaptan in adults and children with ADPKD

Criteria: RCTs only (and extension studies of RCTs), N≥10 per group

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD: eGFR*	6 (2,3,5-8)	3454	Some limitations	Consistent	Direct	None	Moderate	Sum Net Diff 1.3 ml/min/yr (1.0, 1.7) **eGFR decrease ≥33%** **RR 0.63 (0.38, 0.98) [1 study]**	Critical
CKD: TKV	3 (2,3,8)	3828	Some limitations	Consistent	Direct	Meta-analysis effectively a single study †	Low	**Sum Net Diff −2.7%** (−3.3, −2.1) **Ratio of TKV Δ 0.91 (0.88, 0.94)**	Critical
Liver size	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Death	1 (4)	1074	Some limitations	N/A	Direct	Single study Imprecise	Very Low	OR 0.22 (0.03, 1.89) RD (event rate 0.9%) −7 (−15, 2) per 1000	Critical
Pain	1 (3)	1445	Some limitations	N/A	Direct	Single study	Low	**Any kidney pain event** **HR 0.64 (0.48, 0.86)**	Critical
Harms: Liver injury	1 (1)	6711	Some limitations ‡	N/A	Direct	Noncomparative	Low	0.06% serious or potentially fatal liver events; 0 deaths due to tolvaptan	Critical
Quality of life	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Functional	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Bulk symptoms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
ADPKD complications: UTI	2 (3,5)	2810	Some limitations	Consistent	Direct	None	Moderate	**Sum OR 0.65 (0.50, 0.86)** **Sum RD (sum event rate 10%)** **−36 (−51, −14) per 1000**	Important
Harms: Polyuria	2 (2,4)	1142	Some limitations	Partly consistent§	Direct	Large effect size	Moderate	**Sum OR 2.32 (1.70, 3.17) §**	Important
Harm: Serious thirst	2 (2,4)	1165	Some limitations	Inconsistent	Direct	Imprecise	Very Low	Sum OR 1.85 (0.23, 14.4)	Important
Extrarenal manifestation	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Harms: D/C due to AE	3 (2,4,5)	2531	Some limitations	Inconsistent	Indirect**	Imprecise	Very Low	Sum OR 1.73 (0.34, 8.68)	Important
Balance of Potential Benefits and Harms: Tolvaptan slows reduction of eGFR and growth of TKV and may reduce the risk of kidney pain events. Risk of serious liver injury, but no overall evidence of harms compared with no treatment. Evidence does not suggest differential effect based on evaluable clinical factors or patient characteristics.							**Certainty of Overall Evidence:** Moderate		

* We omitted the pooled analysis by Zhou 2022 (PMID 35570988), which included many of the same participants as in the other studies. Findings were consistent. This count of studies

includes three RCTs and extension studies for two of the RCTs. † Two studies included in meta-analysis, one of which (Mekahli 2021 conference abstract) adds only 2% of the weight in the meta-analysis. ‡ Interim analysis with incomplete reporting into database. § Fixed effect meta-analysis since random effects model produced inconsistent result due to extreme heterogeneity of effect size estimates, both of which were statistically significant. ** Unclear if truly treatment-related

Abbreviations: Δ: change; ADPKD: autosomal dominant polycystic kidney disease; AE: adverse events; CKD: chronic kidney disease; D/C: discontinuation; Diff: difference; eGFR: estimated glomerular filtration rate; HR: hazard ratio; htTKV: height-adjusted total kidney volume; N: number; N/A: not applicable; OR: odds ratio; RCT: randomized controlled trial; RD: risk difference; RR: risk ratio; Sum: summary; TKV: total kidney volume; UTI: urinary tract infection; yr: year.

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Supplementary Table S16. Comparison of dietary or lifestyle interventions to slow ADPKD progression in adults with ADPKD: Water intake

Criteria: Comparison, ≥1 year of follow-up, N ≥10/group

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD Progression (ΔeGFR)	1 (1)	184	No limitations	N/A	Direct	Sparse	Very Low	eGFR Net Diff: 0.07 ml/min (−1.00, 1.14)	Critical
Quality of life	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Functional outcomes: Pain	1 (1)	184	No limitations	N/A	Direct	Sparse	Very Low	Grantham PKD Pain Scale: −0.2 (−0.5, 0.1)	Important
Psychosocial outcomes	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
htTKV	1 (1)	184	No limitations	N/A	Direct	Sparse	Very Low	−0.97 mL/m per year (−2.4, 0.4)	Important
Harms: Hyponatremia	1 (1)	184	No limitations	N/A	Direct	Sparse	Very Low	OR 0.23 (0.05, 1.13)	Important
Harms: D/C due to AE	1 (1)	184	No limitations	N/A	Direct	Sparse	Very Low	OR 3.14 (0.62, 16.0)	Important
Balance of Potential Benefits and Harms: No evidence of benefits or harms of increased water intake							**Certainty of Overall Evidence:** Very Low		

Abbreviations: Δ: change; ADPKD: autosomal dominant polycystic kidney disease; AE: adverse events; CKD: chronic kidney disease; D/C: discontinuation; Diff: difference; eGFR: estimated glomerular filtration rate; htTKV: height-adjusted total kidney volume; N: number; N/A: not applicable; PKD: polycystic kidney disease; OR: odds ratio.

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Supplementary Table S17. Comparison of mammalian target of rapamycin (mTOR) inhibitors versus no mTOR inhibitors in adults with ADPKD

Criteria: RCTs only (and extension studies of RCTs), N≥10 per group

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD: eGFR	3 (1-3)	211	No limitations	Consistent	Direct	None	High	Sum Net Diff: 1.6 (−0.3, 7.8) ml/min (2 studies) Sum Net Diff: 0.8% (−0.2, 1.8)	Critical
CKD: TKV	3 (1-3)	209	No limitations	Some inconsistency	Direct	None	Moderate	Sum Net Diff: −0.5% (−1.8, 0.9)	Critical
Liver size	1 (3)	96	No limitations	N/A	Direct	Sparse	Very Low	Sum Net Diff: 1.2%/yr (−1.5, 3.9)	Critical
Death	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Pain	1 (3)	84	No limitations	N/A	Direct	Sparse, imprecise	Very Low	Back pain OR 0.83 (0.25, 2.72)	Critical
Harms, serious	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Harms, liver	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Quality of life	1 (3)	96	No limitations	N/A	Direct	Sparse	Very Low	SF-36 MCS Net Diff 0.6/yr (−1.0, 2.2) SF-36 PCS Net Diff 0.2/yr (−0.9, 1.3)	Critical
Functional	0	0	N/A	N/A	N/A	N/A	(none)		Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)		Critical
Bulk symptoms	1 (3)	84	No limitations	N/A	Direct	Sparse, imprecise	Very Low	Bloating OR 0.33 (0.01, 8.33) GI symptoms score Net Diff 0.04/yr (−0.07, 0.13)	Important
ADPKD complications	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Extrarenal manifestation	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Harms	2 (2,3)	148	No limitations	N/A	Mixed	1 study per harm, but strong association (diarrhea)	Low (diarrhea) Very Low (others)	**Diarrhea OR 4.11 (1.27, 13.4)** Mild hypoglycemia OR 0.96 (0.06, 16.2) SAE OR 0.98 (0.23, 4.16)	Important
Balance of Potential Benefits and Harms: No evidence of difference in kidney function or size or other benefits with mTOR inhibitor use. Diarrhea may be an adverse effect of mTOR inhibitor use.							**Certainty of Overall Evidence:** Moderate		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AE: adverse event; CKD: chronic kidney disease; D/C: discontinuation; Diff: difference; eGFR: estimated glomerular filtration rate ; GI: gastrointestinal; KF: kidney failure; MCS: mental component summary; N: number; N/A: not applicable; OR: odds ratio; PCS: physical component summary; RCT: randomized controlled trial; SAE: small area estimation; SCr: serum creatinine; Sum: summary; TKV: total kidney volume; TLV: total liver volume.

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Supplementary Table S18. Comparison of statins versus no statins in adults and children with ADPKD

Criteria: RCTs only (and extension studies of RCTs), N≥10 per group

Outcome	Population	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
								Certainty of Evidence	Description of Findings	Importance of Outcome
CKD eGFR	Adult	1 (2)	49	Serious limitations	N/A	Direct	Sparse	Very Low	−0.1 ml/min/yr (−0.7, 0.6)	Critical
CKD htTKV	Pediatric	1 (1)	110	Some limitations	N/A	Direct	Sparse	Low	**htTKV Net Diff −9% (−16, −2)** **TKV Net Diff −11% (−19, −3)**	Critical
Liver size	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Death	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Pain	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Quality of life	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Functional	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Bulk symptoms	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
ADPKD complications	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Extrarenal manifestation	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Harms: D/C due to AE	Pediatric	1 (1)	110	Some limitations	N/A	Direct	Sparse, imprecise	Very Low	No events	Important
Balance of Potential Benefits and Harms: ***Adult*** No evidence that statins affect kidney function.								**Certainty of Overall Evidence:** ***Adult*** Very Low		
Pediatric Statins may slow TKV increase without evidence of adverse effects.								***Pediatric*** Low		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AE: adverse events; CKD: chronic kidney disease; D/C: discontinuation; Diff: difference; eGFR: estimated glomerular filtration rate; htTKV: height-adjusted total kidney volume; N: number; N/A: not applicable; OR: odds ratio; RCT: randomized controlled trial; TKV: total kidney volume; Yr: year.

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Supplementary Table S19. Comparison of metformin versus no metformin in adults with ADPKD

Criteria: RCTs only (and extension studies of RCTs), N≥10 per group.
Patients did not have type 2 diabetes

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD: eGFR	3 (1-3)	211	No limitations	Consistent	Direct	None	High	Sum Net Diff: 1.6 (−0.3, 7.8) ml/min (2 studies) Sum Net Diff: 0.8% (−0.2, 1.8)	Critical
CKD: TKV	3 (1-3)	209	No limitations	Some inconsistency	Direct	None	Moderate	Sum Net Diff: −0.5% (−1.8, 0.9)	Critical
Liver size	1 (3)	96	No limitations	N/A	Direct	Sparse	Very Low	Sum Net Diff: 1.2%/yr (−1.5, 3.9)	Critical
Death	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Pain	1 (3)	84	No limitations	N/A	Direct	Sparse, imprecise	Very Low	Back pain OR 0.83 (0.25, 2.72)	Critical
Harms, serious	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Harms, liver	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Quality of life	1 (3)	96	No limitations	N/A	Direct	Sparse	Very Low	SF-36 MCS Net Diff 0.6/yr (−1.0, 2.2) SF-36 PCS Net Diff 0.2/yr (−0.9, 1.3)	Critical
Functional	0	0	N/A	N/A	N/A	N/A	(none)		Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)		Critical
Bulk symptoms	1 (3)	84	No limitations	N/A	Direct	Sparse, imprecise	Very Low	Bloating OR 0.33 (0.01, 8.33) GI symptoms score Net Diff 0.04/yr (−0.07, 0.13)	Important
ADPKD complications	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Extrarenal manifestation	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Harms	2 (2,3)	148	No limitations	N/A	Mixed	1 study per harm, but strong association (diarrhea)	Low (diarrhea) Very Low (others)	**Diarrhea OR 4.11 (1.27, 13.4)** Mild hypoglycemia OR 0.96 (0.06, 16.2) SAE OR 0.98 (0.23, 4.16)	Important
Balance of Potential Benefits and Harms: No evidence of difference in kidney function or size or other benefits with metformin use. Diarrhea may be an adverse effect of metformin use.							**Certainty of Overall Evidence:** Moderate		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; Diff: difference; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; MCS: mental component summary; N: number; N/A: not applicable; OR: odds ratio; PCS: physical component summary; RCT: randomized controlled trial; SAE: small area estimation; Sum: summary; TKV: total kidney volume; yr: year.

References

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Supplementary Table S20. Comparison of somatostatin analogues versus no somatostatin analogues in adults with ADPKD

Criteria: RCTs only (and extension studies of RCTs), N≥10 per group

(Includes ADPKD-specific data from studies that also included patients with ADPLD)

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD: mGFR	4 (1,3-5)	519	Some limitations	Consistent	Direct	None	Moderate	Sum Net Diff 0.6 ml/min (−1.0, 2.3) Worsened kidney function: HR 0.87 (0.49, 1.52) (1 study)	Critical
CKD: TKV	5 (1,3,5,6,9)	542	Some limitations	Consistent	Direct	None	Moderate	**Sum Net Diff −48 ml/min (−93, −2)**	Critical
Liver size	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Death	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Pain	1 (3)	42	Some limitations	N/A	Indirect *	Sparse, imprecise	Very Low	Net Diff 4.7 (−9.9, 19.3)	Critical
Harms: Serious AE	4 (1,2,5,7)	484	Some limitations	Consistent	Direct	None	Moderate	Sum OR 0.79 (0.48, 1.30) Sum RD (event rate 26%) −54 (−133, 77) per 1000	Critical
Harms: Various AE	2 (3,7)	332	Some limitations	Consistent	Direct	Sparse per measure	Low	**Gallstones: OR 6.59 (1.88, 23.1)** **Vomiting: OR 1.92 (1.74, 4.95)** **Diarrhea: Sum OR 68 (34, 135)** **Nausea: OR 8.63 (3.75, 19.9)** **Liver cyst infection: RD 4.6% (1.3, 7.8)**	Critical
Quality of life	2 (3,7)	332	Some limitations	Consistent	Direct	Sparse per measure	Low	No significant difference	Critical
Functional	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Bulk symptoms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
ADPKD complications: UTI	1 (7)	305	Some limitations	N/A	Direct	Sparse	Low	OR 1.82 (0.96, 3.41) RD (event rate 12%) 78 (−4, 159)	Important
Extrarenal manifestation	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Balance of Potential Benefits and Harms: No evidence of effect of SSAs on kidney function or size, pain, quality of life or UTIs, but increased risk of liver cyst infections and gastrointestinal AEs, including gallstones.							**Certainty of Overall Evidence:** Moderate		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AE: adverse event; CKD: chronic kidney disease; Diff: difference; eGFR: estimated glomerular filtration rate; HR: hazard ratio; mGFR: mean glomerular filtration rate; N: number; N/A: not applicable; OR: odds ratio; PLD: polycystic liver disease; RCT: randomized controlled trial; RD: risk difference; Sum: summary; TKV: total kidney volume; UTI: urinary tract infection.

References

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Supplementary Table S21. Comparison of somatostatin analogues versus no somatostatin analogues in adults with PLD

Criteria: RCTs only (and extension studies of RCTs), N≥10 per group

(Includes PLD-specific data from studies that also included patients with ADPKD)

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Liver size	5 (1-5)	300	Some limitations	Consistent	Direct	None	Moderate	**Sum Net Diff −179 ml (−301, −56)**	Critical
Liver cyst volume	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Bulk symptoms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Pain	1 (1)	42	Some limitations	N/A	Indirect*	Sparse	Very Low	Net Diff 4.7 (−9.9, 19.3) [0-100 scale]	Critical
Quality of life	1 (1)	42	No limitations	N/A	Direct	Sparse	Very Low	Net Diff SF-36 MCS −1.5 (−8.0, 5.0) SF-36 PCS 2.0 (−4.3, 8.3) [0-100 scales]	Critical
Functional outcomes	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial outcomes	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Harms: AE	1 (1)	42	No limitations	N/A	Direct	Sparse	Very Low	Diarrhea, Bradycardia, serious AE all NS	Important
Balance of Potential Benefits and Harms: SSAs reduce liver size in patients with PLD, but with unclear evidence about other outcomes or harms.							**Certainty of Overall Evidence:** Moderate		

* SF-36 bodily pain score; not a direct measure of pain.

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AE: adverse event; Diff: difference; MCS: mental component summary; N: number; N/A: not applicable; NS: not significant; PCS: physical component summary; PLD: polycystic liver disease; RCT: randomized controlled trial; Sum: summary.

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Supplementary Table S22. Intracranial aneurysms (ICA): Prevalence of ICA and incidence of ICA rupture in adults with ADPKD

Criteria: Unselected (i.e., complete or random sample of patients), N≥100

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
ICA new diagnosis on screening	6 (1,3,4,5,8,9)	3031	Serious limitations	Inconsistent	Direct	Variable reasons for imaging, imprecise	Low	Sum 12.9% (10.4, 15.4) [Range across studies 9.2% to 18.5%]	Important
Ruptured ICA (all patients screened)	2 (1,7)	9605	Serious limitations	Inconsistent	Direct	Inconsistently reported, imprecise	Low	Sum 0.72% (<0.01, 2.73) [Range across studies 0.24% to 1.71%]	Critical
Ruptured ICA (all images evaluated)	4 (1-3,5)	1850	Serious limitations	Inconsistent	Direct	Inconsistently reported, imprecise	Low	Sum 0.64% (0.24, 1.23) [Range across studies 0% to 1.87%]	Important
Ruptured ICA (all patients or images evaluated)	5 (1.3,5,7)	11,275	Serious limitations	Inconsistent	Direct	Inconsistently reported, imprecise	Low	Sum 0.57% (0.19, 1.14) [Range across studies 0% to 1.87%]	Important
Ruptured ICA after ICA found on imaging	4 (1-3,5)	228	Serious limitations	Inconsistent	Direct	Inconsistently reported, imprecise	Low	Sum 3.05 per 1000 pt-year (0.53, 7.63) [Range across studies 0 to 8.93]	Important
Ruptured ICA after ICA treatment	2 (3,5)	97	Serious limitations	Inconsistent	Direct	Variable reasons for imaging, highly imprecise	Very low	Sum 0 per 1000 pt-year (0, 37.32) [Range across studies 0]	Critical
Ruptured ICA with ICA surveillance	3 (1,2,5)	827	Serious limitations	Inconsistent	Direct	Variable reasons for imaging, imprecise	Low	Sum 1.21 per 1000 pt-year (0.03, 6.72) [Range across studies 0, 12.99]	Critical
Ruptured ICA after no ICA found on imaging	4 (1,3,5,6)	9528	Serious limitations	Consistent	Direct	Sparse evidence, imprecise	Low	Sum 0.39 per 1000 pt-year (0.10, 0.89) [Range across studies 0, 1.05]	Critical
Balance of Potential Benefits and Harms: ICA is common among patients with ADPKD (about 13%). Approximately 0.7 patients have a ruptured ICA per 1000 patient-years of follow-up. For patients with known ICA, approximately 3 rupture per 1000 patient-years of follow-up. With surveillance of known ICAs, approximately 1.2 rupture per 1000 patient-years of follow-up.							**Certainty of Overall Evidence:** Low		

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
For patients with no ICA found on imaging, about 0.4 patients have a ruptured ICA per 1000 patient-years of follow-up.									

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; ICA: intracranial aneurysm; N: number; pt-yr: patient-years; Sum: summary.

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Supplementary Table S23. ICA rupture in adults with ADPKD versus the general population

Criteria: ADPKD vs. general population. N≥30 per group

Outcome	# of Studies	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Ruptured ICA / SAH	4 (1-4)	12,663 vs. 130,813, plus 918,478 kidney transplants	Serious limitations	Consistent*	Direct	Very strong association	Moderate	**Sum ES 6.43 (3.08, 13.40)**	Critical
Balance of Potential Benefits and Harms: Risk of ICA rupture is probably more likely in people with ADPKD than the general population							**Certainty of Overall Evidence:** Moderate		

***** All consistent with large associations (IRR or OR) ≥3.6. The exact association estimates were highly inconsistent across studies.

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; ES: effect size; ICA: intracranial aneurysm; N: number; SAH: subarachnoid hemorrhage; Sum: summary.

References

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Supplementary Table S24. Imaging to diagnose ICA in adults with ADPKD

Criteria: Conducted imaging for ICA, N≥30 (or N≥10 with post-imaging intervention like clipping)
Single arm studies included only for direct sequelae of imaging.
Comparative studies included ICA-related outcomes compared with no screening.

Outcome	# of Studies (References) *	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Death	1 (1)	495	Serious limitations	N/A	Direct	Sparse data 1 comparative study	Very Low	OR 1.73 (0.03, 87.8)	Critical
ICA rupture	1 (1)	495	Serious limitations	N/A	Direct	Sparse data 1 comparative study	Very Low	OR 1.16 (0.19, 7.00)	Critical
Stroke	0								Critical
Surgical or embolization complication	2 (1,2)	993	Serious limitations	N/A	Direct	Sparse data 1 comparative study	Very Low	2/983 (0.2%) vs. 0/314 [2/13 who had repair had complication, both with minor sequelae]	Critical
Psychosocial	0								Critical
Quality of life	0								Important
Functional	0								Important
Balance of Potential Benefits and Harms: Studies underpowered to determine benefits (preventing death, ICA rupture) or harms (intervention complication), with no data on patient-reported outcomes. No clean comparison of similar patients receiving vs. not receiving imaging							**Certainty of Overall Evidence:** Very Low		

* Yoshida et al. (3) reported only non-prioritized outcomes.

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; ICA: intracranial aneurysm; mRS: modified Rankin scale; N: number; N/A: not applicable; OR: odds ratio. Note that comparative study compared imaging in patients with a family history of ICA versus no imaging in patients without a family history of ICA.

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Appendix D. Data supplement - Additional evidence profiles developed as part of the evidence review

Supplementary Table S25. Comparison of different antihypertensive agents in adults with ADPKD*

Criteria: RCT, ≥1 year follow-up

Outcome	Comparison	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
								Certainty of Evidence	Description of Findings	Importance of Outcome
Blood pressure	*All*	7 (1-7)	1176	No limitations	Inconsistent	Direct	Sparse per drug comparison	Very Low	Some single studies found statistically significant differences in change in BP	Critical
	ACEi + ARB v. ACEi	2 (1,2)	1036	Some limitations	Consistent	Direct	None	Moderate	Sum SBP −5.0 (−11.1, 1.2) **Sum DBP −7.4 (−9.3, −5.6)**	
	ARB v. ACEi	3 (1,2,3)	52	Some limitations	Inconsistent	Indirect†	Imprecise	Very Low	Sum SBP −3.9 (−12.0, 4.1) Sum DBP −3.4 (−8.5, 1.7)	
	ACEi v. BB	1 (5)	37	Some limitations	N/A	Direct	Single small study	Very Low	**SBP −2.0 (−3.3, −0.7)** **DBP −2.0 (−3.1, −0.9)**	
	ACEi v. CCB	1 (6)	24	Some limitations	N/A	Direct	Single small study	Very Low	SBP −1.0 (−4.6, 2.6) **DBP −4.0 (−6.4, −1.6)**	
	ARB v. CCB	1 (7)	49	Some limitations	N/A	Direct	Single small study	Very Low	SBP 0 (−6.7, 6.7) DBP −5.0 (−12.7, 2.7)	
	RASi vs. non-RASi	3 (5,6,7)	102	Some limitations	Consistent	Direct	Various comparisons	Moderate	**Sum SBP −1.8 (−3.0, −0.6)‡** **Sum DBP −2.8 (−4.6, −1.0)**	
CKD Progression (Δ eGFR)	*All*	7 (1-7)	1196	No limitations	Consistent	Direct	Sparse for most drug comparisons	Low	Generally, no evidence of differences by drug regimen	Critical
	ACEi + ARB v. ACEi	2 (1,2)	1042	Some limitations	Consistent	Direct	None	Moderate	Sum eGFR −0.01 (−0.29, 0.26) per y	
	ARB v. ACEi	3 (1,2,3)	52	Some limitations	Consistent	Indirect§	Imprecise Sparse per outcome	Very Low	eGFR 0.7 (−19.4, 20.9) (1 study) SCr −0.03 (−0.12, 0.06) mg/dl (1 study)	
	ACEi v. BB	1 (5)	46	Some limitations	N/A	Direct	Sparse	Very Low	eGFR 2.0 (−3.7, 7.7)	
	ACEi v. CCB	1 (6)	24	Some limitations	N/A	Direct	Sparse	Very Low	**eGFR −7.0 (−11.6, −2.4)**	
	ARB v. CCB	1 (7)	49	Some limitations	N/A	Direct	Sparse	Very Low	eGFR 8.4 (−6.0, 22.8)	
	RASi vs. non-RASi	3 (5,6,7)	102	Some limitations	Inconsistent	Direct	Various comparisons	Low	Sum eGFR −0.5 (−8.7, 7.7)	
Ruptured ICA	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical

Outcome	Comparison	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
								Certainty of Evidence	Description of Findings	Importance of Outcome
Mortality	ACEi + ARB v. ACEi	2 (1,2)	1044	Some limitations	Consistent	Direct	Highly imprecise	Very Low	Sum OR 0.83 (0.25, 2.75) RD (HALT PKD A: event rate 0.4%) 0.2 (−10, 10) per 1000 RD (HALT PKD B: event rate 2%) −4.3 (−28, 10) per 1000	Critical
	ARB v. ACEi	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
	ACEi v. BB	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
	ACEi v. CCB	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
	ARB v. CCB	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
Adverse event, serious	N/A	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
LVH	*All*	3 (1,4,5)	611	No limitations	Consistent	Direct	Sparse per drug comparison	Very Low	No evidence of differences by drug regimen	Important
	ACEi + ARB v. ACEi	1 (1)	542	Some limitations	N/A	Direct	Single study	Very Low	LVMI −0.088 per yr (−0.40, 0.22)	
	ARB v. ACEi	1 (4)	32	No limitations	N/A	Direct	Single small study	Very Low	LVMI 8.6 (−3.7, 20.9)	
	ACEi v. BB	1 (5)	37	Some limitations	N/A	Direct	Single small study	Very Low	LVMI −0.3 (−4.0, 3.4)	
	ACEi v. CCB	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
	ARB v. CCB	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
CKD Progression (Δ TKV)	*All*	1 (1)	553	Some limitations	N/A	Direct	Sparse	Very Low	TKV −0.2% per yr (−0.8, 5.0)	Important
	ACEi + ARB v. ACEi	1 (1)	553	Some limitations	N/A	Direct	Sparse	Very Low	TKV −0.2% per yr (−0.8, 5.0)	
	ARB v. ACEi	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
	ACEi v. BB	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
	ACEi v. CCB	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
	ARB v. CCB	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
	RASi vs. no RASi	0	0	N/A	N/A	N/A	N/A	(none)	(none)	
Balance of Potential Benefits and Harms: ACEi or ARB may better control BP than CCB or BB and combination ACEi+ARB may control DBP better than ACEi alone, but choice of antihypertensive may not affect kidney function.								**Certainty of Overall Evidence:** Low		

* Includes data for RASi vs. non-RASi that are also presented in Table S8. † 1 study (N=20) reported only SCr. ‡ SBP meta-analysis largely recapitulates Zeltner 2008 (85% of weight of meta-analyses). §1 study (N=20) reported only SCr.

Abbreviations: Δ**:** change; ACEi: angiotensin converting enzyme inhibitor; ADPKD: autosomal dominant polycystic kidney disease; ARB: angiotensin receptor blocker; BB: beta blocker; CCB: calcium channel blocker; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; ICA: intracranial aneurysm; LVH: left ventricular hypertrophy; LVMI: left ventricular mass index; N: number; N/A: not applicable; OR: odds ratio; RASi: renin–angiotensin–aldosterone system inhibitor; RD: risk difference; SBP: systolic blood pressure; SCr: serum creatinine; Sum: summary (by meta-analysis); TKV: total kidney volume; yr: year.

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Supplementary Table S26. Predictors for progression of TKV in adults with ADPKD: Summary of consistency and direction of associations across multivariable analyses

Criteria: Multivariable analysis, ≥1 year follow-up

Factor	Strong + Assn (Higher Risk)	Weak* + Assn (Higher Risk)	Weak* − Assn (Lower Risk)	Strong − Assn (Lower Risk)	NS	Total	Consistency	Association	Quality
Genetics (PKD 1, trunc or non-trunc)		3 (trunc) 2 (non-trunc)			1 (1nontr)	3	Consistent	Higher, PKD 1nontr and 1tr (likely)	Mixed
Imaging: TKV		2			1	3	Mostly	Higher, likely	Adequate
Urine: Proteinuria/Albuminuria		2			1	3	Mostly	Higher, likely	Mixed
Lab: Kidney function					3	3	Consistent	NS	Mixed
Clinic: Body size (e.g., BMI)	**1**	1			3	5	Inconsistent	Unclear	Inadequate
Dem: Age		2	1		2	5	Inconsistent	Unclear	Mixed
Dem: Sex (Female)			3		2	5	Inconsistent	Unclear	Mixed
Clinic: BP/HTN			1		2	3	Inconsistent	Unclear	Mixed

Includes only factors with data from at least 3 underlying studies.

* Or significant association of a continuous factor (e.g., per year of age).

Abbreviations: Assn: association; ADPKD: autosomal dominant polycystic kidney disease; BMI: body mass index; BP: blood pressure; Dem: demographic; Ht: height; HTN: hypertension; Hx: history; NS: not significant; PKD: polycystic kidney disease; TKV: total kidney volume; Trunc: truncating.

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Supplementary Table S27. Imaging to diagnose kidney or liver cyst infection in adults with ADPKD: ^{18}F-FDG-PET-CT

Criteria: Imaging for kidney or liver cyst infection vs. confirmation of infection

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings*	Importance of Outcome
Cyst infection†	7 (1-7)	186	Serious limitations	Inconsistent	Direct	None	Low	Sensitivity 64-100% Specificity 60-100% PPV 44-100% NPV 38-86%	Critical
Balance of Potential Benefits and Harms: ^{18}F-FDG-PET-CT has fair accuracy to diagnose bacterial cyst infections							**Certainty of Overall Evidence:** Low		

* Various degrees of certainty of diagnosis. † Not meta-analyzed due various groupings of outcome definition (definite, probable, possible cyst infections) and lack of sufficient data for meta-analysis (≤2 studies per outcome) .

Abbreviations: ^{18}F-FDG-PET-CT, ^{18}F-fluorodeoxyglucose integrated with positron emission tomography/computed tomography; ADPKD: autosomal dominant polycystic kidney disease; N: number; NPV: negative predictive value; PPV: positive predictive value

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Supplementary Table S28. Comparison of dietary or lifestyle interventions to slow ADPKD progression in adults with ADPKD: Caffeine/coffee

Criteria: Comparison, ≥1 year of follow-up, N ≥10/group

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD Progression (Δ mGFR, Δ mGFR, Δ CrCl)	2 (1,2)	390	No limitations	Unclear	Direct	Sparse per measure	Very Low	eGFR Net Diff 2.0 ml/min (−0.3, 4.4) (1 study) mGFR slope Net Diff −0.07 ml/min per year (−0.6, 0.5) (1 study) kidney failure adjHR ~1.8 (0.9, 3.6) (1 study)	Critical
Quality of life	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Functional outcomes: Pain	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Psychosocial outcomes	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
htTKV	2 (1,2)	390	No limitations	Consistent	Direct	Sparse per measure	Very Low	**Net Diff slope −0.6% per year (−0.2, −1.1) (1 study)** Net Diff −33 ml/m (−73, 6) (1 study)	Important
Harms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Balance of Potential Benefits and Harms: Limiting coffee or caffeine may slow growth in TKV, with no evidence of effect on kidney function							**Certainty of Overall Evidence:** Very Low		

Abbreviations: Δ: change; ADPKD: autosomal dominant polycystic kidney disease; adjHR: adjusted hazard ratio; AE: adverse events; CKD: chronic kidney disease; CrCl: creatinine clearance; Diff: difference; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease; htTKV: height-adjusted total kidney volume; mGFR: mean glomerular filtration rate; N: number.

References

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Supplementary Table S29. Comparison of dietary or lifestyle interventions to slow ADPKD progression in adults with ADPKD: Low-protein diet

Criteria: Comparison, ≥1 year of follow-up, N ≥10/group

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD Progression (Δ mGFR, Δ mGFR, Δ CrCl)	1 (1)	Unclear	Serious limitations	N/A	Direct	Sparse	Very Low	mGFR Net Diff: Low vs. Usual: −0.1 ml/min (−1.4, 1.2) Very Low vs. Low: −0.9 ml/min (−1.9, 0.1)	Critical
Quality of life	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Functional outcomes: Pain	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Psychosocial outcomes	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
htTKV	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Harms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Balance of Potential Benefits and Harms: No evidence of effect of low protein diet on kidney function							**Certainty of Overall Evidence:** Very Low		

Abbreviations: Δ: change; ADPKD: autosomal dominant polycystic kidney disease; CKD: chronic kidney disease; CrCl: creatinine clearance; Diff: difference; htTKV: height-adjusted total kidney volume; mGFR: mean glomerular filtration rate; N: number.

References

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Supplementary Table S30. Comparison of dietary or lifestyle interventions to slow ADPKD progression in adults with ADPKD: Fish oil (EPA)

Criteria: Comparison, ≥1 year of follow-up, N ≥10/group

Outcome	# of Studies	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD Progression (Δ mGFR, Δ mGFR, Δ CrCl)	1 (1)	41	Some limitations	N/A	Direct	Sparse	Very Low	CrCl Mean Diff −0.5 ml/min (−7.5, 6.4) −1.8% (−14, 10)	Critical
Quality of life	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Functional outcomes: Pain	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Psychosocial outcomes	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
TKV	1 (1)	41	Some limitations	N/A	Direct	Sparse	Very Low	Mean Diff 34 ml/min (−191, 259) Mean Diff 0.8% (−12, 14)	Important
Harms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Balance of Potential Benefits and Harms: No evidence of effect of fish oil on kidney function							**Certainty of Overall Evidence:** Very Low		

Abbreviations: Δ: change; ADPKD: autosomal dominant polycystic kidney disease; CKD: chronic kidney disease; CrCl: creatinine clearance; Diff: difference; EPA: eicosapentaenoic acid; mGFR: mean glomerular filtration rate; N: number; TKV: total kidney volume.

References

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Supplementary Table S31. Comparison of dietary or lifestyle interventions to slow ADPKD progression in adults with ADPKD: Intermittent fasting

Criteria: Comparison, ≥1 year of follow-up, N ≥10/group

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD Progression (Δ mGFR, Δ mGFR, Δ CrCl)	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Quality of life	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Functional outcomes: Pain	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Psychosocial outcomes	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
htTKV	1 (1)	28	Serious limitations	N/A	Direct	Sparse	Very Low	Mean Diff 0.2% (−4, 4)	Important
Harms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Balance of Potential Benefits and Harms: No evidence of effect of intermittent fasting on kidney function							**Certainty of Overall Evidence:** Very Low		

Abbreviations: Δ: change; ADPKD: autosomal dominant polycystic kidney disease; CKD: chronic kidney disease; CrCl: creatinine clearance; Diff: difference; htTKV: height adjusted total kidney volume; mGFR: mean glomerular filtration rate; N: number; N/A: not applicable.

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Supplementary Table S32. Comparison of supplements in adults with ADPKD: Niacinamide versus no niacinamide

Criteria: RCTs only (and extension studies of RCTs), N≥10 per group

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD eGFR	1 (1)	36	Some limitations	N/A	Direct	Sparse	Very Low	Net Diff −1.6 mg/ml/yr (−6.9, 3.7) −2.1%/yr	Critical
CKD htTKV	1 (1)	36	No limitations	N/A	Direct	Sparse	Very Low	Net Diff 22 ml/m/yr (−21, 65) 1.22%/yr	Critical
Liver size	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Death	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Pain	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Harms: Serious AE	1 (1)	36	Some limitations	N/A	Direct	Sparse, imprecise	Very Low	OR 3.17 (0.12, 83.1)	Critical
Quality of life	1 (1)	36	Some limitations	N/A	Indirect*	Sparse	Very Low	Net Diff −2.4 points/yr (−7.4, 2.6)	Critical
Functional	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Bulk symptoms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
ADPKD complications	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Extrarenal manifestation	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Harms: D/C due to AE	1 (1)	36	Some limitations	N/A	Direct	Sparse, imprecise	Very Low	OR 0.32 (0.01, 8.39)	Important
Balance of Potential Benefits and Harms: No evidence of effect of niacinamide on benefits or harms							**Certainty of Overall Evidence:** Very Low		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AE: adverse events; CKD: chronic kidney disease; D/C: discontinuation; Diff: difference; eGFR: estimated glomerular filtration rate; htTKV: height-adjusted total kidney volume; N: number; N/A: not applicable; OR: odds ratio; Yr: year.

References

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Supplementary Table S33. Comparison of supplements in children and young adults with ADPKD: Curcumin versus no curcumin

Criteria: RCTs only (and extension studies of RCTs), N≥10 per group

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD eGFR	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
CKD htTKV	1 (1)	57	No limitations	N/A	Direct	Sparse	Low	Diff in Median −44 ml/m P=0.24	Critical
Death	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Pain	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Harms: Serious AE	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Quality of life	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Functional	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Bulk symptoms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
ADPKD complications	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Extrarenal manifestation	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Harms: D/C due to AE	1 (1)	57	No limitations	N/A	Direct	Sparse, imprecise	Very Low	OR 1.24 (0.34, 4.53)	Important
Balance of Potential Benefits and Harms: No evidence of effect of curcumin on benefits or harms							**Certainty of Overall Evidence:** Low		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AE: adverse events; CKD: chronic kidney disease; D/C: discontinuation; Diff: difference; eGFR: estimated glomerular filtration rate; htTKV: height-adjusted total kidney volume; N: number; N/A: not applicable; OR: odds ratio.

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Supplementary Table S34. Comparison of tesevatinib versus no tesevatinib in adults with ADPKD

Criteria: RCTs only (and extension studies of RCTs), N≥10 per group

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD eGFR	1 (1)	74	Serious limitations	N/A	Direct	Sparse	Very Low	No significant treatment difference	Critical
CKD htTKV	1 (1)	74	Serious limitations	N/A	Direct	Sparse	Very Low	No significant treatment difference	Critical
Liver size	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Death	1 (1)	74	Serious limitations	N/A	Direct	Sparse	Very Low	No significant treatment difference	Critical
Pain	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Harms: Serious AE	1 (1)	74	Serious limitations	N/A	Direct	Sparse	Very Low	OR 3.00 (0.65, 13.94)	Critical
Quality of life	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Functional	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Bulk symptoms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
ADPKD complications	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Extrarenal manifestation	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Harms: D/C due to AE	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Balance of Potential Benefits and Harms: No evidence of effect of tesevatnib on benefits or harms							**Certainty of Overall Evidence:** Very Low		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AE: adverse events; CKD: chronic kidney disease; D/C: discontinuation; Diff: difference; eGFR: estimated glomerular filtration rate; htTKV: height-adjusted total kidney volume; N: number; N/A: not applicable; OR: odds ratio; yr: year.

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Supplementary Table S35. Comparison of venglustat versus no venglustat in adults with ADPKD

Criteria: RCTs only (and extension studies of RCTs), N≥10 per group

Outcome	# of Studies (References)	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
CKD eGFR	1 (1)	175	Some limitations	N/A	Direct	Sparse	Very Low	**15 mg dose: SMD −2.49 (−3.77, −1.21)** **8 mg dose: SMD −2.42 (−3.77, −1.07)** *Worse on venglustat than placebo*	Critical
CKD htTKV	1 (1)	175	Some limitations	N/A	Direct	Sparse	Very Low	15 mg dose: SMD 0.03 (−1.76, 1.82) 8 mg dose: SMD 1.36 (−0.41, 3.13)	Critical
Liver size	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Death	1 (1)	477	Some limitations	N/A	Direct	Sparse	Very Low	No significant treatment difference	Critical
Pain	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Harms: Serious AE	1 (1)	477	Some limitations	N/A	Direct	Sparse	Very Low	**15 mg dose: OR 2.00 (1.01, 3.95)** **8 mg dose: OR 2.75 (1.39, 5.42)**	Critical
Quality of life	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Functional	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Critical
Bulk symptoms	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
ADPKD complications	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Extrarenal manifestation	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Harms: D/C due to AE	1 (1)	477	Some limitations	N/A	Direct	Sparse	Very Low	15 mg dose: OR 2.01 (0.51, 7.93) 8 mg dose: OR 1.71 (0.29, 10.04)	Important
Balance of Potential Benefits and Harms: Harms of Venglustat outweigh benefits; trial stopped early based on the results from the futility analysis (no significant effect on htTKV)							**Certainty of Overall Evidence:** Very Low		

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AE: adverse events; CKD: chronic kidney disease; D/C: discontinuation; Diff: difference; eGFR: estimated glomerular filtration rate; htTKV: height-adjusted total kidney volume; N: number; N/A: not applicable; OR: odds ratio; RCT: randomized controlled trial; SMD: standardized mean difference; yr: year.

Reference

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Supplementary Table S36. Invasive procedures or surgery to manage liver or kidney cysts or pain in adults with ADPKD

Criteria: Comparative or single group, any duration

Outcome	# of Studies (References) *	Total N of Patients	Methodological Quality of Studies	Consistency Across Studies	Directness of the Evidence	Other Considerations	Summary of Findings		
							Certainty of Evidence	Description of Findings	Importance of Outcome
Pain	3 (3,7,14)	165	Serious limitations (single group only)	Consistent	Direct	1 study per measure and procedure	Very Low	Kidney Lap Decort: 83% w/improvement Kidney Foam: 73% w/improvement Celiac block: 82% w/improvement	Critical
Liver/Kidney size	3 (2,7,11)	534	Serious limitations (single group only)	N/A	Direct	2 AspScl studies 1 TAE study	Very Low	Kidney TAE: −46% Kidney Foam: −22% and −26% 85% with >10% reduction	Critical
Cyst volume	3 (2,6,13)	493	Serious limitations (single group only)	N/A	Direct	2 AspScl studies 1 TAE study	Very Low	Liver AspScl: −65% and −85% Liver TAE: −9.2%	Critical
Surgical complications, death	2 (4,10)	635	Serious limitations (single group only)	N/A	Direct	Publication bias 1 study per procedure	Very Low	Kidney TAE: 0.7% Liver hep fenest 2.7%	Critical
Bulk symptoms	1 (7)	22	Serious limitations (High RoB NRCS)	N/A	Direct	Sparse	Very Low	59% with improvement in abdominal distension	Critical
Quality of life	2 (11,13)	181	Serious limitations (single group only)	N/A	Direct	1 study per procedure	Very Low	Liver AspScl: Improvements in 3 measures Kidney TAE: Improvements in SF-36 measures	Critical
Functional	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Psychosocial	0	0	N/A	N/A	N/A	N/A	(none)	(none)	Important
Surgical complications, various, serious	5 (2,7,9,12,13)	1044	Serious limitations (single group only)	Inconsistent	Direct	1 study per procedure and complication	Very Low	Variable by procedure and specific complication (see Results table)	Important
Balance of Potential Benefits and Harms: Uncertain evidence suggesting that invasive procedures decrease liver and liver cyst size, pain and abdominal distension, and improve quality of life, with variable complications that include post-procedure death. No evidence comparing procedures.							**Certainty of Overall Evidence:** Very Low		

* Yu et al. (14) reported only non-prioritized outcomes.

Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; AspScl: aspiration sclerotherapy; Foam: foam sclerotherapy; Hep fenest: partial hepatectomy and cyst fenestration; Lap Decort: laparoscopic cyst decortication; NRCS: non-randomized comparative study; RoB: risk of bias; TAE: transcatheter arterial embolization.

References

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Supplementary Table S37. Predictors for prevalent ICA in adults with ADPKD

Criteria: Association analysis, N ≥30

(Note that no studies reported predictors of ICA rupture.)

Factor	Strong + Assn (Higher Risk)	Weak* + Assn (Higher Risk)	Weak* − Assn (Lower Risk)	Strong − Assn (Lower Risk)	NS	Total	Consistency	Association	Quality
Dyslipidemia				**1**		1	N/A	Strong	Adequate
Imaging: Dolichoectasia	**1**					1	N/A	Strong	Adequate
Smoking	**1**					1	N/A	Strong	Inadequate
Genetics: PKD 1	**1**					1	N/A	Strong	Inadequate
Hypertension	**1 (Age <35)**	1 (duration)			2 (any age)	3	Mixed	Strong (Age <35) Assn w/duration	Inadequate
Family history of ICA/SAH	**1**				1	2	Unclear†	Strong (possibly)	Mixed
Sex: Female	**1**	2			2	5	Mostly consistent	Weak	Mixed
Lab: MMP-1		1				1	N/A	Weak	Adequate
Imaging: Mitral inflow (higher)		1				1	N/A	Continuous association	Adequate
Imaging: TKV (larger)		1				1	N/A	Continuous association	Inadequate
Age (older)		2			2	4	Inconsistent	Unclear	Mixed
Family history of stroke	**1**				1	2	N/A	NS	Inadequate
Kidney function					5	5	Consistent	NS	Mixed
Family history of ADPKD					1	1	N/A	NS	Inadequate
PKD duration					1	1		NS	Inadequate
Imaging: Liver cysts					1	1		NS	Inadequate

* Or significant association of a continuous factor (e.g., per year of age). † The nonsignificant study (Graf 2002 (6)) found a strong effect estimate (OR 3.63), but the study was underpowered (N 43).

Abbreviations: ADPKD: autosomal-dominant polycystic kidney disease; Assn: association; ICA: intracranial aneurysm; MMP: matrix metalloproteinase; N: number; N/A: not applicable; NS: not significant; PKD: polycystic kidney disease; SAH: subarachnoid hemorrhage; TKV: total kidney volume.

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