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TITRE

Hétérogénéité et variabilité des critères de jugement dans les essais contrôlés randomisés chez les adultes atteints de maladie rénale chronique non terminale : une revue systématique

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Résumé

Objectif

La maladie rénale chronique (MRC) est souvent silencieuse et les essais contrôlés randomisés (ECR) favorisent les critères de jugement (CDJ) de substitution plutôt que les CDJ cliniques ou rapportés par le patient. L'objectif de notre étude est d'évaluer l'hétérogénéité et la variabilité des CDJ rapportés dans les ECR chez les patients atteints de MRC.

Méthodes

Nous avons réalisé une revue systématique d'ECR évaluant les patients atteints de MRC stade 1 à 5 hors dialyse ou transplantation rénale, publiés en anglais de Janvier 2015 à Décembre 2020. Chaque CDJ rapporté a été extrait puis classé par domaine et catégorie (clinique, rapporté par le patient ou de substitution).

Résultats

Nous avons retenu 235 ECR correspondant à 427 975 patients et extrait 7236 CDJ correspondant à 116 domaines différents. Parmi les 116 domaines, 46 (40%) étaient des CDJ de substitution, 45 (39%) des CDJ cliniques et 25 (21%) des CDJ rapportés par les patients. Les trois domaines les plus fréquemment rapportés étaient la fonction rénale (182 essais [77 %]), la PA (133 [57 %]) et les événements indésirables (124 [53 %]). Le premier CDJ clinique était la mortalité (91 essais [39 %]) et le premier CDJ rapporté par le patient était la douleur (43 [18 %]).

Conclusions

Les CDJ rapportés dans les ECR concernant la MRC sont très hétérogènes et les CDJ de substitution sont privilégiés par rapport aux CDJ cliniques et rapportés par les patients. Cette étude fait partie de l'initiative SONG dont l'objectif est d'établir un ensemble de CDJ standardisé basé sur l'opinion partagée des patients, aidants et professionnels de santé dans le but d'améliorer la prise en charge thérapeutique des patients.

Heterogeneity and variability of outcomes reported in randomized controlled trials for adults with chronic kidney disease not requiring kidney replacement therapy: a systematic review

Abstract

Objective and background

Chronic kidney disease (CKD) is often considered silent and randomized controlled trials (RCT) favor surrogate outcomes rather than clinical or patient reported outcomes. We aimed to assess the heterogeneity and variability of outcomes reported in RCT conducted in patients with CKD not requiring kidney replacement therapy.

Methods

We conducted a systematic review of RCT conducted in patients with CKD stages 1-5 without dialyses or kidney transplantation published in English from January 2015 to December 2020. We extracted each outcome reported, classified them into outcome domains and categories (clinical, patient reported or surrogate outcome).

Results

We assessed 235 trials corresponding to 427,975 patients and extracted 7,236 outcome measures corresponding to 116 different domains. 46 (40%) of the domains were surrogate, 45 (39%) were clinical and 25 (21%) were patient reported outcomes. The 3 most frequently reported outcomes were kidney function (182 [77 %] trials), blood pressure (133 [57 %]) and unspecified adverse events (124 [53%]). The first clinical outcome was mortality (91 [39 %] trials) and the first patient reported outcome was pain (43 [18%]).

Conclusions

The outcomes reported in RCT studying CKD are highly heterogenous and mainly surrogate outcomes, rather than patient-reported and clinical outcomes. This study is part of the SONG initiative, which aims to establish a core outcome set based on the shared opinion of patients, caregivers and health professionals, in order to lead to a better patient care.

Keywords: chronic kidney disease, systematic review, epidemiology, SONG initiative

Mots clés : maladie rénale chronique, revue systématique, épidémiologie, initiative SONG

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SERMENT D'HIPPOCRATE

En présence des enseignants et enseignantes
de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits aux indigents,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis(e) dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux(euse) et reconnaissant(e) envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs parents.

Que les hommes et les femmes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert(e) d'opprobre
et méprisé(e) de mes confrères et consœurs
si j'y manque.

Table des matières

I – Introduction

Chronic kidney disease (CKD) is defined by the KDOQI (Kidney Disease Outcomes Quality Initiative) as either kidney damage (pathologic abnormalities or markers of damage, including

abnormalities in blood or urine tests or imaging studies) or decreased kidney function (GFR less than 60 ml/min per 1.73 m²) for 3 or more months (1). But beyond this technical definition based on biological markers, CKD is a major public health issue because of its prevalence, causes, complications, costs and impact on patients' quality of life.

In 2016, Hill and al (2) published a systematic review with meta-analysis of a hundred studies conducted from 1994 to 2012 worldwide. The global mean prevalence of CKD stage 1 to 5 was 13.4% (95% CI 11.7-15.1%). The mean population age was significantly positively associated with the prevalence of CKD. More recently, an update published by Kovesdy (3) shows an increasing prevalence of CKD worldwide, associated with an increase of global mortality rate attributed to CKD.

Diabetes mellitus and hypertension, two very common conditions, are the main causes of CKD in all developed and many developing countries (4).

CKD is associated with a lot of complications, the most serious being death but also cardiovascular events (5,6), kidney replacement therapy (KRT) (6), acute kidney failure (7), neurological complications (8), and others.

CKD is an expensive condition. In its 2018 annual data report, the USRDS (United States Renal Data System) finds that Medicare spending for all beneficiaries with CKD without KRT exceed $79 billion in 2016 and increase of 23% from 2015 (9). Medicare spending for beneficiaries with KRT add $35 billion. In a systematic review of 37 worldwide studies published from 2015 to 2019, Elshahat and al. show that the per patient mean annual total health care costs were highly variable, ranging from $1,600 to $25,037 in CKD stages 1-3 and from $5,367 to $53,186 in CKD stages 4-5 (10).

CKD has an important impact on patients' quality of life. A systematic review and meta-analysis of 449 studies published from January 2000 to December 2021 and including almost 200 000 patients shows that quality of life (measured by different scales) is significantly lower in patients with CKD than in other patients (11). The most prevalent symptoms expressed by patients included fatigue and mobility difficulties. In these studies, symptoms and quality of life are identified by patients as more important than clinical outcomes such as survival.

CKD is the subject of numerous randomized controlled trials (RCT). Unfortunately, outcomes in RCT are heterogeneous and often lack relevance. Different elements can explain this heterogeneity in nephrology.

For instance, surrogate outcomes, such as change in proteinuria or doubling of serum creatinine, are common in nephrology research, but they are rarely adequate substitute for the definitive clinical outcomes (12-14). We can note that results of an intervention in a RCT can differ between surrogate and hard renal endpoints, sometimes even be opposite (13).

Moreover, there is a lack of homogeneity in outcomes measure, with for instance at least four distinct possible variables to measure urinary protein excretion (14).

Composite outcomes are also frequently used in nephrology RCT (12), with components of these outcomes often differing in importance and in frequency (14,15).

These elements complicate the performance of meta-analyses as shown by Sautenet and al. in 2016 (12).

These different methodological issues were pointed out in a series of articles in the Lancet in 2011 as being part of the waste of research. One of the solutions proposed to limit this part of waste of research, is the development of Core Outcome Set (COS). A COS is expected to represent the minimum set of outcomes that should be measured and reported in any clinical trial for a specific condition. A COS can include clinical outcomes, surrogate outcomes and patient reported outcomes (PRO). The first users of clinical research are clinicians and patients who look to them for help so there has to be concordance between their considerations and the questions investigated in research (15). And sometimes, clinicians' and patients' priorities differ (16).

In order to compare the results from trials concerning patients with CKD and to improve their therapeutic management, it is essential to use outcomes that are relevant to all health care actors (including patients and their caregivers) and homogeneous between trials.

Our work is part of the standardized process of the SONG (Standardised Outcomes in Nephrology) initiative, whose objective is to develop sets of outcomes to be used in all trials in the nephrology field under consideration, based on the shared opinion of patients, caregivers and health professionals.

We performed a systematic review to describe outcomes used in nephrology trials for patients with CKD stage 1 to 5 not requiring KRT.

II – Materials and methods

A – Selection criteria

The database analysed were Medline, Embase and Cochrane Nephrology and Transplantation Register. We included all randomized controlled trials that included adult patients with CKD stage 1 from 5, published in English from January 1, 2015 to December 31, 2020.

Exclusion criteria were: dialysis (peritoneal dialysis or haemodialysis), kidney transplantation, paediatric population (age under 18), non-interventional trials, duplicate publications/trials, and pharmacokinetic pharmacodynamic studies. Trials including less than 50% of patients younger than 18 years or less than 50% of dialysis patients or kidney transplantation recipients were included.
Trials were selected by two independent reviewers (EG and BS).

B – Data extraction

For each trial, we extracted the following trial characteristics: first author, year of publication, participating countries, sample size, mean age of participants, proportion of men and women, study duration, intervention type, primary outcome, and all outcomes/outcome measures.
An outcome measure was defined as any measurement or event reported separately for all trial arms.

All levels of specification of the outcome measures were extracted if reported: domain (e.g., mortality), specific measurement (e.g., cardiac death), metric (e.g., number), method of aggregation (e.g., percentage), specific metric (e.g., between the start and end of the study period) and time point of measurement (defined as the time frame from trial commencement to when the outcome was measured).

C – Analysis

All outcome measures extracted were grouped into outcome domains by 2 independent reviewers (EG and BS). Domains can belong to three categories: surrogate (biochemical or physiologic outcomes that may or may not be validated, e.g. potassium), clinical (medical event or comorbidity diagnosed by the physician, e.g. end stage renal disease) and PRO (outcomes reported by patients usually relating to quality of life or symptoms, e.g. pain), based on standard nomenclature. Classification into the different categories was reviewed by 2 reviewers (EG and BS). The number of trials that reported each outcome domain was then calculated.

The primary outcome, if specified, was identified and we noted whether multiple primary outcomes were reported in the same trial.

We conducted a detailed analysis of the heterogeneity of measures for the most frequent outcome of each category (surrogate, clinical and patient reported), assessing the specific measurement, method of aggregation, metric and time points.

We assessed the proportion of surrogate, clinical and patient reported outcomes year by year.

We performed descriptive statistical analyses using Excel 2016 (Microsoft) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org/).

III – Results

A – Trial characteristics

From the 4,959 trials identified, we included 235 trials involving 427,975 participants (Figure 1). Trials characteristics are provided in Table 1. The different trials were conducted in 51 countries. The first represented country was the United States of America (29 [12%]), the second one Japan (19 [8%]) and sixteen studies (7%) were multinational. The median duration of trials was 16 weeks (interquartile range [IQR] 12-52) and the median sample size was 108 participants (IQR 51-208).

B – Outcome Measures and Domains

We extracted 7,236 outcomes measures across the 235 trials. The same outcome measure with different time points was counted as different measures, e.g. mean change in serum creatinine at 2 weeks and mean change in serum creatinine at 12 months.

The number of outcome measures per trial (including time points of measurement) ranged from 1 to 175, with a median of 24 per trial (IQR 15-38). The number of unique outcome measures per trial (excluding time points) ranged from 1 to 93, with a median of 19 (IQR 12-28).

We classified the measures into 116 domains and grouped these domains into surrogate (46 [40%]), clinical (45 [39%]) and PRO (25 [21%]).

Some outcome measures were excluded because their corresponding domains were not clinically relevant (eg, pharmacodynamic pharmacokinetic data or cost data).

The number of different domains per trial ranged from 1 to 37 with a median of 9 (IQR 5-14).

Figure 2 depicts the proportion of trials that reported each outcome domain. Only 3 domains, all surrogate domains, were reported in more than 50 % of the trials: kidney function (182 [77 %] trials), blood pressure (133 [57 %] trials) and unspecified adverse events (124 [53%] trials). The first clinical domain was mortality (91 [39 %] trials) and the first PRO was pain (43 [18%] trials). Kidney replacement therapy was reported in 50 (21%) studies. Quality of life and fatigue/energy are reported in 12 (5%) and 18 (8%) trials, respectively. The three quarter of the domains are reported in less than 10 % of the trials (88 [76%]).

The number of trials that reported a minimum of one surrogate outcome domain was 233 (99 %), and 155 (66 %) and 87 (37 %) reported at least one clinical and one PRO, respectively.

C – Outcome Measures – measure, metric, method of aggregation, time points

The number of unique outcomes measures and time points for the top outcome domain for each of the 3 categories (surrogate, clinical and PRO) have been studied. Results are shown in Figure

3, only for clinical and patient-reported outcomes. Results for surrogate outcomes are not graphically representable due to too many measures.

The most frequently reported clinical outcome was mortality with 55 different outcome measures (92 including different time points), including 23 composite outcome measures (Figure 3A).
The most frequent PRO was pain with 39 outcome measures (70 including time points) (Figure 3B).
The most frequent surrogate outcome was kidney function with 204 outcome measures (542 including time points).

D – Characteristics of primary outcomes

Across the 235 trials, 66 (28%) did not specify the primary outcome. 103 (44%) specified one unique primary outcome but 66 (28%) specified at least 2 outcomes as primary outcomes.
The different outcomes specified as primary outcomes corresponded to 56 outcome domains: 33 (59%) were surrogate, 17 (30%) were clinical and the last 6 (11%) were PRO.
The 5 most frequently reported primary outcomes were all surrogate: “kidney function” (36 [21%] trials), “anaemia/haemoglobin/iron” (20 [12%] trials), “glucose metabolism” (16 [10%] trials), “proteinuria/albuminuria” (15 [9%] trials) and “cardiac function” (15 [9%] trials).

E – Categories of outcomes over time

The proportions of outcome categories (surrogate, clinical and PRO) in trials over time are shown in Figure 4. There were no significant changes over time between 2015 and 2020 with surrogate outcomes being measured in almost 100% of trials.

IV – Discussion

There is a huge heterogeneity in outcomes reported between the different trials, with a majority of surrogate outcomes, overall and also among primary outcomes.

Surrogate outcomes are the most frequently reported outcomes in RCT for patient with CKD not requiring KRT. In our review, there were only three domains represented in more than half of trials and they were all surrogate outcomes (kidney function, blood pressure, and unspecified adverse events). For trials specifying a primary outcome, the five most frequently reported were surrogate. Mortality, the first clinical domain, is reported in less than 40 % of the trials. The patient reported outcomes were much less reported, with pain on top of this domain, present in barely 20 % of the trials. All the outcomes reported corresponded to 116 different domains, highlighting an important heterogeneity and difficulties to compare results of interventions from the different trials.

Surrogate outcomes are often used in nephrology research.
In our systematic review, they represent almost 40% of all outcomes.
Similar results are observed in a systematic review conducted in 2018 in haemodialysis patients, with surrogate outcomes being more than 50 % of all the outcomes reported (17).
Surrogate outcomes have many potential advantages, such as requiring a smaller sample size for a shorter time, resulting in less expensive trials. As recalled by Samuels and al (18), these surrogate outcomes are particularly attractive in nephrology because the progression of CKD is often slow and asymptomatic. Blood pressure, doubling of serum creatinine or proteinuria are some of the classic surrogate outcomes used in nephrology research (12). But these surrogate outcomes are not always representative of effectiveness for trials interventions on patient's quality of life and well-being (19),(20).

Clinical outcomes and PRO are less represented.

Patient reported outcomes are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (21). In a systematic review of 413 trials in cardiovascular disease, Rahimi and al. (22) show that only 93 of the 413 trials use a patient important outcome as a primary endpoint and PRO are reported in only 65 trials, being primary or co-primary endpoint in only 6 studies. The systematic review conducted by Gandhi and al. in diabetes in 2008 shows similar results (23). PRO are highly important, especially for patients and their caregivers. For instance, in a systematic review conducted by Almutary and al. in 2013, five symptoms were

common and reported by more than 50% of patients, regardless the stage of chronic kidney disease : fatigue or lack of energy on top of them, followed by drowsiness, pain, pruritus and dry skin (24). Another systematic review conducted by Fletcher and al reported that PRO are often identified by patients as more relevant than clinical outcomes (11).
Despite this consideration, the assumed silent progression of chronic kidney disease is an obstacle to the use of these PRO, and there is a long time before the development of the typically named hard endpoint. But CKD is not silent at all as shown by Faye and al. who conducted a study among almost 3,000 patients suffering of CKD, with 98% of them reporting at least one symptom, the first represented being fatigue (83% of participants) (25).

PRO represent only 21% of outcomes reported in our systematic review, pain being the first of this domain and present in only 18% of trials.
Similar results are observed in other systematic reviews in nephrology, for instance in kidney transplant recipients (26) (patient-reported outcomes reported in less than 3% of the trials), leading to an underestimation of their impact. Quality of life is almost never reported in the trials of our systematic review (only 5% of trials), just as in paediatric population (1% of trials) (27). The lack of PRO limits the ability of trials to help shared decision making. Moreover, the PRO reported in our systematic review did not correspond to the common symptoms in chronic kidney disease found in literature (11).

Clinical outcomes, especially mortality is rarely reported in clinical trials.
This observation is consistent with other systematic reviews, where mortality is even less represented, such as in dialysis population (mortality assessed in only 20% of trials) (17). Mortality and KRT, two major clinical outcomes in nephrology, should be reported in all randomized clinical trials, even if these trials are not designed to assess these endpoints, in order to allow comparison between clinical trials and realization of meta-analysis.
Many trials use serum creatinine and/or reduction of the glomerular filtration rate as a surrogate outcome to predict KRT (12). Reduction in eGFR is a validated surrogate but there is an enormous heterogeneity in measuring renal function in the trials and it is not possible to aggregate the data in order to perform meta-analysis. For instance, kidney function had 204 different outcome measures. Similar results were found in systematic reviews conducted by Sautenet and al. in paediatric population (27), haemodialysis population (17) and kidney transplant population (26). This heterogeneity is present at every level, such as metric, method of aggregation and time point of measurement. This is a major limitation for comparing the effect of interventions across trials and using the results of clinical trials in current practice.

Our trial has some limitations.

We cannot include all randomized controlled trials in CKD for feasibility. We searched from 2015 to 2020 and included trials published in English. There is a potential selection bias, but many of the participating countries were not English speaking. The review is time-limited, with only trials published between 2015 and 2020 but it is a large window of time, and we wanted the review to be as representative as possible of the current situation in order to reflect the situation of clinical research in nephrology.

This review provides evidence and confirms the need to develop a core outcome set for adults with CKD not requiring KRT which should be based on shared priorities of patients, caregivers and health professionals. A core outcome set is a standardized and accepted set of outcomes that should minimally be measured and reported in all clinical trials in a specific health area, such as nephrology. It allows comparison of results of different studies. This does not imply that outcomes in a specific trial should be limited to those in the core outcome set (28), researchers can decide to add other outcomes, more specific to the disease or the study population for instance (29-30). The objective of this initiative is to increase clinical relevance and ability of trials to help decision making, finally leading to improvement of patient care. This systematic review is the first step for the development of a core outcome set in adults with CKD not requiring KRT conducted by the SONG Initiative.

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Figure 1. Flow chart of the selection of the trials

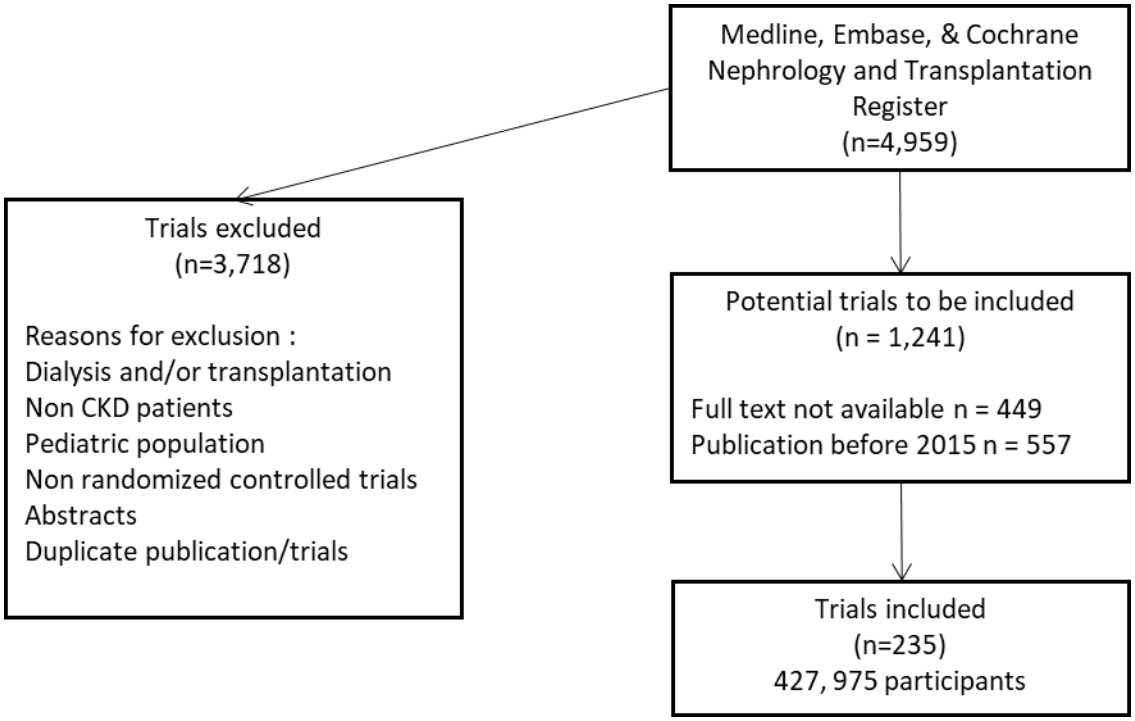
Medline, Embase, & Cochrane Nephrology and Transplantation Register
(n=4,959)
Trials excluded
(n=3,718)
Reasons for exclusion :
Dialysis and/or transplantation
Non CKD patients
Pediatric population
Non randomized controlled trials
Abstracts
Duplicate publication/trials
Potential trials to be included
(n = 1,241)
Full text not available n = 449
Publication before 2015 n = 557
Trials included
(n=235)
427, 975 participants

Figure 2. Number of trials reporting each outcome domain (total 235 trials, 116 outcome domains).

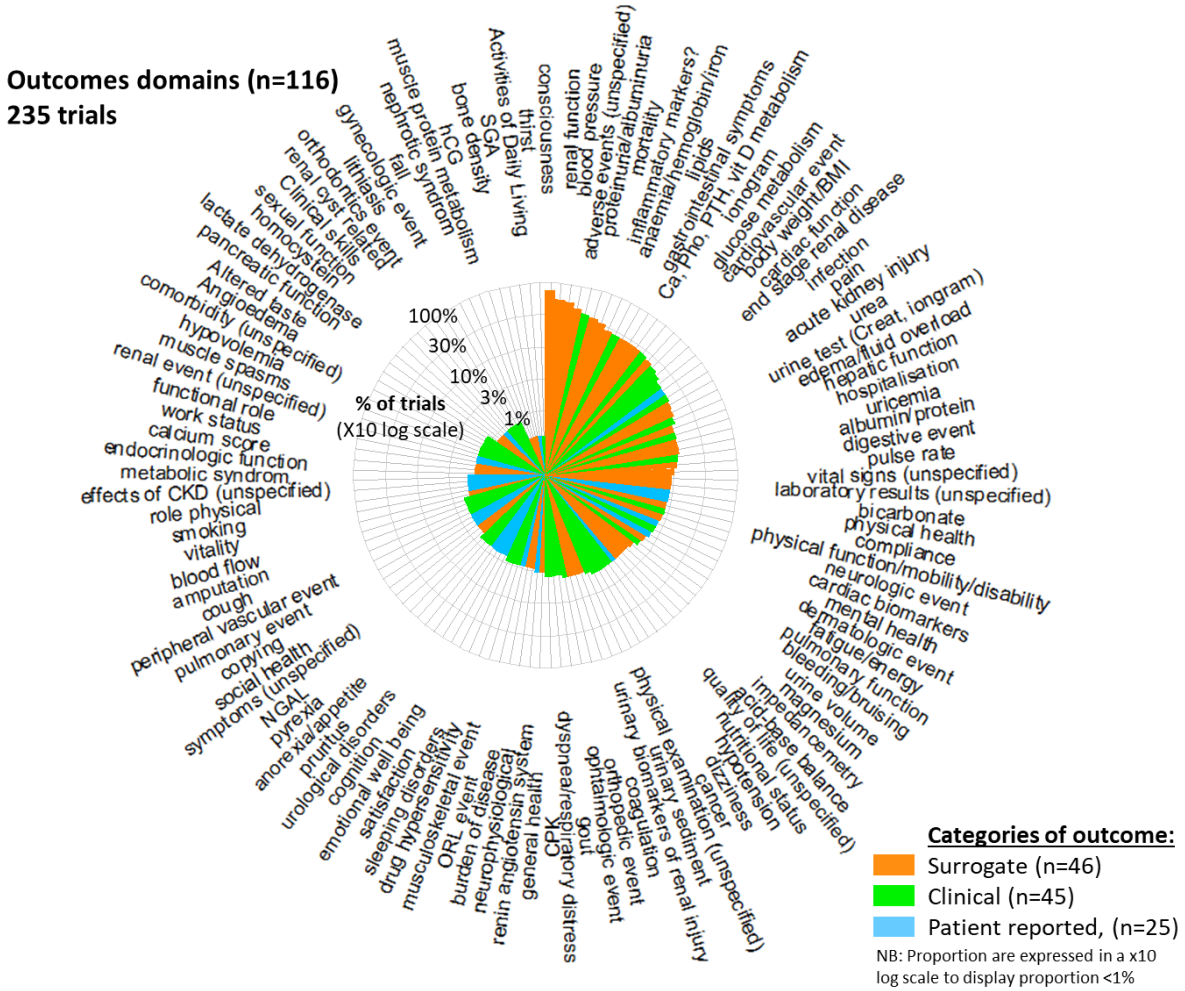

Figure 3A. Different outcomes measures and time points for mortality.

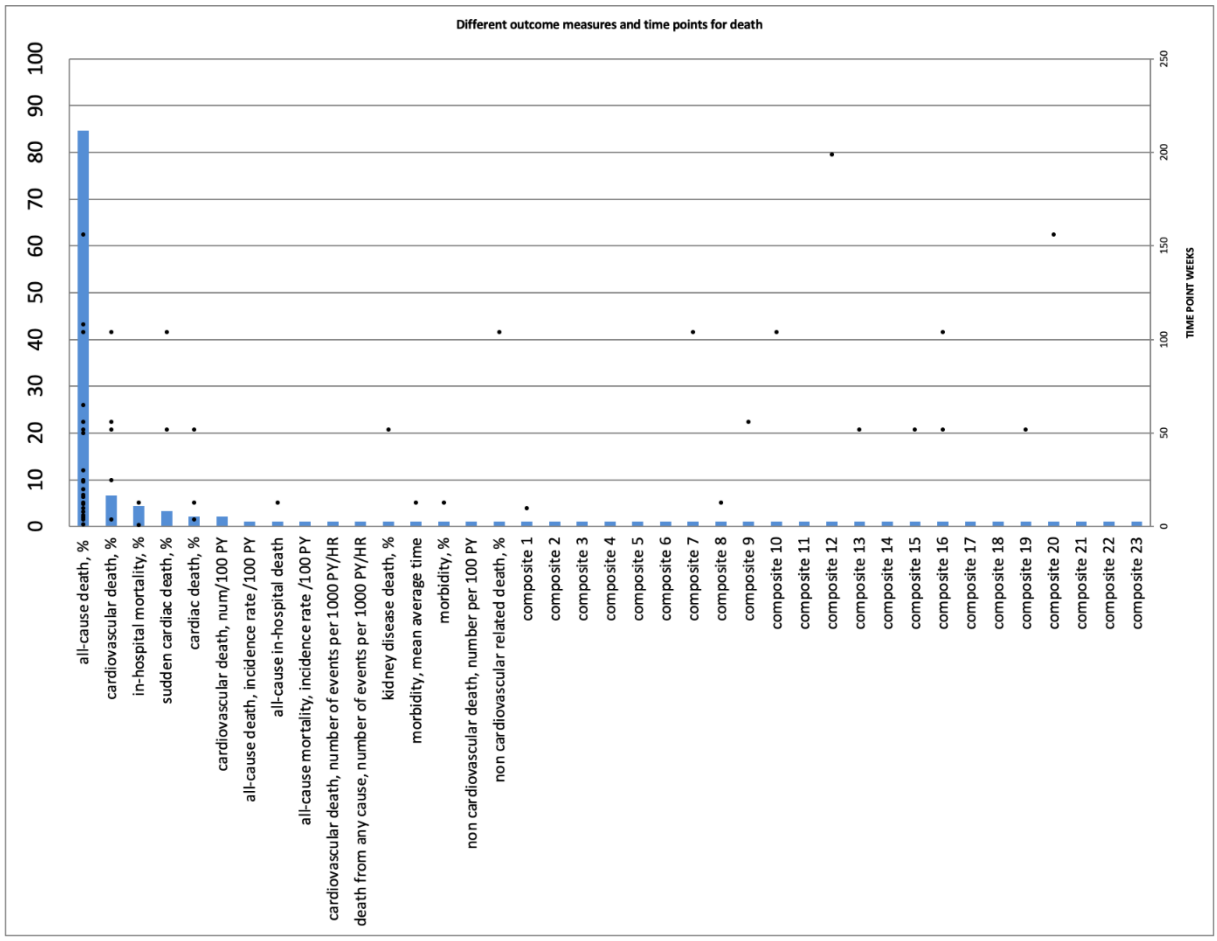

Figure 3B. Different outcomes measures and time points for pain.

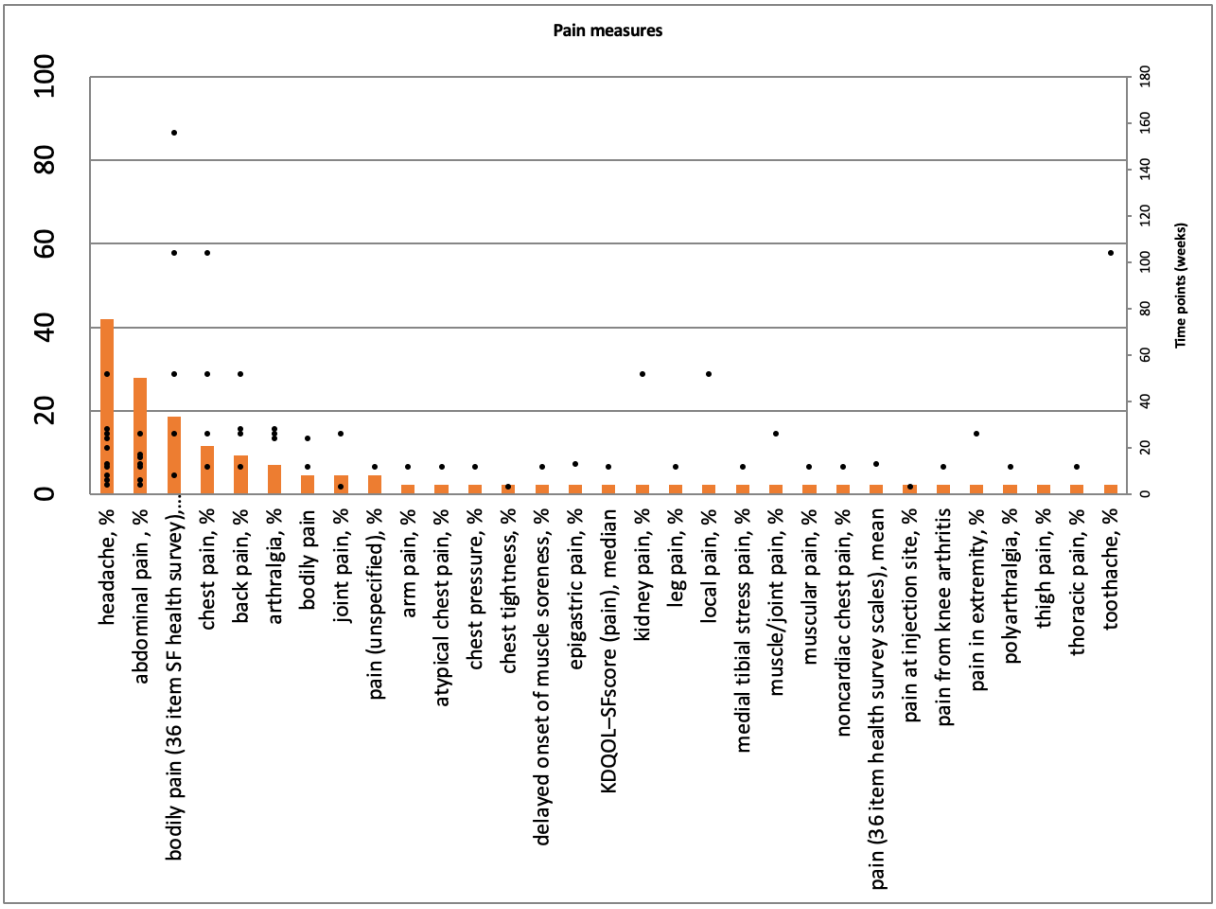

Figure 4. Repartition of outcome categories in trials, by year.

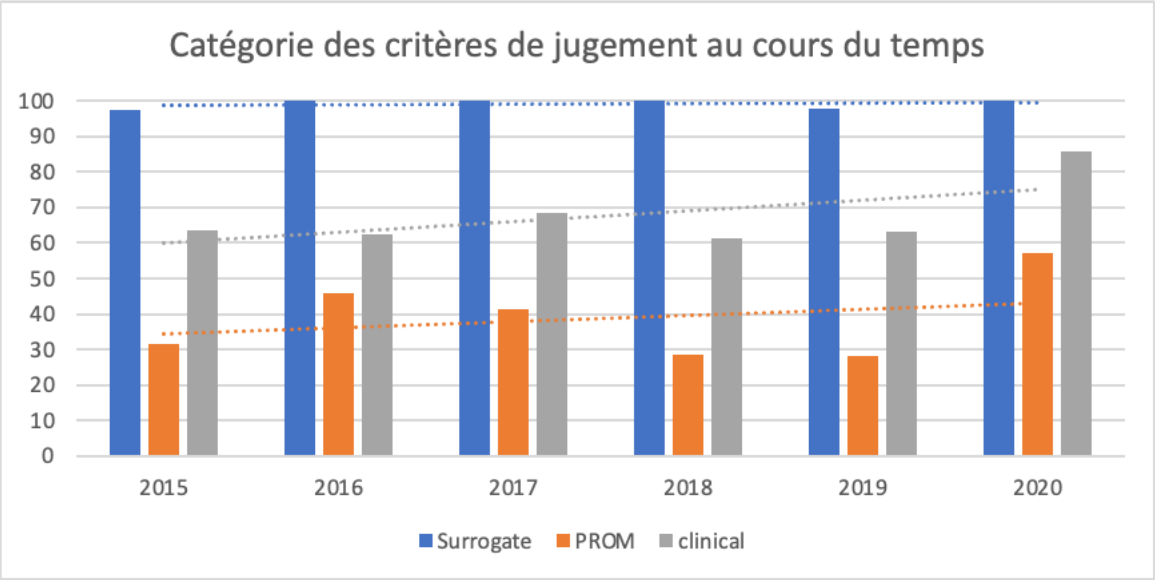

Table 1. Characteristics of included trials (n = 235)

Trial characteristics	No. trials (%)
Year of publication or registration	
2015-2018	189 (80.4)
2019-2020	46 (19.6)
Country	
USA	29 (12.3)
Japan	19 (8.1)
Multinational studies	16 (6.8)
Other	120 (51.1)
Not specified	70 (29.8)
Sample size or estimated enrolment	
1-50	59 (25.1)
51-100	53 (22.6)
101-150	48 (20.4)
151-200	11 (4.7)
> 200	64 (27.2)
Duration of trial, weeks	
< 12	55 (23.4)
12-26	95 (40.4)
27-52	48 (20.4)
> 52	24 (10.2)
Not specified	13 (5.5)
Intervention type	
Non pharmacological	62 (26.4)
Diet	15 (24.2)
Exercise	17 (27.4)
Both	1 (1.6)
Other	29 (46.8)
Pharmacological	173 (73.6)
No. unique outcome measures by trial	
1-10	48 (20.4)
11-25	114 (48.5)
26-50	64 (27.2)
>50	9 (3.8)

Vu, le Directeur de Thèse

Tours, le 31 mai 2023

Vu, le Doyen
De la Faculté de Médecine de
Tours Tours, le

Résumé

Objectif

La maladie rénale chronique (MRC) est souvent silencieuse et les essais contrôlés randomisés (ECR) favorisent les critères de jugement (CDJ) de substitution plutôt que les CDJ cliniques ou rapportés par le patient. L'objectif de notre étude est d'évaluer l'hétérogénéité et la variabilité des CDJ rapportés dans les ECR chez les patients atteints de MRC.

Méthodes

Nous avons réalisé une revue systématique d'ECR évaluant les patients atteints de MRC stade 1 à 5 hors dialyse ou transplantation rénale, publiés en anglais de Janvier 2015 à Décembre 2020. Chaque CDJ rapporté a été extrait puis classé par domaine et catégorie (clinique, rapporté par le patient ou de substitution).

Résultats

Nous avons retenu 235 ECR correspondant à 427 975 patients et extrait 7236 CDJ correspondant à 116 domaines différents. Parmi les 116 domaines, 46 (40%) étaient des CDJ de substitution, 45 (39%) des CDJ cliniques et 25 (21%) des CDJ rapportés par les patients. Les trois domaines les plus fréquemment rapportés étaient la fonction rénale (182 essais [77 %]), la PA (133 [57 %]) et les événements indésirables (124 [53 %]). Le premier CDJ clinique était la mortalité (91 essais [39 %]) et le premier CDJ rapporté par le patient était la douleur (43 [18 %]).

Conclusions

Les CDJ rapportés dans les ECR concernant la MRC sont très hétérogènes et les CDJ de substitution sont privilégiés par rapport aux CDJ cliniques et rapportés par les patients. Cette étude fait partie de l'initiative SONG dont l'objectif est d'établir un ensemble de CDJ standardisé basé sur l'opinion partagée des patients, aidants et professionnels de santé dans le but d'améliorer la prise en charge thérapeutique des patients

GOUIN Elise
30 pages – 1 tableau – 4 figures

Résumé :

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Mots clés : maladie rénale chronique, revue systématique, épidémiologie, initiative SONG

Jury :

Président du Jury :	Professeur Jean-Michel HALIMI
Directeur de thèse :	Docteur Bénédicte SAUTENET
Membres du Jury :	Professeur Philippe GATAULT
	Docteur Christelle BARBET
	Docteur Nicolas GOIN
Date de soutenance :	30 juin 2023