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Assessing the reporting quality of randomized controlled trials for mammalian target of rapamycin inhibitors in polycystic kidney disease using the CONSORT statement

Αξιολόγηση της ποιότητας αναφοράς τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών για τους αναστολείς του στόχου της ραπαμυκίνης στα θηλαστικά στην πολυκυστική νόσο των νεφρών χρησιμοποιώντας τη δήλωση CONSORT

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Abstract

Background: Randomized controlled trials (RCTs) are considered to be the cornerstone of modern medical research. It is not uncommon though that their reporting is not always optimal. Inadequate reporting of RCTs is associated with biased estimates of treatment effects. The CONSORT statement is an evidence-based means to improve the quality of RCTs' reporting by providing a checklist of recommended items.

Purpose: The purpose of this study was to assess the reporting quality of RCTs for mammalian target of rapamycin (mTOR) inhibitors in polycystic kidney disease (PKD) using the CONSORT 2010 checklist.

Methods: Medical electronic databases were searched for mTOR inhibitors in PKD. We included articles published in English and with patients randomized into a minimum of two cohorts of different treatment orientations. CONSORT-recommended items were marked as "reported" or "not reported," and an overall CONSORT compliance metric was calculated. Comparisons were made based on different time periods, CONSORT-endorsement and level of impact factor of the journals.

Results: Twelve eligible trials, published in seven different scientific journals, were found. The average CONSORT compliance score was 65.08% (40.54–86.48%). The mean compliance for articles from 2005 to 2012 was 68.72% and for articles from 2013 to 2020 59,9%. CONSORT-endorsing journals had a mean CONSORT compliance of 79.99%, whereas non-endorsing journals had a mean compliance of 54.43%. The median CONSORT compliance for articles published in low (IF<6) and high-ranked (IF>6) journals was 54.43% and 79.99%, respectively. Only 17 of the 37 CONSORT items (45,94%) were reported in ≥75% of the articles.

Conclusion: Quality of reporting in RCTs focusing on mTOR inhibitors in PKD is not optimal yet. Further improvement of reporting is necessary to evaluate the validity of clinical research.

Περίληψη

Εισαγωγή: Οι τυχαιοποιημένες κλινικές μελέτες (RCTs) θεωρούνται ο ακρογωνιαίος λίθος της σύγχρονης κλινικής έρευνας. Δεν είναι ωστόσο ασυνήθιστο φαινόμενο η ποιότητα της αναφοράς των ευρημάτων τους να μην είναι ιδανική. Η ανεπαρκής ποιότητα αναφοράς των RCTs έχει συσχετισθεί με μεροληπτικές εκτιμήσεις των θεραπευτικών αποτελεσμάτων. Η δήλωση CONSORT είναι ένα τεκμηριωμένο μέσο για τη βελτίωση της ποιότητας αναφοράς των RCTs παρέχοντας μια λίστα με προτεινόμενα αντικείμενα ελέγχου.

Στόχοι: Ο σκοπός αυτής της μελέτης ήταν να εκτιμήσει την ποιότητα αναφοράς των RCTs για τους αναστολείς του στόχου της ραπαμυκίνης στα θηλαστικά (mTOR) στην

πολυκυστική νόσο των νεφρών (PKD), χρησιμοποιώντας τη λίστα ελέγχου CONSORT του 2010.

Μέθοδοι: Έγινε αναζήτηση σε ιατρικές ηλεκτρονικές βάσεις δεδομένων για αναστολείς mTOR στην PKD. Συμπεριλάβαμε άρθρα που δημοσιεύθηκαν στα Αγγλικά και με ασθενείς τυχαιοποιημένους σε τουλάχιστον δύο ομάδες διαφορετικών θεραπευτικών προσανατολισμών. Τα προτεινόμενα από την CONSORT στοιχεία επισημάνθηκαν ως «αναφερόμενα» ή «μη αναφερόμενα» και υπολογίστηκε η συνολική συμμόρφωση με τη λίστα ελέγχου της CONSORT. Πραγματοποιήθηκαν επιπλέον συγκρίσεις με βάση τις διαφορετικές χρονικές περιόδους, την υιοθέτηση ή όχι της CONSORT και το επίπεδο του παράγοντα αντίκτυπου (IF) των περιοδικών.

Αποτελέσματα: Βρέθηκαν δώδεκα επιλέξιμες μελέτες, που δημοσιεύθηκαν σε επτά διαφορετικά επιστημονικά περιοδικά. Η μέση βαθμολογία συμμόρφωσης με την CONSORT ήταν 65,08% (40,54-86,48%). Η μέση συμμόρφωση για άρθρα από το 2005 έως το 2012 ήταν 68,72% και για άρθρα από το 2013 έως το 2020 59,9%. Τα περιοδικά που υιοθετούν την CONSORT είχαν μέση συμμόρφωση 79,99%, ενώ τα περιοδικά που δεν την υιοθετούν είχαν μέσο ποσοστό συμμόρφωσης 54,43%. Η μέση συμμόρφωση με την CONSORT για άρθρα που δημοσιεύθηκαν σε περιοδικά χαμηλού (IF <6) και υψηλού (IF> 6) παράγοντα αντίκτυπου ήταν 54,43% και 79,99%, αντίστοιχα. Μόνο 17 από τα 37 στοιχεία της λίστας της CONSORT (45,94%) αναφέρθηκαν στο ≥75% των άρθρων.

Συμπέρασμα: Η ποιότητα αναφοράς των RCTs που εστιάζουν στους αναστολείς mTOR στην PKD δεν είναι ακόμα η ιδανική. Απαιτείται περαιτέρω βελτίωση της ποιότητας αναφοράς για την αξιολόγηση της εγκυρότητας της κλινικής έρευνας.

Introduction

The development of clinical therapeutic trials is linked with the publication of scientific research results and the reporting of biomedical information. The highest rank within the clinical studies is occupied by the randomized controlled trials (RCTs) that are considered to be one of the most powerful tools in modern clinical research. [1]. RCTs have the potential to improve the quality of health care and control costs through careful comparison of alternative treatments when they are used correctly [2, 3]. Even with recent research methods, such as meta-analyses and umbrella meta-analyses, providing more accurate data, the importance of RCTs remains central, as they represent the structural element of the aforementioned research methodologies. Randomization, the random assessment of interventions, in clinical trials guarantees that the significant findings in the group comparisons regarding the matter under examination can be accredited to the intervention and not to other confounding factors [4].

The evaluation of the methodological quality of any trial is integrally linked with the quality of reporting. That is, the extent to which a report provides information about the design, conduct, and analysis of the trial [5]. Reports sometimes omit important methodological details, which leads to biased estimates of treatment effects. The bias related to defects in the conduct of RCTs varies with the type of outcome. Trials with subjectively assessed outcomes, lack of adequate allocation concealment or blinding tend to result in over-optimistic estimates of the effect of interventions [6]. A well-conducted but badly reported trial will be misclassified and misinterpreted, whereas general, unclear and inaccurate reporting of a trial may reflect faulty methods. In addition, since pharmaceutical industry is the major funder of trials, information on funding sources and the role of the industry is also essential [7, 8, 9].

The overwhelming amount of knowledge available in biomedical journals and databases during the past 50 years has created problems in a variety of areas and may be concealing a wide range of biases, such as publication, selection, and funding biases [10,11]. Readers need and deserve to know the quality of the methods being used, in order to assess the strengths and limitations of any RCT [12,13]. Additionally, healthcare providers rely upon the reporting of methodological factors in the reports of RCTs to allow them to determine the validity of the trials upon which they base their clinical practice and their treatment guidelines [14].

In response to concerns about quality of reporting of RCTs, a global group of scientists and editors developed and published in 1996, a common checklist for items to incorporate in reports of RCTs, known as the Consolidated Standards of Reporting Trials (CONSORT) statement [15, 16]. The original CONSORT statement was revised and updated to its current version in 2010, including a 25-item checklist and a four–stage flow diagram [17,18]. Its aim is to facilitate the complete and transparent reporting of trials and aid their critical appraisal and interpretation [19]. CONSORT urges completeness, clarity, and transparency of reporting, which ultimately reflects the actual trial design and conduct. Since its publication in 1996, the CONSORT statement has been widely supported, has been translated into 13 languages, and has an online presence (http://www.consort–statement.org) to facilitate awareness and dissemination [20]. Its use is suggested by the International Committee of Medical Journal Editors, the Council of Science Editors, and the World Association of Medical Editors. There are currently 585 journals that endorse CONSORT ,including over 50% of the core medical journals listed in the Abridged Index Medicus on PubMed. However, it should not be used as a quality appraisal tool but rather as a guide for reporting of RCTs [21].

Polycystic kidney disease (PKD) is a genetic disease, caused by mutations in any of the three genes PKD1, PKD2, and PKD3, that produce a specific abnormal protein which has an adverse effect on tubule development. PKD causes cysts to grow inside the kidneys making them much larger than they ought to be and damaging their functional tissue. PKD causes chronic kidney disease (CKD), which can lead to kidney failure, or end-stage renal disease (ESRD). Autosomal dominant PKD (ADPKD) is the

most common of all the inherited cystic kidney diseases with an incidence of 1:500 live births. [22,23]. There are two forms of ADPKD: type I, caused by mutations in the *PKD1* gene and accounting for 85–90% of the cases [3], and type II, due to mutations within the *PKD2* gene sequence and accounting for 10–15% of the cases. The protein products of PKD1 and PKD2 genes, polycystin-1 and -2, respectively, are both expressed by renal tubular epithelial cells and have been shown to protect cells from apoptosis under different stress conditions. Signs and symptoms of ADPKD usually are developed between the ages of 30 and 40. Autosomal recessive polycystic kidney disease (ARPKD) is the lesser common of the two types, with an incidence of 1:20.000 live births and is typically identified in the first few weeks after birth, resulting in a 30% death rate in newborns with the mutation. Studies show that 10% of end-stage kidney disease patients being treated with dialysis in Europe and the U.S. were initially diagnosed and treated for ADPKD. [24,25]

Current clinical management of ADPKD focuses primarily on symptom management and reducing associated complications, particularly hypertension. In recent years, improved understanding of molecular and cellular mechanisms involved in kidney cyst growth and renal failure progression has resulted in new pharmaceutical agents to focus on pathogenesis to prevent progressive disease. mTOR inhibitors are a class of drugs that inhibit the mammalian target of rapamycin, which is a serine/threonine-specific protein kinase that belongs to the family of phosphatidylinositol-3 kinase (PI3K) related kinases (PIKKs) [26]. mTOR regulates cellular metabolism, growth, and proliferation by forming and signaling through two protein complexes, mTORC1 and mTORC2. Polycystin-1 has been shown to regulate mammalian target of rapamycin (mTOR) and its downstream effectors. On the basis of these observations clinical trials testing the efficacy of mTOR inhibitors in patients with ADPKD have been conducted, given the compelling preclinical data implicating abnormal mTOR signaling playing a significant role in the pathogenesis of ADPKD. [27]

A number of publications have studied the quality of reports of RCTs in subspecialties of medicine, diseases and attainable treatments. However, no study has investigated RCTs putting focus on mTOR inhibitors in polycystic kidney disease using the CONSORT statement.

Methods

Data Sources, Search Strategies and Studies Selection

The evaluation process was carried out in four steps, as can be seen in the search flow chart (Figure 1). Initial search for entries meeting the set criteria was conducted in PubMed, Cohrane Library and Google Scholar. The search strategy identified reports on RCTs involving patients with PKD receiving mTOR inhibitors as treatment from the 1st of January 2005 to the 15th of July 2020. As a search criterion the combination of the following terms was used: (mammalian target of rapamycin

inhibitors or mTOR inhibitors or rapaloges or sirolimus or everolimus or temsirolimus or ridaforolimus) and (polycystic kidney disease or PKD or autosomal dominant polycystic kidney disease or ADPKD or autosomal recessive polycystic kidney disease or ARPKD). In PubMed the filter 'Randomized Control Trial' was used for the type of article, 'English' for the language and 'Humans' for the species. In order to determine study eligibility at first the title, then the abstract and finally the whole article was scrutinized. All references cited in the retrieved articles were also reviewed to identify additional published work not originally indexed. Trials were eligible if they had randomly assigned participants to at least two medicinal treatment arms and included patients diagnosed with PKD. Non-medicinal treatments, dose comparison studies and any article with information resulting from a previous conducted trial (post-hoc analysis, sub-group analysis, sub-studies) were excluded. Trials were eligible when they were published as full or short papers or letters in a regular issue or supplement of a biomedical journal and they could be reviewed in their entirety. Editorials and review articles were also excluded.

Data Extraction and Reporting Assessment Tool

As assessment tool for reporting quality we used the revised CONSORT 2010 checklist, which is a 25-item checklist with additional sub-items coming to a total of 37 items. As guidelines the CONSORT explanation and elaboration document, which is available at the CONSORT web page, was used. Out of the total of 12 eligible trials 2 articles were published before 2010 when the revised CONSORT version was published and 10 after 2010. We used the revised CONSORT version for all extracted articles either or not published before 2010 when the revised version of CONSORT was published. The full CONSORT checklist can be accessed online on http://www.consort-statement.org.

Explaining more specifically some methodological CONSORT criteria, i) randomization is the method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification); ii) allocation concealment is the method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned or not and iii) implementation of randomization answers the question of who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups. Responses, apart from yes or no, as well as unclear responses to each question were coded as negative responses.

Evaluation – analysis

During the evaluation process the following procedures were followed: (1) all of the checklist items were searched for into the published trials in terms of whether or not they were reported, and not if they were actually performed during the trial. In cases where a methodology followed by the trials' authors was insinuated in the results or other sources, albeit there was no lucid reference in the article, the CONSORT item

was marked as “non-reported.” (2) In cases where a procedure of the trial was not mentioned in the main manuscript of the trial but there was a reference to it in a supplementary file provided, the procedure was considered as adequately reported. This rule was not applied to item 8a, where the CONSORT Explanation and Elaboration Document specifically requires that “information on the process of randomization is included in the body of the main article and not as a separate supplementary file; where it can be missed by the reader”. The reported items were categorized into five groups as follows: (1) Title/Abstract and Introduction, (2) Methods, (3) Results, (4) Discussion, and (5) Other information.

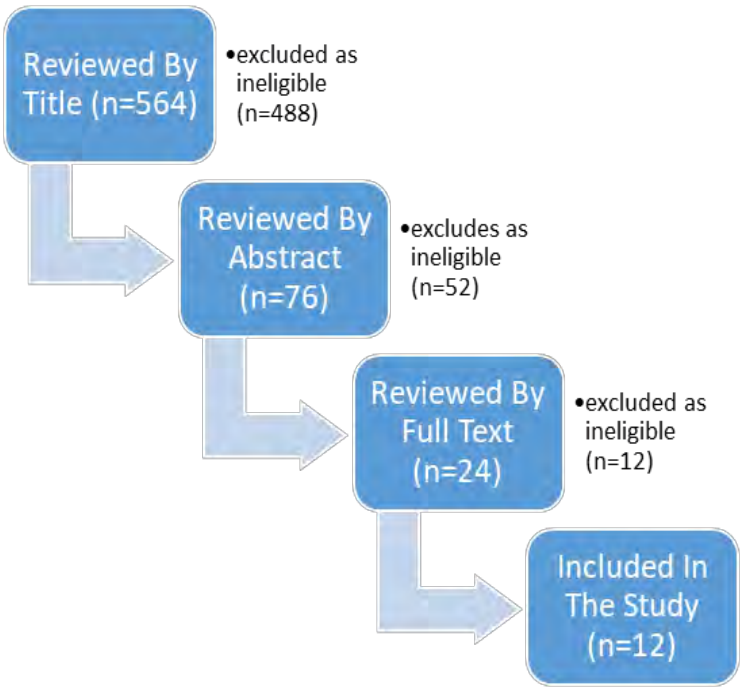
The basic quality-of-reporting metric was the “CONSORT compliance,” meaning the percentage of the 37 CONSORT items that each article addressed. We calculated the equal or greater than 75% compliance with the CONSORT statement items, as compliance with the CONSORT items to the extent of greater than 75% was considered an adequate cutoff point in a number of other similar studies [28,29].. We further calculated the median CONSORT compliance of the articles published in journals with a current impact factor greater than 6 (considered high), lower than 6 (considered low) and in journals endorsing and not endorsing the CONSORT statement. The comparison of the ≥75% compliance among the different groups of articles was made using the Pearson chi-square statistic for a 2×2 table. We also calculated the percentage of each item that was reported in articles in total and in each group of time period, impact factor and CONSORT-endorsement. This metric is an indicator of which CONSORT items were adequately reported or under-reported by the articles in comparison to the compliance, which is a measure of every article’s total reporting quality. The cutoff point for statistical significance was set at the two-sided 0.05 level.

Results

Four hundred and eighty-eight articles were excluded due to irrelevance, use of non-medicinal intervention (behavioral treatment, exercise, herbal), or not referring to randomized trials. The abstracts of the remaining 76 articles were reviewed and an additional 52 articles were excluded for the same reasons. The remaining 24 articles were retrieved in full text, 12 of which were found ineligible for reasons explained before, and finally 12 articles were included in our study.

Figure 1

Flow diagram of citations through the retrieval and the screening process



Of the total 12 eligible trials 7 were published between 2005 and 2012 and 5 between 2013 and 2020. The mTOR inhibitors used were sirolimus (rapamycin) in 11 trials and everolimus in 1 trial. Seven different scientific journals hosted the included articles. Three of them are currently CONSORT-endorsing, corresponding to 41,66% (5) of the articles. The mean CONSORT compliance of articles published in these journals reached 79,99%. The remaining seven articles, published in four non-endorsing journals, had a mean CONSORT compliance of 54,43%. These percentages were found to be significantly different (p = 0.0001, Chi-square=14,739). The median CONSORT compliance scores of articles published in low (IF<6) and high-ranked (IF >6) journals were 54,43 and 79,99%, respectively. These percentages were also found to be significantly different (p = 0.0001, Chi-square=14.739). The mean compliance for articles from 2005 to 2012 was 68.72% and for articles from 2013 to 2020 was 59,99%. The difference between them was not found significantly different (p=0.193, Chi-square=1.687). The eligible RCTs were relatively small, with an average count of randomized patients of 69. Only four of them (33,33%) randomized more than 50 patients.

Table 1 shows the percentage of articles that reported each individual item divided into publishing period groups. The percentage of articles that reported each item categorized by impact factor and CONSORT-endorsement are shown in Table 2. A list of included RCTs along with their CONSORT score is shown in table 3.

Table 1

Compliance with the CONSORT Checklist per Item and Time Period

Data Item	Combined 2005–2020 (*n* = 12)	2005–2012 (*n* = 7)	2013–2020 (*n* = 5)
Abstract/Title			
1a	3 (25%)	1 (14.2%)	2 (40%)
1b	9 (75%)	4 (57.1%)	5 (100%)
Introduction			
2a	12 (100%)	7 (100%)	5 (100%)
2b	12 (100%)	7 (100%)	5 (100%)
Methods			
3a	10 (83.3%)	7 (100%)	3 (60%)
3b	0 (0%)	0 (0%)	0 (0%)
4a	12 (100%)	7 (100%)	5 (100%)
4b	8 (66.6%)	4 (57.1%)	4 (80%)
5	11 (91.6%)	6 (85.7%)	5 (100%)
6a	12 (100%)	7 (100%)	5 (100%)
6b	3 (25%)	3 (42.8%)	0 (0%)
7a	5 (41.6%)	4 (57.1%)	1 (20%)
7b	7 (58.3%)	5 (71.4%)	2 (40%)
8a	5 (41.6%)	4 (57.1%)	1 (20%)
8b	5 (41.6%)	4 (57.1%)	1 (20%)
9	4 (33.3%)	3 (42.8%)	1 (20%)
10	5 (41.6%)	4 (57.1%)	1 (20%)
11a	7 (58.3%)	5 (71.4%)	2 (40%)
11b	1 (8.3%)	1 (14.2%)	0 (0%)
12a	11 (91.6%)	7 (100%)	4 (80%)
12b	5 (41.6%)	3 (42.8%)	2 (40%)

Results			
13a	12 (100%)	7 (100%)	5 (100%)
13b	11 (91.6%)	7 (100%)	4 (80%)
14a	8 (66.6%)	5 (71.4%)	3 (60%)
14b	8 (66.6%)	6 (85.7%)	2 (40%)
15	11 (91.6%)	6 (85.7%)	5 (100%)
16	12 (100%)	7 (100%)	5 (100%)
17a	11 (91.6%)	6 (85.7%)	5 (100%)
17b	5 (41.6%)	2 (28.5%)	3 (60%)
18	3 (25%)	2 (28.5%)	1 (20%)
19	11 (91.6%)	7 (100%)	4 (80%)
Discussion			
20	11 (91.6%)	7 (100%)	4 (80%)
21	8 (66.6%)	5 (71.4%)	3 (60%)
22	12 (100%)	7 (100%)	5 (100%)
Other Information			
23	5 (41.6%)	3 (42.8%)	2 (40%)
24	5 (41.6%)	3 (42.8%)	2 (40%)
25	9 (75%)	5 (71.4%)	4 (80%)

Table 2

Compliance with the CONSORT Checklist per Item and Impact Factor/CONSORT-endorsement

Item	IF>6 (n=5)	IF<6 (n=7)	CONSORT-endorsing (n=5)	CONSORT-non endorsing (n=7)
Abstract/Title				

1a	1 (20%)	2 (28.5%)	1 (20%)	2 (28.5%)
1b	4 (80%)	5 (71.4%)	4 (80%)	5 (71.4%)
Introduction				
2a	5 (100%)	7 (100%)	5 (100%)	7 (100%)
2b	5 (100%)	7 (100%)	5 (100%)	7 (100%)
Methods				
3a	4 (80%)	6 (85.7%)	4 (80%)	6 (85.7%)
3b	0 (0%)	0 (0%)	0 (0%)	0 (0%)
4a	5 (100%)	7 (100%)	5 (100%)	7 (100%)
4b	5 (100%)	3 (42.8%)	5 (100%)	3 (42.8%)
5	5 (100%)	6 (85.7%)	5 (100%)	6 (85.7%)
6a	5 (100%)	7 (100%)	5 (100%)	7 (100%)
6b	1 (20%)	2 (28.5%)	1 (20%)	2 (28.5%)
7a	4 (80%)	1 (14.2%)	4 (80%)	1 (14.2%)
7b	4 (80%)	3 (42.8%)	4 (80%)	3 (42.8%)
8a	3 (60%)	2 (28.5%)	3 (60%)	2 (28.5%)
8b	3 (60%)	2 (28.5%)	3 (60%)	2 (28.5%)
9	3 (60%)	1 (14.2%)	3 (60%)	1 (14.2%)
10	3 (60%)	2 (28.5%)	3 (60%)	2 (28.5%)
11a	3 (60%)	4 (57.1%)	3 (60%)	4 (57.1%)
11b	1 (20%)	0 (0%)	1 (20%)	0 (0%)
12a	5 (100%)	6 (85.7%)	5 (100%)	6 (85.7%)
12b	4 (80%)	1 (14.2%)	4 (80%)	1 (14.2%)
Results				
13a	5 (100%)	7 (100%)	5 (100%)	7 (100%)
13b	5 (100%)	6 (85.7%)	5 (100%)	6 (85.7%)
14a	5 (100%)	3 (42.8%)	5 (100%)	3 (42.8%)

14b	5 (100%)	3 (42.8%)	5 (100%)	3 (42.8%)
15	5 (100%)	6 (85.7%)	5 (100%)	6 (85.7%)
16	5 (100%)	7 (100%)	5 (100%)	7 (100%)
17a	5 (100%)	6 (85.7%)	5 (100%)	6 (85.7%)
17b	3 (60%)	2 (28.5%)	3 (60%)	2 (28.5%)
18	2 (40%)	1 (14.2%)	2 (40%)	1 (14.2%)
19	5 (100%)	6 (85.7%)	5 (100%)	6 (85.7%)
20	5 (100%)	6 (85.7%)	5 (100%)	6 (85.7%)
21	5 (100%)	3 (42.8%)	5 (100%)	3 (42.8%)
22	5 (100%)	7 (100%)	5 (100%)	7 (100%)
Other Information				
23	5 (100%)	0 (0%)	5 (100%)	0 (0%)
24	5 (100%)	0 (0%)	5 (100%)	0 (0%)
25	5 (100%)	4 (57.1%)	5 (100%)	4 (57.1%)

Table 3

List of included RCTs along with their CONSORT score

Study Identification	**Year**	**Journal**	**Compliance Score**
Liern et al.[30]	2015	General Medicine: Open Access	54.05%
Soliman et al.[31]	2009	Transplantation Proceedings	45.94%
Serra et al.[32]	2009	Nephrology Dialysis Transplantation	67.56%
Stallone et al.[33]	2012	Nephrology Dialysis Transplantation	81.08%
Melemadathil et al.[34]	2016	Journal of Evidence Based Medicine and Healthcare	40.54%
Perico et al.[35]	2010	Journal of the American Society of Nephrology	72.97%
Soliman et al.[36]	2012	Transplantation Proceedings	40.54%
Braun et al.[37]	2014	Clinical Journal of the American Society of Nephrology	67.56%
Walz et al.[38]	2010	The New England Journal of Medicine	86.48%

Ruggenenti et al.[39]	2016	Clinical Journal of the American Society of Nephrology	86.48%
Davis et al.[40]	2018	Transplantation Proceedings	51.355
Serra et al.[41]	2010	The New England Journal of Medicine	86.48%

The mean CONSORT compliance score was 65.08% (40.54–86.48%). The RCTs that covered more than 75% of the CONOSRT items were 4 out of 12 (33,33%). By time period we have: 3 out of 7 (42.85%) from 2005 to 2012 and 1 out of 5 (20%) from 2013 to 2020. This difference is considered significant (p=0.0005, chi-square=12.067). Studies covering at least 75% of the items are; by impact factor 3 out of 5 (60%) with IF>6 and 1 out of 7 (14.28%) with IF<6, by CONSORT-endorsement 3 out of 5 (60%) CONSORT-endorsing and 1 out of 7 (14.28%) non CONSORT-endorsing. There is a significant difference between the two groups based both on IF (p=0, chi-square=44.94) and CONSORT endorsement (p=0, chi-square=44.94). When the 12 studies are considered together only 17 of the 37 CONSORT items (45,94%) were reported in ≥75% of the articles, while 14 of them (37,83%) were reported in less than 50% of the articles, such as sample size, allocation concealment and implementation of randomization.

Discussion

The present study provides evidence that, according to the CONSORT statement, the quality of reporting of mTOR inhibitors in PKD is still not optimal. Only 45,94% of the items of the checklist were addressed in 75% or more of the studies published in the period between 2005 and 2020. Some of the reporting items were generally underreported, such as 1a (Identification as a randomized trial in the title). And some of them were not applicable in most of the trials like the item 3b (Important changes to methods after trial commencement, with reasons), 6b (Any changes to trial outcomes after the trial commenced, with reasons), 11b (If relevant, description of the similarity of interventions) and 18 (Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory). In addition, important methodological information was also underreported like item 8a (method used to generate the random allocation sequence) and 8b [Type of randomization; details of any restriction (such as blocking and block size)], which were reported in 41.6% of the articles and item 9 (mechanism to implement the random allocation sequence describing any steps taken to conceal the sequence until interventions were assigned), and 10 (Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions) which were described respectively in 33.3% and 41.6% of the articles. Inadequate description of randomization and blinding procedures classifies RCTs as of unclear risk of bias lowering the grade of acquired evidence [42]. It is, therefore, of utmost importance to ensure reporting of these methodological items, even by

considering classifying their clarification as a mandatory requirement. Articles have addressed this issue in the past, with the underreporting of the aforementioned features appearing to be a general scourge [43].

Items regarding the results section were sufficiently reported (above 65%), with the exception of items 17b (For binary outcomes, presentation of both absolute and relative effect sizes is recommended) and 18 (Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory). Similar results were presented by Gnech et al. [44], Huang et al. [45] and Chen et al. [46]. Items referring to trial registration (23), protocol (24) and funding (25) are arguably the most objectively assessed, along with item 1a (title). Items 23 (Registration number and name of trial registry) and 24 (where the full trial protocol can be accessed, if available), which were just included in the 2010 checklist revision, were underreported (41.6%) showing a slow pace of interpolation of them by researchers, while item 25 [Sources of funding and other support (such as supply of drugs), role of funders] was reported more adequately (75%). Study protocol, generally, appears to be the item more frequently underreported among these items, as demonstrated by Nagai et al. and Rikos et al. [47, 48]. Item 1a was reported in 25% of the studies and item 1b (Structured summary of trial design, methods, results, and conclusions using CONSORT for abstracts), in 75% of the studies. The reporting quality of abstracts acquires increasing importance, due to the rapidly increasing number of publications, and a great number of articles put their focus on the adherence of abstracts to the CONSORT guidelines, since abstracts are commonly utilized as a filtration tool. [47–50]. Overall compliance with the CONSORT statement is not impressive, since less than half (33.33%) of the articles addressed more than 75% of the checklist items.

Our results did not establish a significant improvement of reporting over time, with the mean compliance for articles from 2005 to 2012 being 68.72% and for articles from 2013 to 2020 59,99%. The difference between them was not found significantly different (p=0.193). This finding comes in contradiction with most previous relevant articles that have demonstrated improvement of reporting over time [48,51,52], but it has been reproduced elsewhere [53,54]. Impact Factor consists one of the most frequently appraised determining factors of the reporting quality. Previous studies have established that journal ranking assumes an important role in the compliance of authors with the CONSORT checklist [55]. Our study has enhanced this evidence by obtaining significant difference (p = 0.0001) between articles published in low (IF<6) and high-ranked (IF >6) journals (54.43 and 79.99% mean compliance respectively). The aforementioned association is reasonable, since IF is usually a valid indicator of a medical journal's quality. A study by Plint et al. [17] examined the effectiveness of the CONSORT statement in journals that have formally adopted it, and they concluded that its endorsement is associated with improved reporting of RCTs. That comes in line with our findings, as there was found a significant difference (p = 0.0001) between CONSORT endorsing and non-endorsing journals (mean compliance of 79.99% and 54.43% respectively).

The results of this study should be interpreted with caution and some points need to be taken into consideration. First, we used the 2010 revised CONSORT checklist for all RCTs regardless of their publication date. We decided to use the time periods 2005-2012 and 2013-2020 because the effort of improving the quality of RCTs was still ongoing from the original CONSORT statement through today and the items of the 2001 revision checklist still exist in the current version. Thereupon, an imbalance would occur in the amount of articles compared in the two periods if we chose 2010 as a cutoff point. Moreover, the allocation of a negative or positive response on the checklist has not always been clear and straightforward, making it prone to subjectivity. In addition, since trials which are difficultly retrieved tend to be of lower methodological quality bias might be introduced [56]. Only articles published in English were considered and examined, which could lead to language bias, as authors tend to publish RCTs in English-language journals if the results are of statistical significance [57]. We did not assess the RCT methodological quality directly, since we did not verify the information from the authors or their protocols, hence important methodological details of the trials may not be evaluated. In their observational study Devereaux et al. concluded that authors of RCTs often use allocation concealment and blinding, despite the failure to report them [58]. The reporting of methodological aspects of RCTs does not necessarily reflect the conduct of the trial [59].

In conclusion, the results we obtained were compatible with moderate adherence to the CONSORT statement. It is important that the reporting quality of RCTs for mTOR inhibitors in polycystic kidney disease is improved, especially with respect to randomization and blinding. Further improving their quality and increasing their external and internal validity could assist to reach more conclusive results, to achieve more preferred presentation of data, to elucidate better the clinical significance of RCTs and to direct more specifically future medical research. In this time and age with the hectic pace in the healthcare system and especially during a period of constant pharmaceutical and genetic discoveries, higher quality reports are likely to improve RCTs interpretation, minimize biased conclusions, and ultimately facilitate decision-making about treatment effectiveness.

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