Aus der Medizinischen Klinik und Poliklinik IV

Klinikum der Ludwig-Maximilians-Universität München

Quantity and Reporting Quality of Kidney Research

A systematic review

Dissertation

zum Erwerb des Doktorgrades der Humanmedizin

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

vorgelegt von

Markos Kyriakos Tomidis Chatzimanouil

aus Thessaloniki, GR

2021

Mit Genehmigung der Medizinischen Fakultät
der Ludwig-Maximilians-Universität München

Berichterstatter:	Prof. Dr. Hans-Joachim Anders
Mitberichterstatter:	Prof. Dr. Anne-Laure Boulesteix Prof. Dr. Alexander Buchner PD Dr. Ulrich Dendorfer
Dekan:	Prof. Dr. med. dent. Reinhard Hickel

Tag der mündlichen Prüfung: 18.02.2021

Die vorliegende Arbeit wurde von August 2017 bis Dezember 2018 in der Medizinischen Klinik und Poliklinik IV des Klinikums der Universität München durchgeführt.

Betreut wurde die Arbeit durch Herrn Prof. Dr. med. Hans-Joachim Anders.

Aus dieser Arbeit hervorgegangene Veröffentlichungen

Originalarbeit: M. K. Tomidis Chatzimanouil, L. Wilkens, and H. Anders, "Quantity and Reporting Quality of Kidney Research," *J. Am. Soc. Nephrol.*, vol. 30, no. 1, pp. 13–22, Jan. 2019. [1]

Table of Contents

Summary

In 2004, researchers reported that the number of nephrology clinical trials was low and that the reporting quality of such trials was suboptimal. Furthermore, the number or quality of preclinical kidney-related studies had not been systematically evaluated.

We performed a systematic review of randomized clinical trials published in 1966–2017 (listed in the Cochrane Library) and preclinical studies published in 1945–2017 (listed in PubMed). For reporting quality analysis, we evaluated the final main paper of 118 clinical trial reports and 135 preclinical studies published in leading journals in 1996, 2006, and 2016 on the basis of modified criteria based on the widely used CONSORT and ARRIVE guidelines.

The annual number of reports of clinical kidney-related trials more than doubled between 2004 and 2014 along with reports in other medical disciplines. Hypertension remains the dominant focus of study, but on-going trials also centre on CKD, ESKD, and AKI. The reporting quality analysis revealed improvements, but deficits in reporting of clinical trial design, mode of randomization, and intention-to-treat analysis remain. Annual numbers of kidney-related preclinical studies remained low between 1945 and 2017 compared with other disciplines. Reporting quality analysis of preclinical studies revealed substantial reporting deficits across all leading journals, with little improvement over the last 20 years, especially for group size calculations, defining primary versus secondary outcomes, and blinded analysis.

Nephrology studies keep increasing in number but still lag behind other medical disciplines and the quality of data reporting in kidney research can be further improved.

Zusammenfassung

Im Jahr 2004 konnte eine geringe Anzahl klinischer Studien auf dem Gebiet der Nephrologie und eine suboptimale Berichtsqualität solcher Studien festgestellt werden. Die Anzahl und Qualität präklinischer Studien in der Nephrologie wurde bisher noch nicht systematisch ausgewertet.

Wir führten eine systematische Übersichtsarbeit der in den Jahren 1966-2017 veröffentlichten randomisierten kontrollierten Studien (verwendete Datenbank: Cochrane Library) und der in den Jahren 1945-2017 veröffentlichten präklinischen Studien (verwendete Datenbank: Pubmed) durch. Im Rahmen der Qualitätsanalyse der Forschungsberichte bewerteten wir die endgültige Version des Originalartikels 118 klinischer und 135 präklinischer Studien, welche in den Jahren 1996, 2006 und 2016 in führenden Journalen veröffentlicht wurden. Wir verwendeten dabei modifizierte Bewertungskriterien, welche auf den weit verbreiteten CONSORT und ARRIVE Richtlinien basierten.

Die jährliche Anzahl der Berichte über klinische Studien mit Bezug zur Nephrologie hat sich zwischen 2004 und 2014, ähnlich wie bei Berichten aus anderen medizinischen Disziplinen, mehr als verdoppelt. Hypertonie bleibt der dominierende Schwerpunkt von Studien, laufende Studien konzentrieren sich jedoch vermehrt auf die chronische und terminale Niereninsuffizienz sowie auf die akute Nierenschädigung. Die Berichtsqualitätsanalyse ergab Verbesserungen im Laufe der Zeit, es bestehen jedoch weiterhin Defizite bei der Berichterstattung über das Design klinischer Studien, die Art der Randomisierung und die Intention-to-treat-Analyse. Die jährliche Zahl präklinischer Studien mit nephrologischem Bezug blieb zwischen 1945 und 2017 im Vergleich zu anderen Fachdisziplinen auf einem niedrigen Niveau. Die Analyse der Berichtsqualität präklinischer Studien ergab erhebliche Defizite in allen führenden Journalen, wobei sich in den letzten 20 Jahren geringe Verbesserungen zeigten, insbesondere bei der Stichprobenberechnung, bei der Definition von primären und sekundären Endpunkten sowie bei der Verblindung.

Die Zahl der nephrologischen Studien nimmt weiter zu, bleibt jedoch hinter anderen medizinischen Disziplinen zurück, und die Qualität der Berichterstattung in der nephrologischen Forschung kann weiterhin verbessert werden.

1. Introduction

1.1. The kidney and medical research

The kidney is a paired, beaned shaped organ, located in the retroperitoneal space, with an average length from 10–13 cm. The structural and functional unit of the kidney is the nephron, with each human kidney containing around 1 million of them. The kidneys play an essential role in human physiology, with many important diverse excretory and endocrine functions. The excretory functions include the excretion of urinary substances, the regulation of the water and electrolyte balance and of the acid-base balance. The most prominent endocrine functions are the production of erythropoietin for erythropoiesis, calcitriol for regulating calcium metabolism and renin for blood pressure control [2].

Nephrology is the medical specialty which addresses diseases of kidney function, such as chronic kidney disease (CKD), acute kidney injury (AKI) or glomerulonephritis (GN). These diseases play a major role in morbidity and mortality worldwide. CKD, for example, was the ninth-leading cause of death in the United States in 2017. Approximately 37 million Americans have CKD and more than 100,000 Americans begin dialysis each year. Twenty percent die within a year; fifty percent die within 5 years. As in most medical fields, the advancement of kidney health, the improvement of the diagnostic procedures and the discovery and application of new, more effective therapeutic strategies is closely tied to the quantity and the quality of the medical research conducted on the field, both in form of preclinical studies and of clinical trials [3].

Perhaps the most familiar form of health research are studies designed on human participants. The two main forms are the aforementioned clinical trials and observational studies. Observational studies improve the knowledge of a disease through observation of interventions or procedures as part of the medical care or follow up visits, but contrary to clinical trials, participants are not assigned to a specific intervention by the investigators.

Clinical trials, or interventional studies, on the other hand try to investigate the efficacy and safety mainly of drugs, new or existing ones, by assigning participants to specified study interventions. Comparisons of a new medical intervention to a standard already established,

to a placebo with no active substances or to no intervention at all are possible. Clinical trials are designed to answer specific biomedical or behavioural questions, to test the safety and effectiveness of new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and to examine known interventions that warrant further study and comparisons.

In addition, we use, and have for a long time used, cells, tissues, animals to discover what healthy biological processes look like, how they change with disease, how we can intervene in those processes and what are the consequences of our interventions. This form of research, called basic or bench science, begins before the clinical or human trials, involves scientific principles that help deepen our preclinical understanding and has as its main goals the identification of new, possibly helpful, biological pathways or targets, the investigation of new drug applications or the determination of safety doses for first clinical trials, which may apply to drugs, gene therapy solutions, antibodies, diagnostic tools or medical devices.

The bridge between the clinical and the preclinical part of the research field, in other words the way from bench to bedside, is called translational medicine. The translational research tackles to improve ways to connect the basic fields of preclinical trials with clinical applications, in an effort to build on basic scientific research, in order to create new therapies, drugs, medical or diagnostic procedures.

1.2. Clinical research

1.2.1. Phases of clinical trials

Drugs and medical interventions undergo a lengthy process before been put on the market. Even testing in humans is not allowed before excessive laboratory testing. The development of a drug or a medical intervention can last in total almost 15 years. Clinical research in human participants is divided in different phases, which are separate clinical studies with different and unique objectives. In total, there are 5 different phases of clinical trials, from 0 to IV. Generally, as a drug or substance moves through the phases of trials, the sample size of the trial will typically increase, and its efficacy, safety and adverse events will be further

examined. In contrast, if during a phase a substance is found to be unsafe or inadequate, further testing will not be conducted [4].

Phase 0 and I

Phase 0 or Phase I trials are usually the first trials conducted among human participants. In Phase 0 trials usually a very small dose, beyond any therapeutic benefit to the human body, is given to a small group (10-15) of people. The main object of such trials is to examine the pharmacodynamics and kinetics of the substance to the human body. Often Phase 0 trials are skipped in favour of Phase I trials.

Phase I trials include the testing of a substance, usually on healthy volunteers (15-30 people), with main objectives the examination of the substances safety and the determination of the ideal dose with the fewest side effects. Usually those trials include dose raging, also called dose escalation studies, which means the examination of different doses of the drug and its effects on the human body, starting by giving microdoses of the drug, up to higher doses, until side effects become too severe [4][5].

Phase II

Once Phase I trials are successfully completed, the initial safety of the substance has been established and a dose or range of doses is determined, the drug will move to a Phase II trial, which has as its main goals the further assessment of the drug's safety and if and how well it works. Phase II trials are usually conducted on larger groups of participants, with sample sizes ranging to a few hundred people, and are often aimed at patients with the specific disease that the drug aims to treat.

Phase II trials are the most common step when the development of a potential new agent fails due to toxic effects or lack of effectiveness.

At this point it is also important to note that some of the Phase II trials are designed as randomized controlled trials (RCT), where patients are assigned to different study groups and some of them receive the examined therapy whereas others receive a placebo or the already established treatment. RCTs are most commonly Phase III trials, which also include way more participants than Phase II trials. A more detailed explanation of such form of trials and their importance can be found below [4][5].

Phase III

Phase III trials are designed to assess the effectiveness of a treatment and thereby its value in the clinical practice. They often comprise the final trial phase before a new drug is evaluated by the regulatory authorities for market access. This kind of trials provides the necessary information about safety, efficacy and adverse events, which determine whether a drug or a medical intervention can be approved. Phase III trials are often either placebo-controlled, or the current gold standard treatment may be used to compare the effectiveness of the examined substance. They are usually randomized trials, meaning participants are assigned to study groups by chance, and the randomization process is often

Table 1: Summary and Comparison of the phases of clinical trials

Phase	Objective	Dose	Population And Sample Size	General Data Focus	Design Features	Success Rate*
Phase I	Testing of drug on healthy volunteers for safety; involves dose-ranging	sub-therapeutic with ascending doses	30–100 healthy volunteers	-Vital Signs -Plasma and Serum Levels -Adverse Events	-Single, ascending dose tiers -Unblinded -Uncontrolled	70%
Phase II	Testing of drug on patients to assess efficacy and side effects	therapeutic dose	100–300 patients with specific diseases	-Dose Response and Tolerance -Adverse Events -Efficacy	-Placebo/ Active Controlled Comparisons -Well defined Entry Criteria	33%
Phase III	Testing of drug on patients to assess efficacy, effectiveness and safety	therapeutic dose	300–3,000 patients with specific diseases	-Laboratory Data -Efficacy -Adverse Events	-Randomized -Blinded -ITT -Controlled	25-30%
Phase IV	Postmarketing surveillance	therapeutic dose	anyone seeking treatment	-Efficacy -Epidemiology -Adverse Events	-Uncontrolled -Observational	N/A

*According to the FDA (U.S. Food and Drug Administration)

stratified, in order to minimize false study result due to inhomogeneity between the groups compared. Phase III trials also usually involve a much larger number of participants than trials of previous phases and are often conducted in multiple centres simultaneously. Because of their size, complex design and duration, this kind of trials are usually expensive and difficult to design and run, but are a necessary step in order to minimize bias and false results, and to produce statistically significant data mainly about the efficacy and safety of a drug [4][5].

Phase IV

Phase IV trials are post marketing surveillance trials. This means that they try to evaluate the drug's profile after it has been licensed and while been part of the clinical practise. The aim is to establish the drug's long term efficacy and safety through time and in even larger groups of people. Phase IV trials may also include further testing for a substance, for example to identify and to examine interactions with other drugs, or on certain population groups, for example in pregnant women or children [4][5].

1.2.2. Randomized controlled trials

Irrespective of the phase of a clinical trial, one of the most significant and influential forms of trial design are the RCT. RCTs, when appropriately designed, conducted and reported, represent the gold standard in evaluating healthcare interventions [6] and are the most rigorous way of determining a cause and effect relation between the intervention and the outcome. This is mainly due to the controlled exposure of the study, which ensures that many of the biases which potentially can provide falsified results are either completely absent or are at least greatly diminished [7].

Of course, the validity of a RCT is massively influenced by the underlying methodological quality. Not all RCT are adequately designed, conducted or reported. The key risks of bias in a randomized trial , the danger in other words to over- or underestimate the intervention's effect or its safety reflect method flaws in major areas of the trial [8]. There are several critical aspects that have to be taken into consideration for a trial to truly provide unconfounded estimates on intervention effects, more prominent among them the sample

size of the study, the randomization or the allocation concealment procedures, the blinding or masking of the trial, loss to follow-up, intention to treat analysis and firmly defined end points. Each physician but even more generally, everyone coming across the results of a trial, should be able to critique its underlying methodology, so as to be able to interpret the significance of said trial. Thus, in the following paragraphs a more detailed view of the more crucial items that define the quality of an RCT will be presented.

Generally, the steps for performing an RCT is to initially formulate the hypothesis to be tested, identify the sample from which the participants are to be drawn, randomize subjects to the intervention or control groups, perform the intervention as appropriate to the randomization of the participants and analyse the results. Ideally, features of a well-designed RCT are:

- Determination of an appropriate and representative sample of the population to recruit and recruitment of enough participants in order to produce statistically significant results.

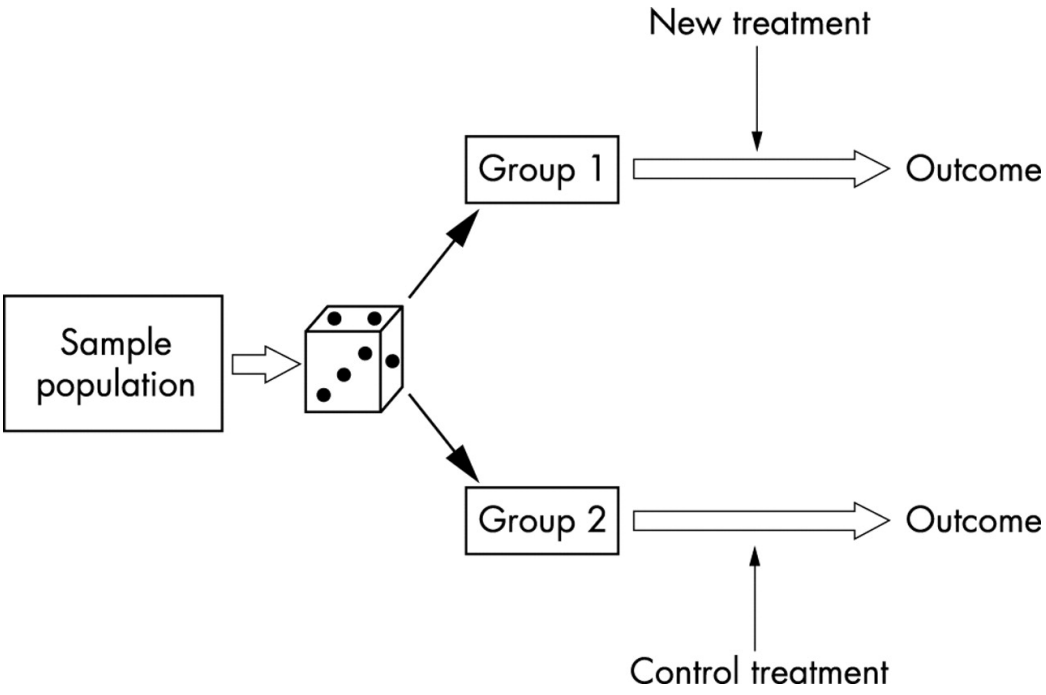


Figure 1: The randomized control trial. Reproduced from Emergency Med. Journal, "Designing a research project: randomised controlled trials and their principles.," J. M. Kendall, vol. 20, no. 2, pp. 164–8, Mar. 2003 with permission from BMJ Publishing Group Ltd. [9]

- Effective Randomization and simultaneously concealment of the allocation to the study groups (intervention/ control group(s)).
- Blinding, ideally of both the investigators and of the patients. Additionally but equally important blinding of the investigators assessing outcome.
- Primary end point analysis conducted with patient included to the group of their original allocation, irrespective of crossover, drop outs or loss to follow-up (Intention to treat analysis).
- Prespecified end-points and outcomes to be assessed.

Main errors of clinical research and design characteristics for their avoidance

Avicenna or Ibn Sina (980-1037), one of the most prominent and significant physicians, scientists and philosophers of the Islamic world, stressed the importance of internal and external validity in clinical research almost 1000 years ago. External validity refers to the validity of applying the scientific results of a study outside of its strict context. Important factors for the external validity of a trial are the selection process of patients, the intervention regimens, and the outcome variables [10].

Internal validity refers to the restriction of bias through proper design, conduction, analysis and reporting of a trial and refers to the validity of conclusions drawn within the context of a specific study. One can distinguish three main forms of bias, the first called selection bias, referring to systematic differences between groups being studied, the second called observer bias, occurring when the information collected from groups to be studied is processed differently. The third form of bias, called confounding, refers to an outside factor which can influence both the dependent and the independent variable of a trial, thus mixing the effect of the exposure under a study on a given outcome with the effects of the additional factor, or factors, and consecutively distorting the true relationship between intervention and outcome.

Equally important is to consider the existence of a random error in a study, which can usually appear in studies with a small number of participants, for example through unequal

distribution of prognostic factors between groups. The most important design strategy to minimise random error is to have a large enough sample size. The beauty and the significance of RCTs stems from exactly the fact that when designed, conducted and reported adequately, all these forms of error can be greatly reduced or even be extinguished [9].

Target population and sample size

The determination of the target population to which the healthcare intervention is meant to be examined and its results are intended to be applied is essential. Trials should prespecify inclusion and exclusion criteria defining target populations appropriate to the research hypothesis, but also excluding persons thought to be particularly vulnerable to harm from the study's intervention.

Equally important is to carefully plan the sample size for a trial. A sample size calculation is important both for scientific but also for ethical reasons, and a large enough sample size allows the study to detect a clinically important difference between intervention and control groups. The size of effect deemed important is inversely related to the sample size necessary to detect it; so in order to detect small differences large sample sizes have to be included [9] [11].

Randomization

One of the main strengths of RCTs and perhaps their main feature is the randomization process. The patients are randomly, through various methods, assigned to the different study groups. True randomization allows participants to have an equal and random chance of being placed in the intervention or the control groups of a study and is the basis for establishing a casual interpretation.

Different baseline characteristics of the participants should be measured at the stage of the initial recruitment of the trial, such as weight sex, age, name, but more importantly should include any potential prognostic factors. Even though proper random assignment automatically prevents selection bias, it does not guarantee equivalence of the groups at baseline [11]. All these baseline characteristics also have to be interpreted as potentially confounding factors and thus have to be divided equally among the groups to be compared later. Only if the groups are structurally equivalent can differences in the analysis of the

study be attributed to treatment effect rather than confounding influences [12]. Here is important to note that randomization cannot completely guarantee the equal distribution of confounding factors, as they may arise by chance. Also essential is to guarantee concealment of the allocation to the investigator, to minimize observer bias.

At this point a mention and short description of the various randomization techniques would be useful. Other than the simple randomization, which with a 1:1 allocation is analogous to a coin toss, there are other forms, called restricted randomization, which allow for a more controlled distribution of confounding factors than chance alone might achieve. These forms of randomization are especially important to trials with smaller sample sizes.

The two most common forms are:

- Blocked randomization, which can ensure that the number of participants in each group is equal. For example, instead of allocating each participant through random chance to a study group, blocks of 20 are formed, ensuring that within each block 10 patients are allocated to the control and 10 to the intervention group.

Table 2: Typical steps taken in a randomization process

•	Determine the method (for example, a computer generated list of random numbers) and generate the sequence generation.
•	Define mechanisms used to implement the random allocation procedure (such as sealed envelopes) and take steps to conceal the sequence until interventions are assigned
•	Define who will generate the allocation sequence, who will enrol patients and who will assign them to interventions
•	Implementation Enrol participants and administer intervention

- Stratified randomization, which can ensure a good balance of baseline characteristics between groups and, when further confounding factors are known, their equal distribution. Stratified randomisation is achieved by performing a separate randomisation procedure within each of two or more subsets of participants (for example age, or disease severity) [11].

Of course, in the clinical reality, also further parameters other than the type of randomization have to be taken into consideration to ensure the appropriate randomization of a trial. Typical steps for a robust randomization process are described in Table 2.

Blinding

Another important method to minimize bias in RCTs is achieved through blinding, which ensures that some of the people participating in a trial are unaware of the patients' treatment allocation. Blinding of the investigators is crucial when possible, since it ensures that conscious or subconscious bias through extra attention to the intervention group can be avoided, meaning that all study arms are treated equally and any outcome differences are due to the investigated treatment [7]. On the other hand, blinding of the patients themselves to their treatment allocation is equally important, since their attitude can potentially affect their compliance and even their response to treatment.

Blinding is achieved by making the intervention and the control appear similar. Often this happens by manufacturing placebo or control medication that is indistinguishable from the tested substance, something which can be costly and complex. Furthermore, blinding is not always possible. For example, in surgical trials or kidney trials testing alternate day to every day dialysis blinding can prove quite difficult or even impossible to achieve [9].

Various degrees of blinding may be applied to a study. Double blind are studies where neither the physicians nor the patients are aware of the patients' treatment allocation. If only one party is blinded, the study is called single blind, and if no blinding at all occurs, it is called open. Naturally, the highest possible degree of blinding should be chosen, but even if blinding is not possible, a blinded third party can measure outcome [9][12].

Crossover, loss to follow-up and the intention–to-treat principle

Ideally, each randomized patient will receive his or hers allocated and intended treatment, whether that is the tested intervention or the placebo/ standardized one. Unfortunately this pure division and smooth trial conduction not always happens in real life.

The term crossover refers to a patients switch from one group to another, which can happen for example through mistake in allocation procedures, patient noncompliance or through administration of the tested substance through outside medical personnel. Crossover leads to more similar outcomes between the compared groups, as shown in Figure 2.

Loss to follow-up can influence a trial's outcome to an even higher degree. Non-random exclusion of participants who are lost to follow-up can introduce bias in unpredictable way, but it usually results in larger estimates of treatment efficacy compared to trials in which all randomized participants were evaluated [8]. This tends to happen because participants with specific characteristics are more likely to be lost to follow-up than others, for example patients with clinical deterioration or severe adverse effects in the intervention group are more likely to drop out than others.

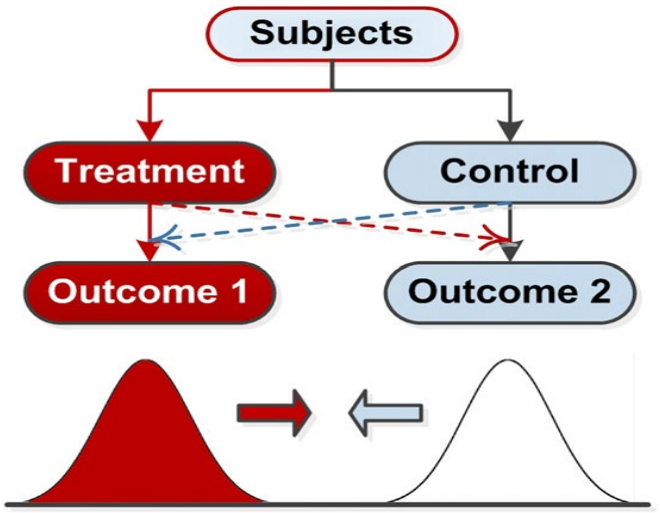


Figure 2: The effect of crossover in a clinical trial. Note that increasing crossover ''waters down'' any difference between groups and makes them more similar. Reprinted from Adv. Chronic Kidney Dis., vol. 19, no. 1, J. A. Samuels and D. A. Molony, "Randomized Controlled Trials in Nephrology: State of the Evidence and Critiquing the Evidence" pp. 40–46, 2012 with permission from Elsevier [7].

Irrespective of whether patients refuse to continue treatment, are lost to follow-up, lost to analysis or have crossed over to an alternate study group, for a RCT to produce unbiased results and to retain its fidelity, each study subject should be analysed as if they had remained in the group and received the allocated treatment to which they had been originally randomized and all originally randomized participants should be included in the analysis. If these two conditions are met then the analysis is called intention-to-treat (ITT) analysis, which is the form of analysis widely considered as the most reliable one. Such analyses allow for the preservation of the advantages of the randomization, such as the structural equivalence between the groups, and since ITT analyses include all patients randomized, even those who discontinued treatment due to adverse side effects or deterioration, have crossed over or did not even take place in the study from the beginning, produce conservative results, meaning the efficacy of a drug intervention is not falsely highlighted through an altered analysis sample [12].

1.2.3. Importance of reporting and the CONSORT statement

Having described some of the main features of a well-designed RCT, it becomes evident that not only the design and the conduction of a trial are important, but also the trial's reporting. Transparent reporting can reveal deficiencies in research, if they exist. If a thorough publication process is established, requiring the explanation and the reporting of all main quality features of a RCT, inadequate trials would not be able to publish false results.

Editors from many biomedical journals have started collaborating since 1984 in order to develop a guideline for adequate reporting of RCTs. Efforts accelerated in the mid-90s, resulting in the publication of the first CONSORT (Consolidated Standards of Reporting Trials) guidelines in 1996. Further methodological research resulted in the revision of 2001, which provided comprehensive checklists for investigators to ensure that RCT are reported accurately and comprehensively.

While those statements improved the reporting quality for some trials, many trial reports still remained inadequate. For example only 45% of trial reports indexed in PubMed in 2000 and 53% in 2006 defined a primary end point, and only 27% in 2000 and 45% in 2006 reported a sample size calculation, while it is not rare to find inaccurate statements in trial

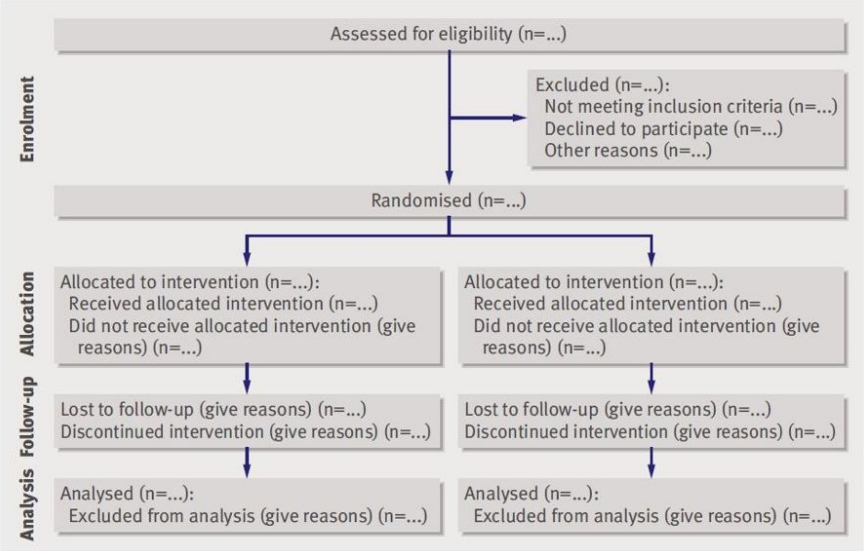


Figure 3: **Flow diagram of the progress through the phases of a parallel randomised trial of two groups** (that is, enrolment, intervention allocation, follow-up, and data analysis). Reproduced from BMJ, "CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials", K. F. Schulz, D. G. Altman, and D. Moher, vol. 340, no. mar23 1, pp. c332–c332, Mar. 2010 with permission from BMJ Publishing Group Ltd [6].

reporting, such as claims of an ITT analysis where clearly its main principles were not followed [11].

The last CONSORT revision took place in 2010 and it comprises a checklist of 25 items that should be included in reports of RCTs and a flow diagram of the progress through the phases of a RCT (Figure 3). The main objectives of CONSORT are to provide guidance to authors but also provide readers a tool to critique a trial's quality. More than 400 journals, including the majority of leading journals, explicitly support the CONSORT initiative [6][11].

1.3. Preclinical Research

1.3.1. Importance and common concerns of preclinical studies

Animal models and preclinical research share a unique and significant connection with human trials, since they are the main experimental tool used to drive the development of human therapeutics. The purpose of preclinical research, studies with animal models, tissues or cells, is to identify human disease processes, uncover new biochemical pathways, identify promising target therapies and test potential drug and intervention agents. Human trials are

often justified based on promising results from animal studies. This connection can on the one hand highlight the importance of basic research, but can also become problematic, when results of preclinical studies cannot be replicated or are unfit to be translated in clinical research. Progress in science is dependent on a strong foundation of reliable results. The ability of scientists to reproduce and build upon each other's results is essential to the advancement of medical research.

Often the scientific community assumes that the results of a study can be taken at face value, that the main message of the study and the main data will be reproducible and stand repeated testing [13]. The truth is that, unfortunately, most of the time, investigators cannot reproduce many of the published basic and preclinical studies. The last few years this problem has been highlighted with many published articles shedding light on the size and importance of irreproducible results and sparking the so called "reproducibility crisis" [14].

An analysis in 2015 showed that around 50% of scientific research is not reproducible, concluding that as much as $28 billion each year are spent in the United States on basic and preclinical research that cannot be replicated [15], while a study in 2013 examined the problem of identifiability, meaning the inability to uniquely identify research resources, making it often impossible to reproduce experiments, highlighting that 54% of the publications examined do not define resources in the biomedical literature [16]. This level of uncertainty in preclinical results has various ramifications on many levels. Not only can it potentially waste millions of funding money on dead-end research, but raises also important ethical and scientific concerns, especially in the field of animal testing.

1.3.2. Preclinical study design, reporting, and reproducibility

Ideally, preclinical publications should come with enough information as to allow the reader to understand what, why and how it was done, as well as providing the ability to judge the validity and reliability of the experiment. In real life, and as many systematic reviews have exposed recently, preclinical studies often show major vulnerabilities. Problems with data reproducibility can arise at various levels of the research process, ranging from methodological flaws in study design and conduction, or as shown above, to incomplete data reporting, hindering even attempts to try and reproduce results. A plethora of factors, such

as sex and age of subject material, housing conditions, time of the interventions, errors in statistical design or lack of blinding and randomization, can lead to variability in the outcomes of animal studies.

The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3R) "evaluated methodological reporting in the literature for *in vivo* studies using rodent models or non-human primates. Detailed information was collected from 271 publications about the objective or hypothesis of the study, the number, sex, age and/or weight of animals used, and experimental and statistical methods. Only 59% of the studies stated the hypothesis or objective of the study and the number and characteristics of the animals used. Most of the papers surveyed did not use randomisation (87%) or blinding (86%) to reduce bias in animal selection and outcome assessment. Only 70% of the publications that used statistical methods described their methods and presented the results with a measure of error or variability" [17]. These findings are a cause of concern, since it is clear that the entire scientific community is reliant on scientific research being designed adequately and reported transparently and accurately.

Randomization and blinding in preclinical studies

Randomization and blinding are important components of any robust experimental design and while considered routine in clinical trials, their application in preclinical studies is often scarce. Evidence has suggested that randomization, allocation concealment and blinding can also reduce bias in animal research [18]. A systematic review concluded that "failure to randomize is likely to result in overestimation of the apparent treatment benefits of interventions across a range of disease areas and outcome measures" and demonstrated the need for randomization and blind outcome assessment [19]. Despite of that, in a review of the first 100 articles published in Cancer Research in 2010 that included animal research, only 28% of them reported any type of randomization [20]. Similar to lack of randomization, lack of blinding can exaggerate preclinical efficacy and leave a study unguarded against confirmation bias, resulting in following clinical trials on the topic be based on data that leave a lot to be wanting [21].

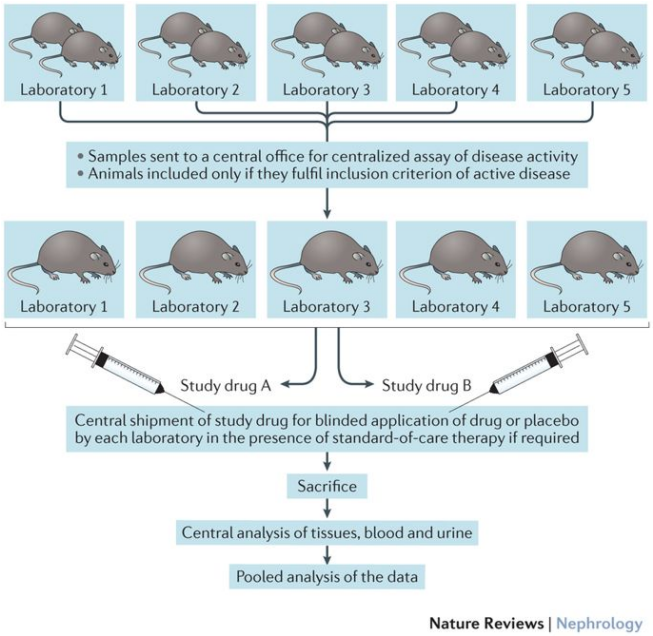


Figure 4: **Design of a multicentre randomized controlled trial in rodents**. To improve the applicability of findings from interventional studies in rodents to randomized controlled trials in humans, robust clinical trial design must be adapted for rodent studies. Animals that fulfil predefined inclusion and exclusion criteria should be centrally randomized to receive different treatments that are administered in a blinded manner. Blinded evaluation of samples shipped from multiple centres to a core facility generates a high threshold for therapeutic effects and avoids investigator bias. A drug with proven efficacy under these rigorous conditions might be more likely to produce similar outcomes in a similarly designed trial in humans.
Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature Reviews Nephrology, "Hurdles to the introduction of new therapies for immune-mediated kidney diseases", H. J. Anders, D. R. W. Jayne, and B. H. Rovin, 2016 [22].

An example to the randomization of animals in preclinical studies can be found in Fig. 4, which was conducted by researchers testing the efficacy of anti-CD49d antibody in two mouse models of acute brain ischemia [22].

Sample size

Sample size calculation is another important parameter when considering a robust scientific design of a preclinical study. The sample should be large enough, in order to allow investigators to produce results that can be characterized as statistically significant, having a high probability to detect a treatment effect. On the other hand, a too large sample can have negative economical, practical but also ethical consequences on a study. An underpowered study for example, could prove to be unethical through the vain sacrifice of animals without a high probability of proving the efficacy of the intervention, while an overpowered study, through the means of a too large sample, can lead to the unnecessary use of animals [23].

Thus, it becomes clear that the required sample size for any given study should be calculated before the study's conduction, and equally importantly, should be clearly reported in the published manuscript.

Sex as a variable in preclinical studies

Sex, not to be confused with the social construct of a gender, is defined as either being XY or XX, and is closely associated and mediates biologic functions and should be considered an important variable in preclinical research. After sex determination, sex plays a crucial function in the organism's biology and many interactions, such as hormone secretion, are controlled by sex throughout life. Until now, a historic reliance on male organism has resulted on a lack of quality data regarding female participants in many human trials [24]. Incorporating both sexes in preclinical research or at least recognising and reporting sex as a study variable can prove to be an important step in performing research that has a high probability of clinical translation in both male and female participants [25][26].

1.3.3. Efforts to improve design and reporting and the ARRIVE guidelines

Many studies and reviews have been published, both analysing the current common problems preclinical design and reporting are facing and suggesting ways to improve their quality. Caestecker, *et al.* [27] identified and suggested 5 areas of improvement in study design based on the existing literature on Acute kidney injury: 1) Randomization and blinding to treatment, 2) Statistical rigor, 3) Publication bias favoring the publication of positive results, 4) Lack of sex heterogeneity, and 5) Adequate dosing.

But not only randomization, sample size or sex consideration are proven to be lacking in the reporting and design of preclinical studies. As evidenced by the systematic review of the NC3R [17], lack of statistical reporting, description of species or strain of animals, unclear identified study objectives and hypotheses and lack of clear mention of the interventions conducted are common and crucial problems in preclinical research. Having in mind the essential role of basic science, it is of paramount importance for the research community to ensure that reporting and design of animal studies is improved and that research articles

include all relevant information to allow experiment reproducibility, avoid unnecessary duplication and identify credibly promising research fit for clinical translation.

One of the more promising steps in that direction was the introduction of reporting guidelines for animal research in 2010, which were mainly inspired from the CONSORT Statement [6] and were based on the NC3B study [17]. The guidelines, referred to as ARRIVE (Animals in Research: Reporting In Vivo Experiments), consist of a checklist of 20 items, "describing the minimum information that all scientific publications reporting research using animals should include, such as the number and specific characteristics of animals used (including species, strain, sex, and genetic background); details of housing and husbandry; and the experimental, statistical, and analytical methods (including details of methods used to reduce bias such as randomisation and blinding)" [28]. Whether these guidelines have helped to improve the state of preclinical reporting, especially in the nephrological field, was one of the main inspirations for this current project.

1.3.4. External validity as a cause of failed translation

To improve the applicability of findings from preclinical animal studies to human disease and to avoid irrelevant use of animals, cost and time, not only must study designs improve, in many ways more closely reflecting clinical trials, but also better disease models are often needed. Even if no methodological flaws are to be found, and the design, conduct and report of a study all are sound, the lack of external validity, or in other words, generalizability, of the animal models used may cause a failed translation of often promising preclinical results [23]. If the models used do not sufficiently reflect the human disease examined, then the disparities between model and human trial are doomed to be too significant to produce any meaningful results.

Of course it would be ideal to perform preclinical studies in models that closely reflect the human disease. In real life however, only a limited amount of such models are currently available. Animal models for monogenetic disorders, such as the Alport syndrome, meet these requirements at best. More polygenetic or multicausal disorders, like AKI, focal segmental glomerulosclerosis or diabetic nephropathy are already quite heterogeneous in humans, so animal models accurately mimicking these diseases are difficult to find [29].

Table 3: **Approaches to improve findings from animal studies and their translation to human disease**

	Application to animal studies
Animal models	Animal models should reflect the human disease process
Age	Age of animals should match the age of the study participants
Sex	Animal studies should consider sex and sex-match patients
Sample Size	Determine appropriate sample size before study conduction
Randomization	Randomly assign animals to treatment groups to ensure minimization of bias
Replication	Report all relevant information to allow replication of the study

But by optimizing the strategy of animal experimentation and by clearly defining the examined disease, matching the objectives, end points and interventions between preclinical studies and human trials, the resemblance of animal models to human conditions and their contribution in translational medicine can greatly improve.

Other than the pathophysiological similarity of an animal model to a human disease, another important parameter is the consideration of the age and comorbidities in the animal models. Often the animals used do not accurately mirror the human target population in age and comorbidities, but also as discussed above in sex or even co-medication [22].

Table 3 summarizes some of the most important factors subject to improvement in preclinical research, both for the betterment of reliability and improved translation to new human therapies.

1.4. What this all means for nephrology

Relevant nephrological trials leading to therapeutic advantages have proven challenging and kidney diseases remain one of the main causes of mortality globally. From 2000 to 2010 kidney diseases have seen a 21% increase in mortality, and were attributed for around 50.000 deaths annually in the USA, while showing an upward trajectory in the ranks of causes of mortality [30]. CKD affects almost 10% of the population in high income countries, and in countries where diabetes is more common and therapy remains at low standards, acts as a major mortality factor [7]. Other kidney diseases, such as AKI or hypertension, are also very common and contribute substantially to both morbidity and mortality. The need for improvement in research in nephrology, both regarding valid RCTs and reliable and informative preclinical studies, is apparent.

Many recent articles highlighted that the quantity, the quality and the translation of the kidney research remain insufficient. While it is widely accepted that animal models of human AKI do not accurately predict therapeutic responses in humans, resulting in a debate about their usefulness, De Caestecker, *et al.* tried to evaluate "whether improvements in preclinical study design and statistical rigor can be identified, that will increase the likelihood of translating basic research using the animal models that we are currently using into care of patients with AKI" [27] [31].

On the side of clinical nephrological research, it has been apparent that far fewer reliable RCTs have been performed to tackle the major questions of the field than in other medical disciplines. In 2000, Campbell, *et al.* [32] performed an extensive search and evaluation of the medical literature for 6 core topics in ESKD (End Stage Kidney Disease) and identified only 39 clinical trials that were of sufficient rigor to meet the Cochrane standards for inclusion in a systematic review. Deo, *et al.* [33] on the other hand focused on conducting an evaluation of RCTs in patients with CKD regarding reporting and accounting of data missing

in outcome analysis. They evaluated aspects of quality in trials published in 2007 and 2008. One fourth of the studies examined did not clearly describe a primary outcome, while fewer than half included a flow diagram as instructed by the CONSORT guidelines, and of those with one, only around 60% included the numbers analysed in the study. Almost 60% of the studies showed a discrepancy between the numbers randomly assigned and analysed, and the number of participants excluded was different between intervention arms most of the time, suggesting a strong potential for bias. Of note, only half of the studies reported an ITT analysis, and of those who did, half were not complete, as they did not include in the analysis all patient randomized. The investigators concluded that "in many CKD trials, it is not clear who is included or excluded in the primary analysis, for what reasons, and who had measured or imputed outcome data", making it challenging to extract reliable data from most of the studies.

Strippoli, *et al.* analysed the state of RCT in nephrology compared to other medical disciplines, first reporting their findings in 2004 and then updating them in 2011. In 2004, they observed that the absolute number of RCTs for the timeline analysed was the lowest for any specialty of internal medicine (Fig 5). During the past decade, there has been some improvement in the number of RCTs reported in nephrology; however, the increase has been at a slower rate than in all other specialties in medicine (Fig 6) [34].

In 2004, they also reviewed a sample of the RCTs for quality. As a disappointing finding, kidney-related clinical trials were not only low in number compared with other medical disciplines but also of poor quality, either as conducted or reported. 89% lacked clear allocation concealment, with the majority of trials not reporting the methods by which patients were allocated to the randomized intervention. Double – blinding was more common but was not reported in the majority of trials, and 92% of RCTs failed to blind assessors of the outcomes. ITT analysis was performed in only 29.7% of RCT and was not reported in 51.0%. In almost 20% of the trials ITT analysis was not even possible to assess because of lack of data on the numbers randomized and analysed. The authors concluded: "The challenges of improving the quality and quantity of trials in nephrology are substantial,

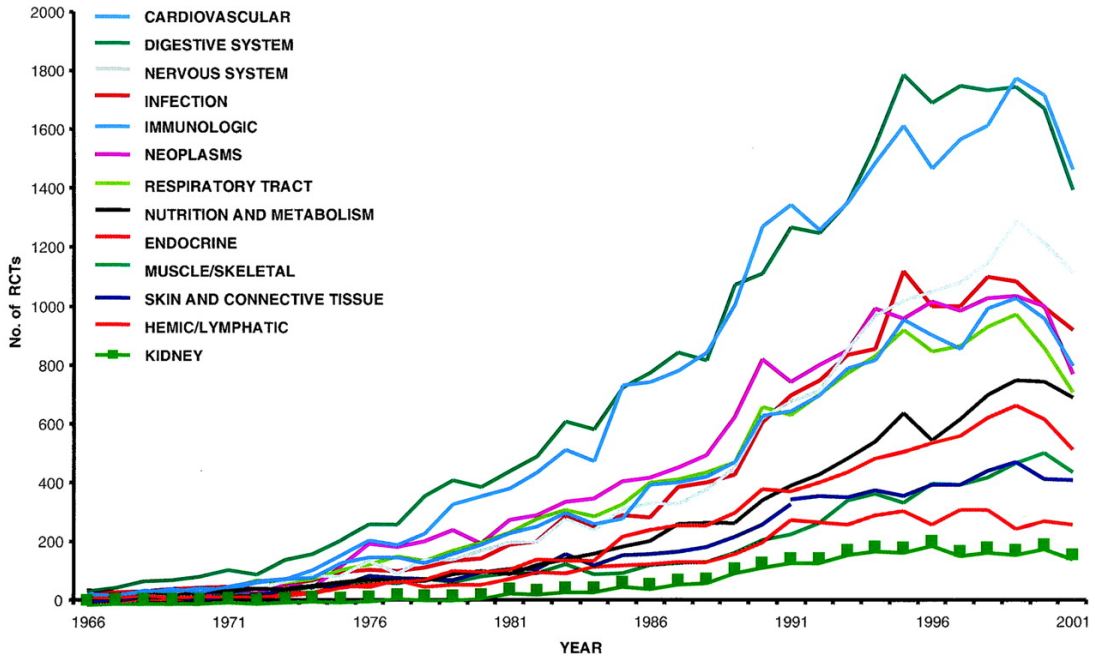


Figure 5: **Number of randomized controlled trials (RCT) published in nephrology and 12 other specialties of internal medicine from 1966 to 2002.** Reprinted from J. Am. Soc. Nephrol, vol. 15, no. 2, G. F. M. Strippoli, J. C. Craig, and F. P. Schena, "The Number, Quality, and Coverage of Randomized Controlled Trials in Nephrology", pp. 411–419, 2004 with permission [34].

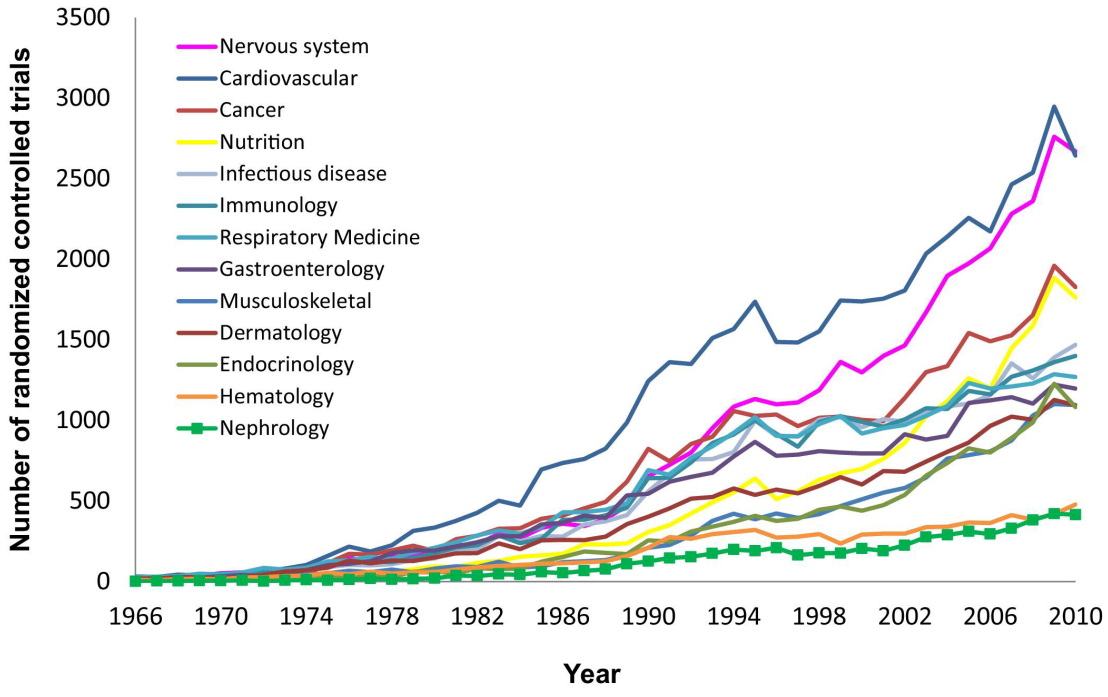


Figure 6: **Number of randomized controlled trials (RCT) published in nephrology and 12 other specialties of internal medicine from 1966 to 2010**. Reprinted from Am. J. Kidney Dis., vol. 58, no. 3, S. C. Palmer, M. Sciancalepore, and G. F. M. Strippoli, "Trial quality in nephrology: How are we measuring up?", pp. 335–337, 2011 with permission from Elsevier [8]

but they can be overcome by using standard guidelines and checklists for trial reporting, greater attention to the trial methods and not just the results" [34].

1.5. Objectives and hypothesis

Since 2004 guidelines for the conduct and reporting of clinical trials and preclinical studies were established, such as the CONSORT 2010 Checklist and Flow Diagram or the ARRIVE guidelines for preclinical. In addition, an increasing amount of abstract submission to international kidney conferences, an increase in number of nephrology journals and increasing scientific productivity of evolving countries has been observed during the last decade.

Therefore, we speculated on an increasing quantity and reporting quality of kidney-related studies within the last 15 years, both in the clinical and the preclinical fields. The aim of this study is to repeat an evaluation of the quantity and the reporting quality in the field of nephrology, but this time considering both clinical trials and preclinical studies, something which to our best knowledge has not been systematically evaluated before.

Methods: Parts of the chapters 2., 2.1.1., 2.1.5. as well as of the chapters 2.2.1., 2.2.2., 2.2.3. and 2.3. have already been published in “Quantity and Reporting Quality of Kidney Research,” M. K. Tomidis Chatzimanouil, L. Wilkens, and H. Anders,J. Am. Soc. Nephrol., vol. 30, no. 1, pp. 13–22, Jan. 2019. [1].

The doctoral candidate performed all experiments described in these paragraphs.

2. Methods

The study consists of two main parts. One is the quantitative analysis regarding the numbers (both total and per year) of randomized controlled trials (RCTs) and preclinical studies in the field of nephrology compared with other disciplines of internal medicine as well as the distribution of kidney studies inside the field. Furthermore, analyses examining the current state of RCTs in the field and the phase categorization of clinical trials were conducted. The other part is a qualitative analysis of a sample of papers (RCTs and preclinical studies) on the basis of criteria for trial reporting using established guidelines, such as the CONSORT Statement and the ARRIVE guidelines. A test analysis using ten RCTs and ten preclinical studies was also performed, as well as ancillary analysis regarding trial registration and reporting vs. design deficits [1].

2.1. Quantitative Analysis

2.1.1. Database selection

One of the most important aspects of the quantitative analyses was the selection of databases, from which the data were to be extracted. The selection of a database depends on many different factors, such as the specific features available regarding the search process, limits available and the content of the database.

Based also on the work of previous publications [34], the Pubmed database was initially used to identify kidney-related RCTs and to compare them with those of other specialties of internal medicine. Pubmed utilizes an expanded limits feature, allowing the user to restrict results by article type, publication date, species and others. It also possesses a quick Download CSV function which allows for quick results by year classification (Fig. 7).

The other main database used, mainly for the clinical aspect of the study, was the Cochrane Library, and specifically the Cochrane Central Register of Controlled Trials

Figure 7: **The Pubmed database interface.** Highlighted are the limits feature on the left and the CSV function on the right.

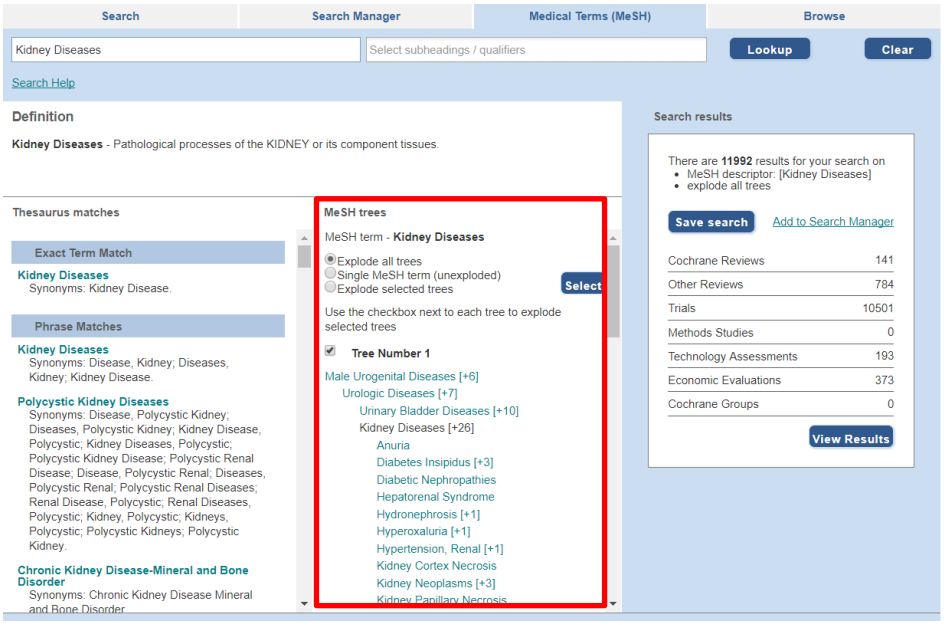


Figure 8: **The CENTRAL interface**. Also its intergrated MeSH trees system.

(CENTRAL), which is "a highly concentrated source of reports of randomized and quasi-randomized controlled trials. Most CENTRAL records are taken from bibliographic databases (mainly PubMed and Embase), but records are also derived from other published and unpublished sources, including ClinicalTrials.gov" [35]. CENTRAL uses a system with established fixed MesH Terms for each subject, while simultaneously using Trees and Subtrees to connect MesH Terms with SubMesH Terms for various fields (Fig. 8).

We initially decided to examine research questions regarding the number and proportion of

Table 4: Comparison between the 2 databases used for the clinical part of the quantitative analysis

	Pubmed	CENTRAL
Pros	**Expanded Integrated Limits feature** allowing the user to restrict results by article type, publication date, species and others	**MesH Terms with Trees and Subtrees** specific general MesH Term for each field with the addition of SubMesH Terms Leads to a very good overview of the analysis
	Download CSV function allowing a quick results by year classification	
Cons	**No overview** of what SubMeshTerms each Mesh-Term used contains	**No 'Results by Year' feature**

RCT in nephrology in comparison to other specialties and the coverage of RCT within nephrology using both databases, to be able to identify the more reliable one but also to compare result-reproducibility.

Ultimately, the main database selected for the clinical analysis was the Cochrane Library, mainly because of its use of an integrated system of trees and subtrees for each MesH term, which provided a better overview of the research process as compared to other databases. Since the Cochrane Library is limited to clinical trials, PubMed was used for the preclinical studies [1].

2.1.2. Number of RCT in nephrology compared with other disciplines

For the question on the number of RCT in nephrology in comparison to other medical disciplines, a MesH term, thought to most accurate summarize the data in question, or a combination of two or more relevant MesH Terms, was used for each specialty, based also on previous work of similar publications [34] (Neurology → Nervous System Diseases, Cardiology → Cardiovascular Diseases, Oncology → Neoplasms, Nutrition → Metabolic Diseases OR Nutrition Disorders, Respiratory Medicine → Respiratory Tract Diseases,

Immunology → Immunologic Diseases, Infectious Diseases → Bacterial Infections OR Mycoses OR Virus Diseases OR Parasitic Diseases, Gastroenterology → Digestive System Diseases OR Gastrointestinal Diseases, Dermatology → Skin Diseases OR Connective Tissue Diseases, Endocrinology → Endocrinological Diseases, Rheumatology → Musculoskeletal Diseases, Hematology → Hematologic Diseases OR Lymphatic Diseases, Nephrology → Kidney Diseases). These MesH Terms were inserted into the Pubmed database individually, using the Limits Article Type: Randomized Controlled Trial, Publication dates: 1966-2017 and Species: Human.

After the decision to repeat the construction of the diagrams using the Cochrane Library, due to its previous mentioned advantages, the terms mentioned above were converted to match the established terms of the CENTRAL tree System (Neurology → Nervous System Diseases, Cardiology → Cardiovascular Diseases, Oncology → Neoplasms, Nutrition → Nutritional and Metabolic Diseases, Respiratory Medicine → Respiratory Tract Diseases, Immunology → Immune System Diseases, Infectious Diseases → Virus Diseases OR Bacterial Infections and Mycoses OR Parasitic Diseases, Gastroenterology → Digestive System Diseases , Dermatology → Skin and Connective Tissue Diseases, Endocrinology → Endocrine System Diseases, Rheumatology → Musculoskeletal Diseases, Hematology → Hemic and Lymphatic Diseases, Nephrology → Kidney Diseases). The results of these Cochrane searches were limited by 'randomized controlled trial' and "trials" as publication type to estimate the total number of RCT publications in each field, and then categorized by year of publication for the years 1966 through 2016, for the construction of a per-year diagram.

We also tried to conduct a phase analysis from the total number of publication for each specialty using the CENTRAL database. We inserted the previously used MeSH terms, identifying the total number of trials for each field for the years 1966-2017 and limiting results using "randomized controlled trial" and "trials" as publication type. We then limited results using the terms "Phase 1"OR "Phase I" for phase 1 trials, "Phase 2"OR "Phase II" for phase 2 trials, "Phase 3"OR "Phase III" for phase 3 trials and lastly "Phase 4" OR "Phase IV" for phase 4 trials, respectively. These results were used for the construction of bar diagrams, while the difference from the total numbers of trials for each field to the sum of the phase-specified trials was characterized as "Not Phase limited" trials.

2.1.3. Distribution of RCT within nephrology

To access coverage of RCTs inside the field of nephrology, 10 major areas of nephrology (Hemodialysis, Renal Insufficiency, Chronic , Kidney Transplantation, Urinary Tract Infections, Diabetic Nephropathies, Acute Kidney Injury, Peritoneal Dialysis, Glomerulonephritis, Hypertensive Nephropathy, Kidney Calculi) were identified, and these MesH Terms were inserted into the Pubmed database individually, using the Limits Article Type: Randomized Controlled Trial, Publication dates :1966-2017 and Species: Human.

A similar procedure as described above was followed for the CENTRAL analysis, converting the initially used terms to match the MesH terms of the Cochrane Tree and Subtree System (respectively for each term: 'Renal Dialysis' (includes the subMesH Term 'Peritoneal Dialysis' so another term , 'Renal Dialysis' w/o 'Peritoneal Dialysis' was added), 'Renal Insufficiency, Chronic', 'Kidney Transplantation', 'Urinary Tract Infections', ' Diabetic Nephropathies', ' Acute Kidney Injury', 'Peritoneal Dialysis', 'Glomerulonephritis', 'Hypertension, Renal', 'Kidney Calculi'). The term 'Hypertension' was also added later, irrespective of the fact that it is not an exclusive nephrological area, for comparative reasons. The results of the searches were limited using the term 'randomized controlled trials' and limited for the years 1966 – 2016.

After the analysis of the coverage of RCT within the field of nephrology, it came to our attention, that four of the major researched areas of nephrology, excluding "Hypertension", were not included under the MesH Term used to summarize the nephrological RCT trials ("Kidney Diseases"). The terms in question were "Renal Dialysis", "Peritoneal Dialysis", "Kidney Transplantation" and "Urinary Tract Infections". The 3 first terms were also subterms of the more general MesH term "Renal Replacement Therapy" in the system of the Cochrane Library (Fig. 9). We therefore created another term, named "Kidney Exp.", which consists of the following MesH Terms: "Kidney Diseases" OR "Renal Replacement Therapy" OR "Urinary Tract Infections". "Kidney Exp." was later added to the diagrams concerning the number and proportion of RCT in nephrology compared with other

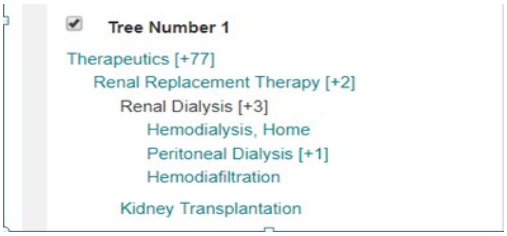


Figure 9: **The terms included under Renal Replacement Therapy in CENTRAL**.

specialties. “Hypertension”, while included in the diagrams regarding the coverage within nephrology, is not included under either the term “Kidney Diseases” or “Kidney Exp.”, in all diagrams, as it is not seen as an exclusively nephrological area.

After receiving feedback from the academic community, it came to our attention, that while originally included as a major nephrological area and included in similar previous projects, “Urinary Tract Infections” (UTI) should not be considered as a major part of nephrology, rather than an area of the urology domain. With that in mind, we constructed new diagrams tackling the comparison of nephrological studies to other specialties, but this time the term “Kidney Exp.” only consisted of the terms: “Kidney Diseases” OR “Renal Replacement Therapy”. From the line diagrams referring to coverage of nephrology, both clinical and preclinical, the line “Urinary Tract Infections” was not removed, since it did not alter the results.

2.1.4. Current state of RCT

A similar search regarding the current state of research for clinical trials was conducted through clinicaltrials.gov, both for the nephrology as a whole, compared to other medical specialties, but also for the major areas identified inside the field of nephrology. The search was conducted by applying the initial MesH terms, and then converting them to match the suggestions of the database[(terms used for the specialties analysis: Oncology→ Neoplasms, Neurology →Nervous System Diseases, Cardiology → Cardiovascular Diseases, Infectious Diseases→ Infectious Diseases, Gastroenterology → Digestive System Diseases OR Gastrointestinal Diseases, Nutrition → Nutritional Disorders OR Metabolic Diseases,

Respiratory Medicine →Respiratory Tract Diseases, Immunology→ Immunologic Diseases, Dermatology → Skin Diseases OR Connective Tissue Diseases, Endocrinology → Endocrine System Diseases, Rheumatology → Musculoskeletal Diseases, Nephrology Exp. → Kidney Disease OR Kidney Transplantation OR Hemodialysis OR Peritoneal Dialysis OR Urinary Tract Infections, Hematology → Hematologic Diseases OR Lymphatic Diseases, Nephrology → Kidney Diseases), (terms used for the coverage within nephology analysis: Hypertension, Chronic Kidney Disease, Hemodialysis, Acute Kidney Injury, Kidney Transplantation, Renal Hypertension, Urinary Tract Infections, Urinary Calculi, Glomerulonephritis, Diabetic Kidney Disease, Peritoneal Dialysis)], limited to "interventional'' trials "currently recruiting", "not yet recruiting", "available", "active", "not recruiting", and "enrolling by invitation" as listed in the U.S. National Library of Medicine registry. For the research the 'Others Bar', not the 'Conditions Bar' was used, a fact that broadened the search, adding relevant papers that were not specified for the condition (e.g. AKI, but also for broader search, e.g. Cardiovascular Diseases), while on the other hand a small number of not very relevant papers may be included. The term 'randomized' was also added to limit results to only include RCTs.

The phase-limits on the interface of the database were also used, to categorize the total number of ongoing trials by phase (phase 1-4), in order to create phase diagrams for each specialty/nephrology area. The results for "Early Phase 1"and "Phase 1"were summed up together under the term "Phase 1/I" for both diagrams. The difference from the total numbers of trials for each field/area to the sum of the phase-specified trials was characterized as "Not Phase limited" trials.

2.1.5. Number and proportion of preclinical studies in nephrology compared with other specialties

The search regarding the preclinical studies was conducted using Pubmed, since the Cochrane Library only applies to clinical trials, by applying the same MesH terms, before the conversion to match the Cochrane System, used for the RCT search (Infectious Diseases → Bacterial Infections OR Mycoses OR Virus Diseases OR Parasitic Diseases, Oncology → Neoplasms, Neurology → Nervous System Diseases, Cardiology → Cardiovascular Diseases,

Gastroenterology → Digestive System Diseases OR Gastrointestinal Diseases, Nutrition → Metabolic Diseases OR Nutrition Disorders, Immunology → Immunologic Diseases, Respiratory Medicine → Respiratory Tract Diseases, Endocrinology → Endocrinological Diseases, Dermatology → Skin Diseases OR Connective Tissue Diseases, Hematology → Hematologic Diseases OR Lymphatic Diseases, Rheumatology → Musculoskeletal Diseases, Nephrology exp.→ Kidney Disease Or Urinary Tract Infections Or Renal Replacement Therapy, Nephrology → Kidney Diseases). In order to limit the results specifically to animal trials, the limit 'Animals' in the Pubmed interface was used, and the results were extracted for the timeline 1945-2016. A per year categorization was applied for the construction of the per year diagrams [1].

2.1.6. Coverage of preclinical studies within nephrology

Similarly as the procedure followed for the clinical coverage within nephrology, 10 major areas identified, plus the term hypertension, were inserted into the Pubmed database, using the terms prior to their conversion to match the Cochrane System (Hypertension, Glomerulonephritis, ,Kidney Transplantation, Acute Kidney Injury, Renal Insufficiency, Chronic, Diabetic Nephropathies, Hemodialysis, Hypertensive Nephropathy, Urinary Tract Infections, Peritoneal Dialysis, Kidney Calculi), again limiting results for the years 1945-2016 and using the limit "Animals". As stated above, modified versions of the preclinical diagrams were constructed, this time excluding the term "Urinary Tract Infections" from Nephrology Exp..

2.2. Qualitative Analysis

2.2.1. Paper selection criteria

We searched the PubMed database. As representative RCT sample periods, we selected the years 1996, 2006, and 2016 and identified all kidney-related RCTs from the top five journals as assessed by impact factor (IF) and the number of kidney- related RCTs per year: The New

England Journal of Medicine (NEJM) [36]-[54], The Lancet [55]–[59], Kidney International [60]–[87], Journal of the American Society of Nephrology (JASN) [88]–[116], and American Journal of Kidney Diseases (AJKD) [117]–[160].For the qualitative analysis of preclinical studies, we used the same years (1996, 2006, and 2016) but limited sample collection to January to March of each year from the journals JASN [161]–[226], Kidney International [227]–[310] and Nephrology Dialysis Transplantation (NDT) [311]–[360]; selected by IF and tendency to publish preclinical studies in the kidney domain using the PubMed database [1].

The search for the RCTs was conducted using the MeSH term “kidney diseases” and the limits “Randomized Controlled Trial” and “Humans,” limited each time by the specific journal of publication and the appropriate year. We did not predefine sample size; rather we considered all papers that were retrieved according to the aforementioned selection criteria. For the animal trials, the same MeSH term “kidney diseases” was used and limited by “Animals,” and the search was conducted per year for each of the three journals. Only results published inside the first three months of each year were included. The result of the entire 3 years produced a too large sample size to analyze; hence we decided to reduce that by limiting results from the first of January to the thirty first of March of each year. We have no reason to assume a particular bias on paper quality being published between the first three months of each year in comparison to April till December, so we are confident that no relevant sampling bias applied. Inclusion criteria for both the RCTs and the preclinical studies were that the papers were original articles, in English, and published online. Review articles, editorials, special articles, and commentaries were excluded. From the RCT analysis, observational, prospective, and nonrandomized trials were excluded. Because the ARRIVE criteria apply to in vivo animal experiments, preclinical studies exclusively mechanistic or only in vitro studies were excluded [1].

2.2.2. Quality assessment of RCT

The methodological quality of all of these studies was assessed by one independent investigator (M.K.T.C.) using criteria mainly on the basis of the original CONSORT 2010 checklist for RCTs and the ARRIVE guidelines for the preclinical studies. Only the main body of the final paper was analysed and supplementary information and previously published

study protocols were not considered. For the RCT analysis, we extracted data by allocating points (zero for insufficient, one for unclear or insufficiently reported, and two for adequate reporting) to each of the 19 core items of the CONSORT Statement regarding "Title and Abstract", "Introduction", "Methods" and "Results" and each of the subitems. In addition, to match the previous analyses from Strippoli, *et al.* [34] and Deo, *et al*. [33] two extra items were added (i.e., "Intention-to-treat analysis" and "Loss-to-analysis"). "Intention-to-treat analysis" was rated as adequate when sufficient data were included to confirm that the analysis regarding the primary end point was undertaken according to the treatment assignment and that the numbers of participants randomly assigned were identical to the numbers of participants analysed, irrespective of whether "intention- to-treat" was stated or not in the article. We also tried to calculate the "Loss-to-analysis" for each trial included so as to try to determine what percentage of participants randomly assigned was not included in the analysis. In total, 35 items regarding trial reporting for RCTs were graded. A more detailed view of the criteria used to assess the quality of clinical trials and the grading system used to evaluate each item separately can be found in Table 5 [1].

2.2.3. Quality assessment of preclinical studies

For the analysis of the preclinical studies, the 15 core items of the ARRIVE guidelines regarding "Introduction," "Methods," and "Results" were included. In addition, for the core items 3, 6 (sub item "d: A time line diagram or flow chart" was included by initiative of the researchers), 10 and 13 the subitems were assessed separately; otherwise, they were included in the grading method of the core item (zero for insufficient, one for unclear or insufficiently reported, and two for adequate reporting) for a total of 23 graded items regarding trial reporting for animal trials. A more detailed view of the criteria used to assess the quality of the preclinical trials and the grading system used to evaluate each item separately can be found in Table 6 [1].

Table 5: Modified criteria for assessment of CONSORT recommendations

		0 : Not reported	1 : Insufficiently reported / Unclear	2 : Sufficiently Reported
Title	*Identified as a randomized trial in the title*	Not stated	_	Stated
Abstract	*Structured summary of trial design, methods, results, and conclusions*	No clear summary	_	Structured Summary
Background	*Scientific background and explanation of rationale*	Subjective		
	Specific objectives or hypotheses clearly stated	Not reported	Other word formulation (expressing findings and not objectives)	Clearly stated objectives and hypotheses (The objectives were, the aim of the study, main hypothesis, we examined, we investigated)
Trial Design	*Trial design (such as **parallel, factorial**) including allocation ratio.*	Not mentioned	Mention of trial design, without allocation ratio &/ parallel, factorial ...	Thoroughly reported
	*Important changes to methods after trial commencement (such as **eligibility criteria**), with reasons.*	Not stated	_	Stated
Participants	***Eligibility criteria** for participants*	Not stated	Insufficiently reported (i.e. Only exclusion criteria)	Thoroughly reported
	***Settings and locations** where the **data** were collected.*	Not stated	Insufficiently reported (i.e. only multicenter mentioned, no specific location)	Thoroughly reported
Interventions	*The **interventions** for each group with sufficient details to allow replication, including **how** and **when** they were actually administered.*	Not stated	Insufficiently reported	Thoroughly reported

Outcomes	*Completely defined pre-specified **primary** and **secondary outcome measures**, including how and when they were assessed*		Not stated	Insufficiently reported	Thoroughly reported
	*Any **changes** to trial outcomes after the trial commenced, with reasons.*		Not stated	_	Stated
Sample Size	*How sample size was determined*		Not stated	Insufficiently reported	Thoroughly reported
	Explanation of any interim analyses and stopping guidelines.		Not stated	Insufficiently reported	Thoroughly reported
Randomization	***Sequence generation***	*Method used to generate the random allocation sequence*	Not stated	_	Stated
		Type of randomization; details of any restriction (such as blocking and block size).	Not stated	_	Stated
	Allocation concealment mechanism	*Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned.*	Not stated	_	Stated
	Implementation	*Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions*	Not stated	_	Stated

Blinding	*Status*	Unblinded or no mention	Blinded	Double blinded
	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes).	Not reported	Insufficiently reported	Thoroughly reported
	If relevant, description of the similarity of interventions.	Not stated	Insufficiently reported	Thoroughly reported
Statistical Methods	*Statistical methods used to compare groups for primary and secondary outcomes.*	Not reported	Insufficiently reported	Thoroughly reported
	Methods for additional analyses, such as subgroup analyses and adjusted analyses.	Reported	Insufficiently reported	Thoroughly reported
Participant flow	*Diagram*	No	_	Yes
	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Not reported	One of : n randomly assigned, n: received intended treatment, n: analysed for the primary outcome not reported	Thoroughly reported
	For each group, losses and exclusions after randomization, together with reasons.	Not reported	Reported, without reasons	Thoroughly reported
Recruitment	*Dates defining the periods of recruitment and follow-up*	Not reported	Either recruitment / follow-up	Thoroughly reported
	Why the trial ended or was stopped.	Not reported	_	Reported
Baseline Data	*A table showing baseline demographic and clinical characteristics for each group.*	Not reported	Insufficiently reported (either demographic or clinical data missing, no table)	Reported
Numbers Analysed	*For each group, number of participants (denominator) included in each analysis.*	Not reported	Insufficiently reported	Thoroughly reported
Intention-to-treat	*regarding the primary endpoint*	inadequate/ not stated	inadequate / stated, unclear	adequate / stated (adequate/ not stated)

Loss - to - Analysis	*(n randomly assigned -n in analysis)/ n randomly assigned*	Numerical		
Outcomes & Estimation	*For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval).*	Not reported	Reported, No CI, Estimated Effect Size	Thoroughly reported
	For binary outcomes, presentation of both absolute and relative effect sizes.	Not reported	Absolute / Relative	Both, Thoroughly reported
Ancillary Analyses	*Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory.*	Not reported	Insufficiently reported	Thoroughly reported
Harms	*All important harms or unintended effects in each group.*	Not reported	Insufficiently reported	Thoroughly reported

2.2.4. Reproducibility analysis

To assess interobserver variability, a second investigator (Louise Wilkens) analysed a representative sample of the papers, selected by the main investigator (M.K.T.C.), consisting of 10 RCT papers and 10 preclinical papers. This sample contained papers from all journals and from all years examined. We assigned a single point to each criterion, for a total of 37 points for each RCT paper (35 criteria shown in the “RCT Criteria” table plus ''number of patients randomly assigned'' and ''number of patients in analysis' for each trial) and a total of 23 points for each preclinical paper. This adds up to a total of 600 points.

2.2.5. Registration analysis

An additional analysis was conducted, in order to try and define the percentage of kidney-related RCTs registered in a public trials registry, according to the International Committee of Medical Journal Editors (ICMJE) recommendation for clinical trials, which applies to all

Table 6: Assessment criteria for ARRIVE recommendations

		0 : Not reported	***1: Unclear / Insufficiently Reported***	***2: Sufficiently Reported***
1. Title	*Provide as accurate and concise a description of the content of the article as possible*	Subjective, not examined by the researchers		
2. Abstract	*Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusion of the study*	Subjective, not examined by the researchers		
3. Background	*a. Study context and* ***experimental rationale***	Subjective		
	How and why animal ***species*** *and models being* ***used address the objectives****, study's* ***relevance to human*** *biology*	No reference	Referenced, but not clearly stated	Stated why models/species address the objective /& relevance to human biology
4. Objectives	*Primary and any secondary objectives or hypotheses*	Not reported	Other word formulation (expressing findings and not objectives), unclear primary and secondary objectives	Clearly stated objectives and hypotheses (The objectives were, the aim of the study, main hypothesis, we examined, we investigated)
5. Ethical statement	*Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.*	animal license not stated	–	stated

6. Study design	*a. The number of **experimental and control groups***	Not reported	References through the trial of experimental & control groups, not clearly reported	Clearly stated number of experimental and control groups
	*b,c. **Randomization** and details of the experimental unit*	No mention of randomization	Randomization mentioned/ reported for some of the experiments	Randomization mentioned/ reported for all experiments
	*b. **Blinding** performed*	No mention of blinding	Blinding mentioned/ reported for some of the procedures	Blinding mentioned/ reported for all experiments
	*d. A time-line diagram or **flow chart***	Not included	_	Included
7. Experimental procedures	*For each experiment and each experimental group, including controls, provide precise details of all procedures carried out.*	No report of experimental procedures	Insufficient reporting of experimental procedures	Experimental procedures thoroughly reported
8. Experimental animals	*a,b. Provide details of the animals used, including **species**, strain, **sex**, developmental stage, **weight** and other relevant information(e.g. **Source**, genetic modification status)*	No details of experimental animals reported	At least species, strain, source of experimental animals reported	Species, Strain of experimental animals reported + one other characteristic (developmental stage, sex...)
9. Housing and husbandry	*Housing, husbandry and welfare-related assessments*	No details of housing, husbandry or welfare-related assessments	At least one detail regarding housing/ husbandry / welfare-related assessments reported	At least one detail regarding housing/ husbandry / welfare-related assessments reported + further details
10. Sample size	*a. Specify the **total number of animals** used in each experiment, and the **number of animals** in each experimental group.*	Not reported	At least number of animals in each experimental group reported throughout the study	Total number of animals for each experiment / + number of animals in each experimental group clearly stated in the methods section
	*b. Explain how the number of animals was arrived at. Provide details of any **sample size calculation** used.*	Reported	_	Not reported
	*c. Indicate the number of independent **replications** of each experiment, if relevant.*	Not reported	Independent experiments reported	Replication details given for at least one experiment throughout the study

11. Allocating animals to experimental groups	*a,b. Details of allocation method*	Not reported	_	Reported
12. Experimental outcomes	*Primary and secondary experimental outcomes assessed*	Not reported	Unclear	Detailed & Specific mention of experimental outcome assessment in the statistical section of the paper
13. Statistical methods	*a. Provide details of the **statistical methods used** for each analysis.*	Not reported	_	Reported
	*b. Specify **the unit of analysis** for each dataset (e.g. **single animal, group of animals, single neuron**).*	Not reported	Unclear	Specific mention in the statistical method section of the study
	*c. Describe any methods used to assess **whether the data met the assumptions of the statistical approach**.*	Not reported	_	Reported
14. Baseline data	*For each experimental group, relevant characteristics and health status of animals prior to treatment or testing.*	Not reported	At least 1 mention of relevant characteristics or health status of animals at baseline	Thoroughly reported
15. Numbers analysed	*Numbers analysed (included numbers of animals not included and why)*	Not reported	Sufficient data regarding data analysed throughout the study, no specific mention of data analysed	Thoroughly reported
16. Outcomes and estimation	*Report the results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval).*	Not reported	Outcomes reported throughout the study, no measure of precision reported	Thoroughly reported
17. Adverse events	*Details of all important adverse events and modifications*	Not reported	_	Reported

clinical trials that started enrolment after July 1, 2005 [361] [362][363].

To this end, a random sample of 100 kidney-related articles was retrieved from the PubMed database [364]–[451], using the MesH Term 'kidney diseases' and limited results to the last 10 years of publication (09/2018-10/2008), with article type Randomized Controlled Trial and Species Human. We then tried to identify a Registration Number throughout the article, or identify the trial or trials the article refers to, to try and find if the trials in question are registered.

To further examine the question above, we then tried to identify the trials, which not only had a registration number, but were already registered prior to enrolment of the first participant, by comparing the 'First Submitted Date' with the 'Study Start Date'. Trials that had already begun enrolment before July 1, 2005 and were registered were graded positively in this category regardless of submission date, according to the ICJME recommendation for registration of trials prior to July 1, 2005.

2.2.6. Trial reporting vs. trial design

As discussed below, one of the main limitations for the qualitative analysis conducted was that it could not distinguish between trial design deficits or underreporting. The analysis was not designed or meant to examine proper trial design or conduction, but rather examine the state of reporting quality in kidney research.

Nevertheless, to further examine the difference between reporting quality and trial design, and to assess whether the results of the current study could also have a meaningful translation to design quality, we conducted a subgroup analysis from a representative sample of the 125 RCTs originally assembled (12 articles total, 4 from 2016, 5 from 2006, 3 from 1996). We then tried to collect further information for the articles in question, not only included in the article originally examined, but also from other articles, supplementary material, appendixes and protocols for the trial in question, and compared them with the results of the original analysis, which only referred to the main body of each article.

2.3. Statistical analysis

Data are presented as mean ± SD. Comparison of groups was performed using ANOVA, and post hoc Bonferroni correction was used for multiple comparisons. A value of $P < 0.05$ was considered to indicate statistical significance.

Results: Parts of the chapters 3.1.1., 3.1.4., 3.1.7., 3.1.8, 3.2.1 and 3.2.2. as well as some of the figures of the above chapters have already been published in “Quantity and Reporting Quality of Kidney Research,” M. K. Tomidis Chatzimanouil, L. Wilkens, and H. Anders, J. Am. Soc. Nephrol., vol. 30, no. 1, pp. 13–22, Jan. 2019. [1].

The doctoral candidate performed all experiments described in these paragraphs.

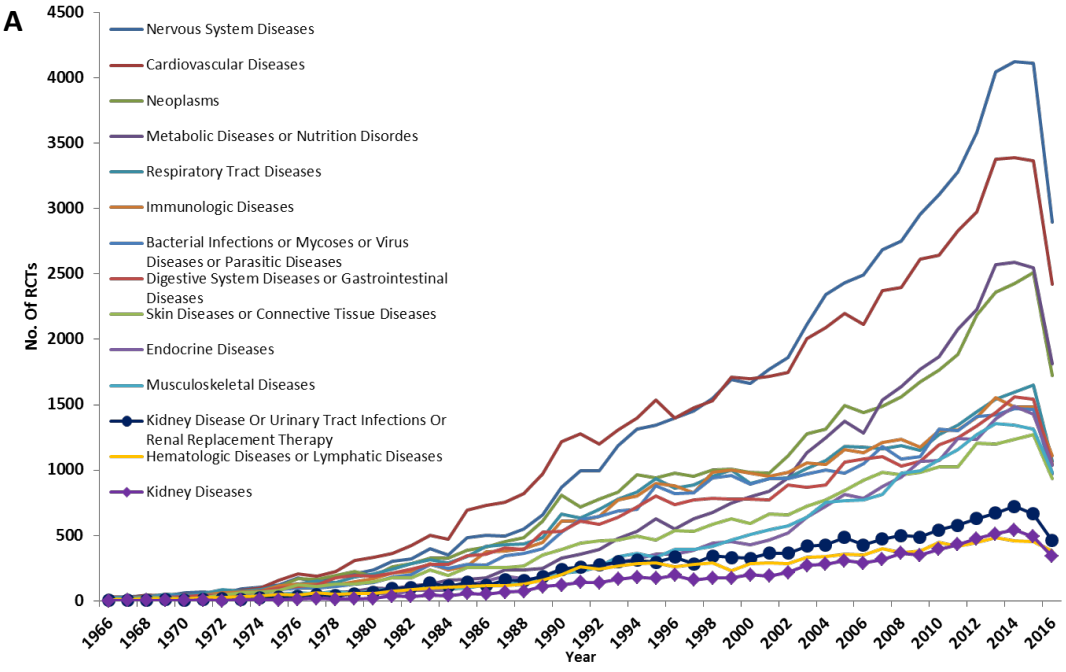
3. Results

3.1. Quantitative Analysis

3.1.1. Kidney RCT compared with other medical disciplines

Figure 10A presents the diagram from the Pubmed analysis regarding the comparison of various specialties. As explained above, we consider the following diagrams constructed through the CENTRAL database of the Cochrane Library to be more reliable, but figure 10A is included for comparative reason both to figures 10B and C but also 5 and 6, diagrams of previous relevant publication constructed through Pubmed.

Our Cochrane MeSH tree analysis presented the reported clinical trials across medical disciplines (Fig. 10B). Neurology and cardiology kept reporting the most clinical trials since the early 1990s, whereas both MeSH term “kidney diseases” and its definition extended by RRTs (“Kidney Exp.”) remained at the lowest ranks of medical disciplines (Figure 10B). The average slope of additional clinical trials reported each year from 1966 to 2003 was 27.7 ± 14.6 for all disciplines, and slopes were 7.5 and 11.0 for kidney diseases and expanded kidney diseases (excluding UTI), respectively (both P values versus all disciplines <0.001).



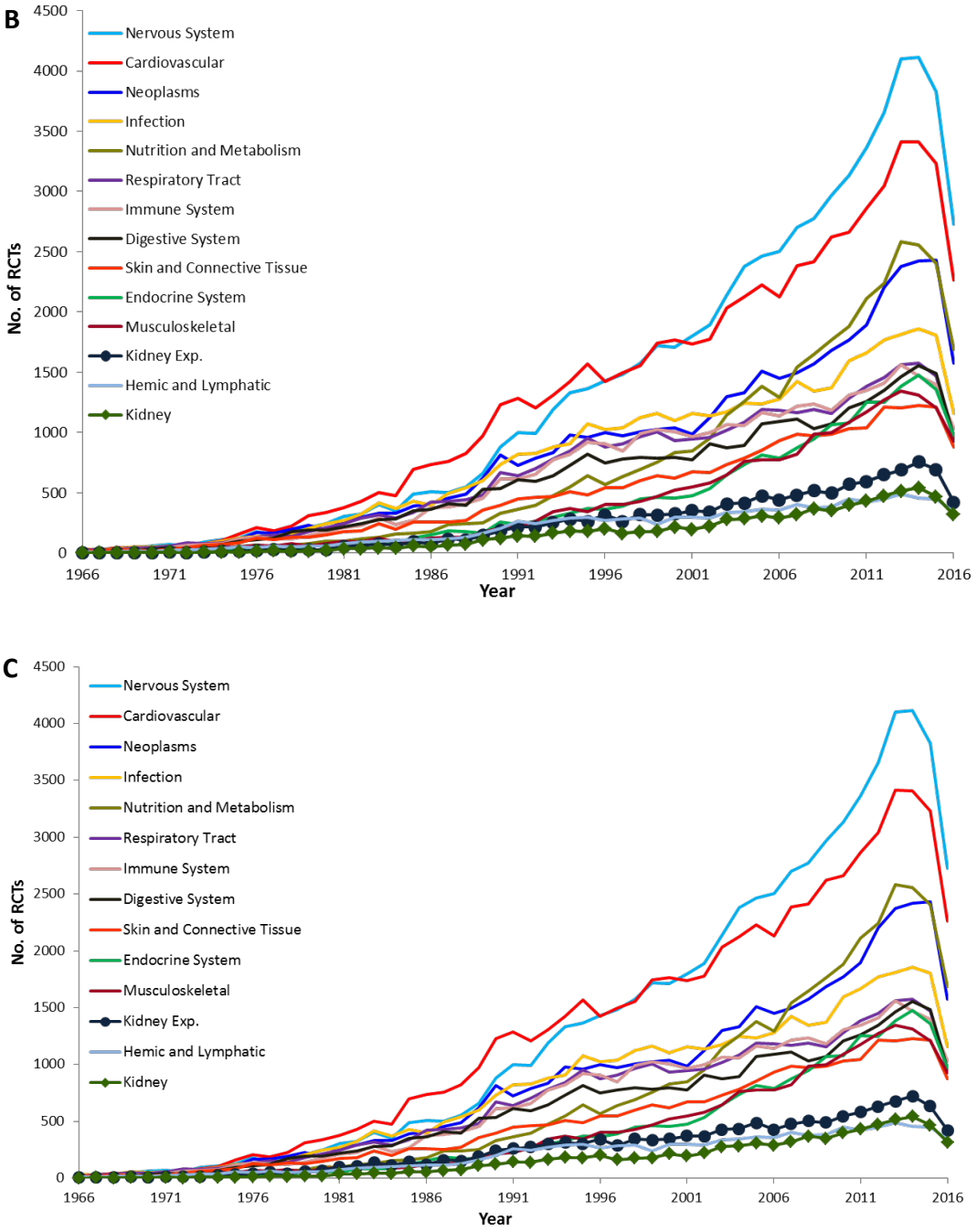


Figure 10: **Quantitative analysis of clinical trials in medical disciplines**. Several MeSH terms were applied to best cover each discipline as described in Methods. Nephrology ("Kidney") is represented by the MeSH term "kidney diseases". (A) Annual numbers of clinical trials per discipline identified from the Pubmed database. (B) Annual numbers of clinical trials per discipline identified from CENTRAL. Expanded (Exp.) nephrology ("Kidney Exp.") covers the MeSH term "RRT" (subterms included "renal dialysis," "peritoneal dialysis," and "kidney transplantation"). (C) Annual numbers of clinical trials per discipline identified from CENTRAL. Expanded (Exp.) nephrology covers the MeSH terms "RRT" (subterms included "renal dialysis," "peritoneal dialysis," and "kidney transplantation") and "Urinary Tract Infections". The sudden decline in numbers in the years 2015–2016 should relate to delays in data inclusion.

Since the evaluation in 2004 (years 2004–2014), the slope has increased to 68.4 ± 42.2 for all disciplines, indicating a profound increase in number and spread among the disciplines in annual clinical trial reporting [1].

In the same period, kidney diseases and their expanded definition reported an increase to 23.3 and 31.2, respectively (both P values versus all disciplines < 0.001). Even including UTI in the expanded version of kidney diseases has minimal effect on the values above, only increasing the slope from 1966 to 2003 by 0.4 (Figure 10C).

Over the entire period, all disciplines displayed an annual increase of reported clinical trials of 38.4±21.2, (38.4±21.3 including UTI) whereas kidney diseases displayed an annual increase of reported clinical trials of 11.3 and expanded kidney diseases displayed an annual increase of reported clinical trials of 15.8 (15.0 including UTI) (all P values versus all disciplines < 0.001). Together, the number of kidney-related clinical trials has increased but less so compared with other disciplines [1].

The years 2015 and 2016 were excluded from this analysis, because delays in MeSH term indexing within the PubMed database led to declining curves for all disciplines, also affecting the CENRAL database. This explains the plateau from around 2015 on, which is evident for most of the figures present in this study, and is the main reason why the figures do not include the year 2017. Through direct communication with both the Cochrane Library and the United States National Library of Medicine we were able to clarify that the Cochrane Library does not index articles, rather than repurpose indexing provided by Pubmed or Embase: “In general, the percentage of articles in the PubMed database that are indexed with MeSH terms declines in recent years. This is because of the volume of articles that we receive and the increased time it takes to index. If you are running your searches by tagging the MeSH terms (e.g., cancer[mh]) then you will see fewer results in recent years. For untagged searches, I would expect the numbers to be more consistent. I can't speak to each subject in terms of whether research is staying steady or declining. There are certainly trends over time for all areas. But the MeSH indexing could certainly impact the results as well” (M. Collins, United States National Library of Medicine, personal communication).

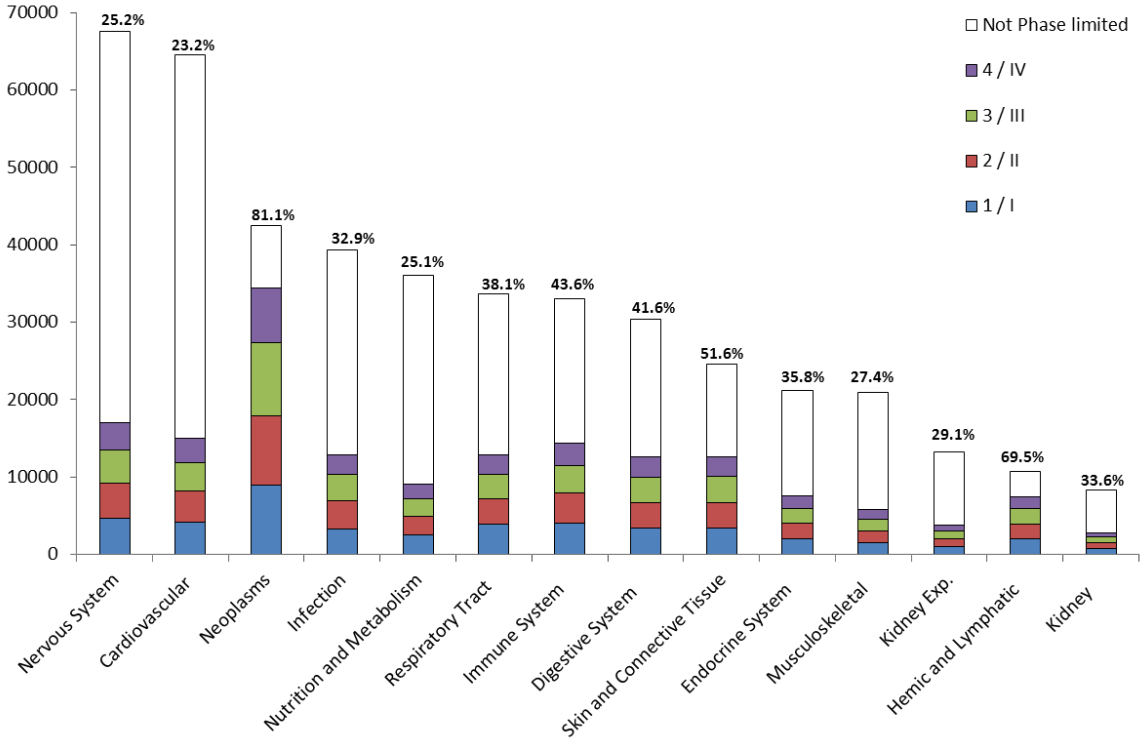


Figure 11: **Total numbers and phase analysis of clinical trials identified from the CENTRAL database**. Each column represents the total number of trials published in CENTRAL for the years 1996-2017. The different bars represent the different phases. The percentages represent the trials classified.

3.1.2. Phase analysis of clinical trials in nephrology compared with other medical disciplines

We wondered whether we could also analyze trial numbers by phase. Searching the Cochrane database between 1966 and 2017 revealed that the majority of the trials published in the various medical disciplines were not categorized by phase, with the exception of oncology, hematology and dermatology, with 81.1%, 69.5% and 51.6% respectively (Figure 11). In the field of nephrology the respective percentages were 33.6% and 29.1% for kidney disease trials or expanded kidney disease trials, respectively (Figure 11).

Considering all medical disciplines, phase one, two and three trials were almost equally common, with 10.3%, 10.0% and 9.8% of the total trials respectively. Phase 4 were 7.8% of the whole, while 62.2% of trials were not categorized by phase. Regarding nephrology, 9.1%

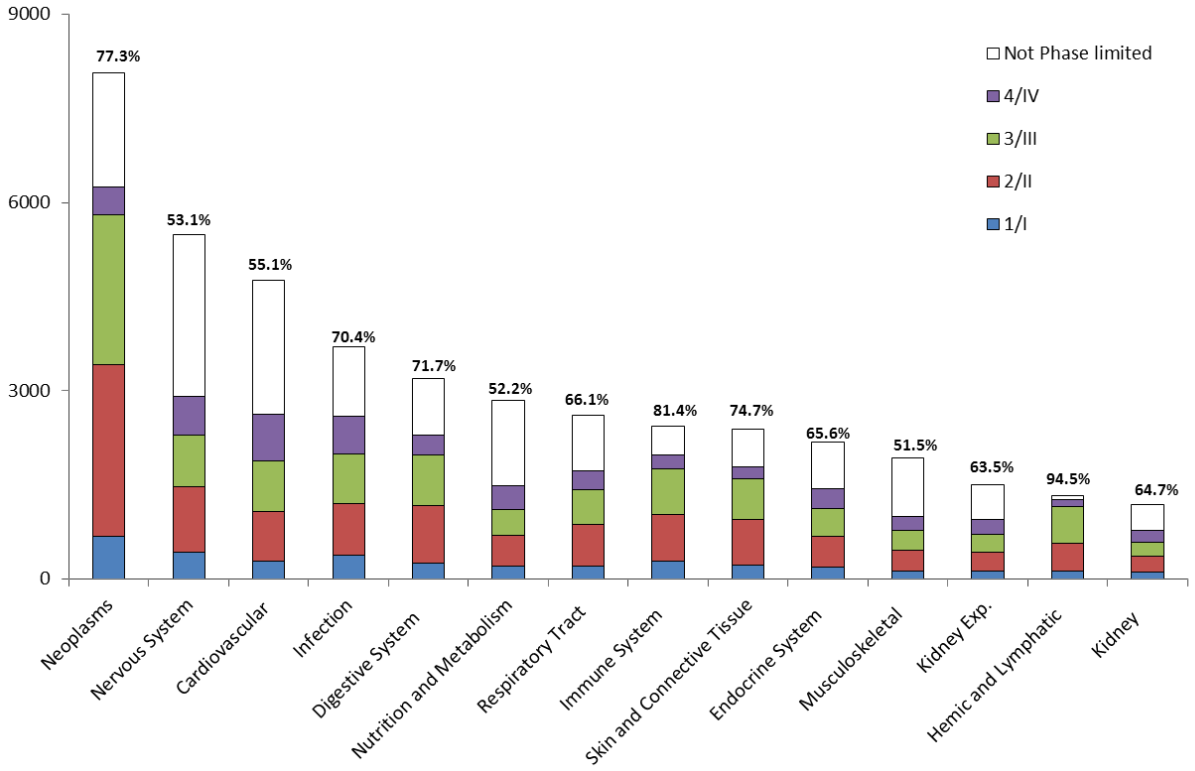


Figure 12: **Total numbers and phase analysis of current clinical trials identified from clinicaltrials.gov.** Each column represents the total number of trials for each field. The different bars represent the different phases. Several MeSH terms were applied to best cover each discipline as described in Methods. Nephrology ("Kidney" and "Kidney Exp.") is represented by the MeSH term "kidney diseases" and "Kidney Exp." includes the terms "Kidney Diseases", "Kidney Transplantation", "Hemodialysis", "Peritoneal Dialysis", "Urinary Tract Infections".

and 7.9% were categorized as phase 1 trials for "Kidney" and "Kidney Exp." respectively, 8.8% and 7.7% as phase 2, 8.6% and 7.5% as phase 3 and 7.0% and 6.0% as phase 4 trials. Together, we see minimal deviation for the kidney percentages compared to the total results.

3.1.3. Current state of nephrological trials compared with other medical disciplines

To address the current trends and to exclude reporting bias in this regard we also analyzed the U.S. National Library of Medicine registry, accessible at https://clinicaltrials.gov/. In this way we tried to include in the analysis not only trials concluded and published until 2017, but also to see what trials were in the recruitment, design or conduction process. This way not only the current but also the future trends of clinical research could be assessed.

In this registry, contrary to Figure 11, only a minority of clinical trials were unclassified, in total 33.4%. With kidney disease-related trials from 63% to 65% phase specified being well in the range of the other disciplines (Figure 12). Considering all medical disciplines we observe a much higher percentage of phase 2 and 3 trials, 24.7% and 22.5% respectively, while phase 1 and 4 trials represent 8.3% and 11.4% of all trials. Nephrology adheres to the trend of more phase 2 and 3 trials, with 9.0 % and 8.3% of the trials being categorized as phase 1 trials for “Kidney” and “Kidney Exp.” respectively, 21.4% and 21.3% as phase 2, 19.4% and 19.3% as phase 3 and 14.8% and 15.5% as phase 4 trials.

However, also here kidney disease-related trials were the lowest in number when compared with the other medical disciplines, and second lowest when including RRT and UTI.

3.1.4. Clinical trial distribution of different kidney disease entities

Figure 13A presents the preliminary diagram from the Pubmed analysis regarding the coverage of the different kidney disease entities. Figure 13A is included for comparative reason both to figure 13B and diagrams of previous relevant publication constructed through Pubmed [34]. We consider the diagrams constructed through the CENTRAL database of the Cochrane Library to be more reliable.

Cochrane database MeSH tree analysis for trial coverage of different disease entities within the field of nephrology showed that clinical trials addressing hypertension are the most in number starting from the 1970s and that they continue to predominate (Figure 13B). Kidney-replacement therapies-related trials were already much lower in number and disease entities such as glomerulonephritis, AKI or kidney calculi, although all being prevalent, contribute only a few papers to clinical trial activity (Figure 13B) [1].

3.1.5. Phase analysis of the different kidney disease entities

Similar to the comparison of different medical fields with each other, we again conducted a phase categorization of the various disease entities of nephrology (Figure 14A). In Figure 14B the column “Hypertension” is excluded, in order to provide a better overview of the

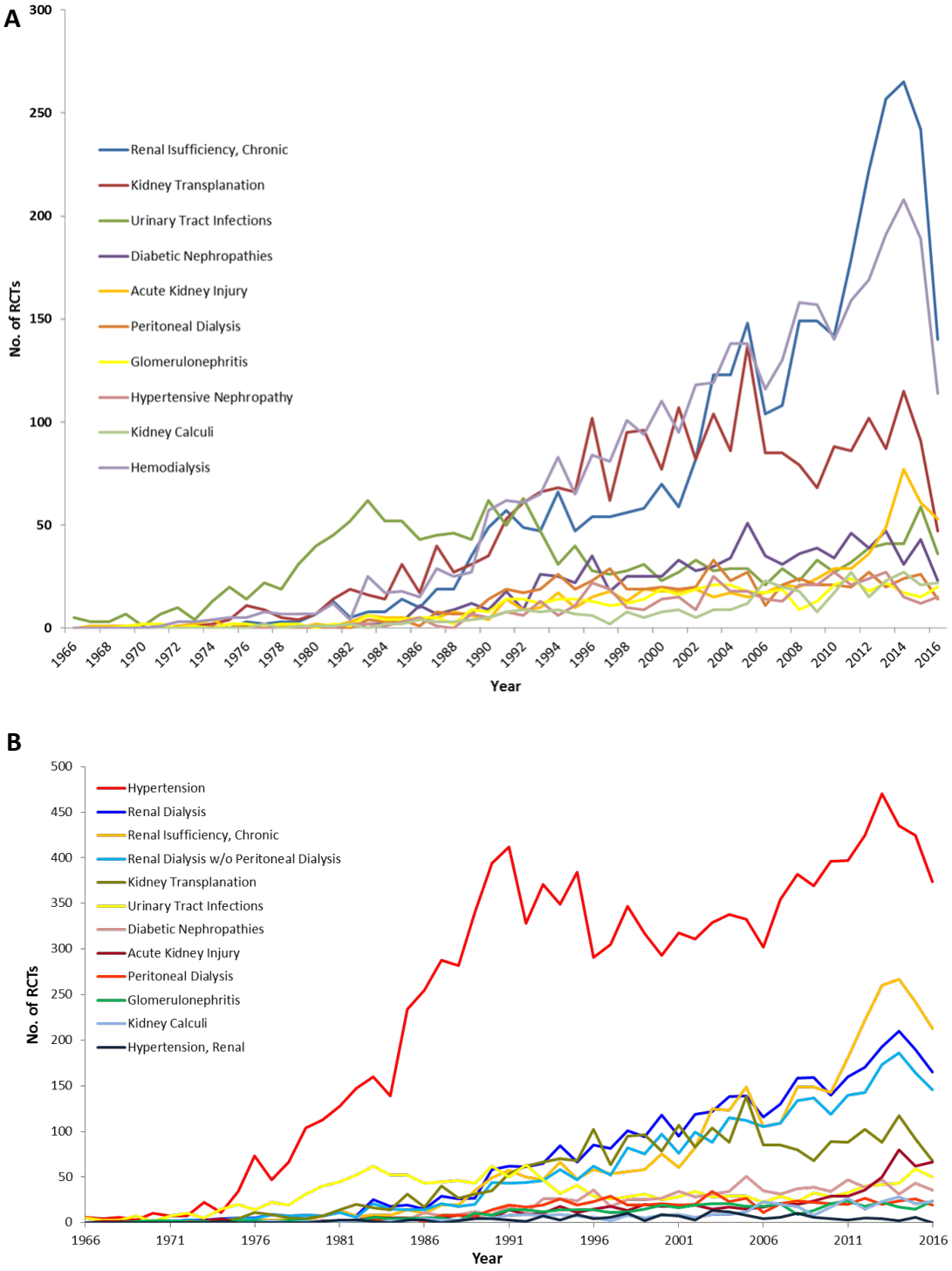


Figure 13: **Topic coverage of clinical trials in the field of nephrology**. Disease entities as defined by the available MeSH terms were quantified as described in Methods. (A) Annual numbers of the major areas of nephrology identified from the Pubmed database. (B) Annual number of clinical trials per kidney disease entity from 1966 to 2016 identified from CENTRAL. The sudden decline in numbers in the years 2015–2016 should relate to delays in data inclusion.

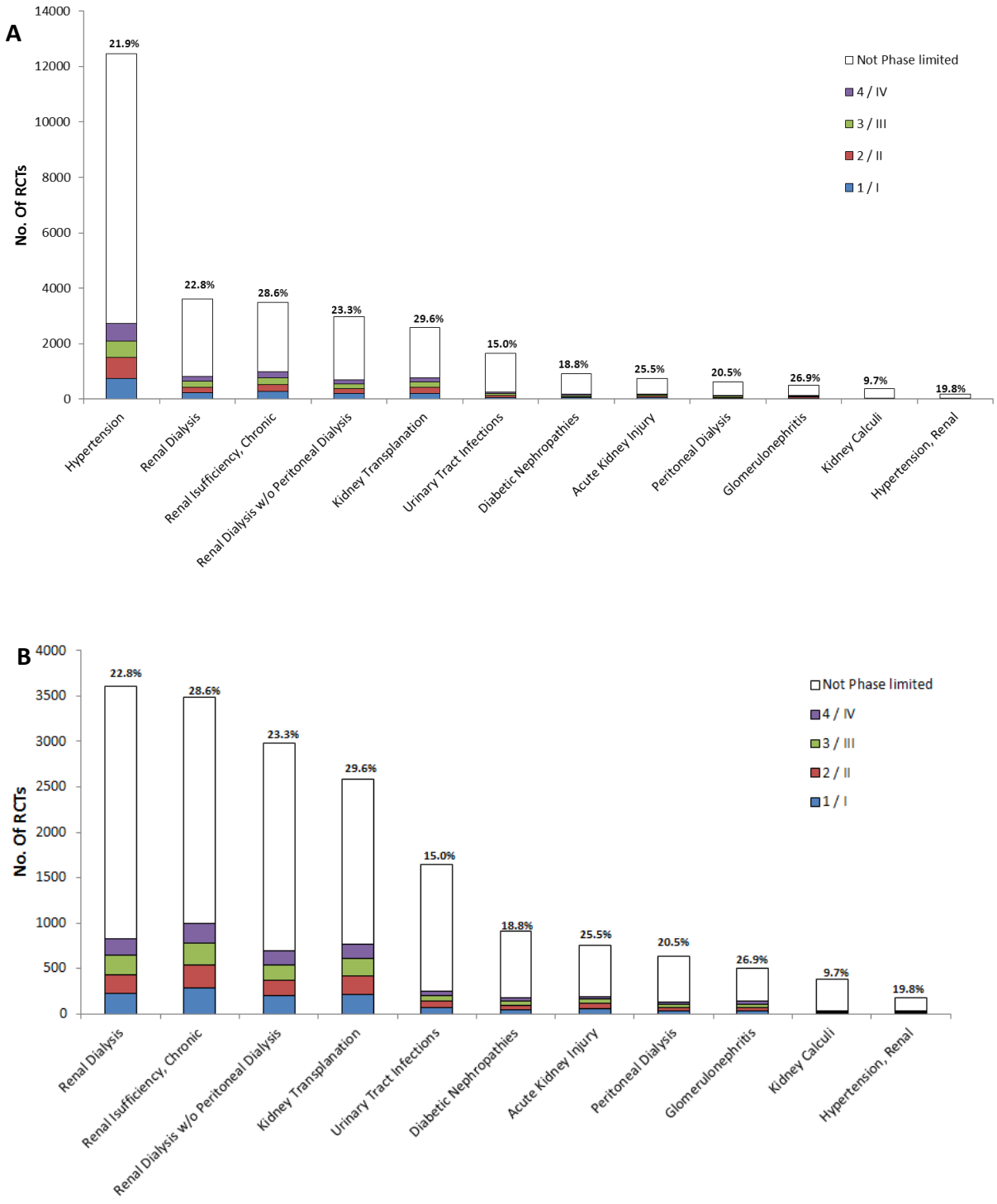


Figure 14: **Total numbers and phase analysis of nephrological disease entities identified from the CENTRAL database.** (A) Including "Hypertension". (B) "Hypertension" is excluded, in order to provide a better overview of the other nephrological areas. Each column represents the total number of trials published in CENTRAL for the years 1996-2017. The different bars represent the different phases. The percentages represent the trials classified.

other nephrological areas. Again, it quickly becomes evident, that most of the trials could not be categorized by phase, as this time 76.9% of them were unclassified. For the allocation of the classified articles, the frequency was in descending order, meaning 6.4% were categorized as phase 1, 6.2% as Phase 2, 5.5% as Phase 3 and 5.0% as Phase 4 trials.

3.1.6. Current state of research for different kidney disease entities

Again the diagram of the ongoing clinical trials at https://clinicaltrials.gov/ (Figure 15) shows a much better phase classification of the trials compared to Figure 14. Unclassified trials were this time 46.2%. Considering all nephrological entities included, we observe, similar to the trend for all medical disciplines, that again phase 2 and 3 trials dominate, representing 16.5% and 17.3% of all trials, while phase 4 trials are 14.8% of the whole sample and phase 1 trials again come last at 5.2%. Interestingly, AKI trials are much better represented in the ongoing trials than during the period 1966-2017.

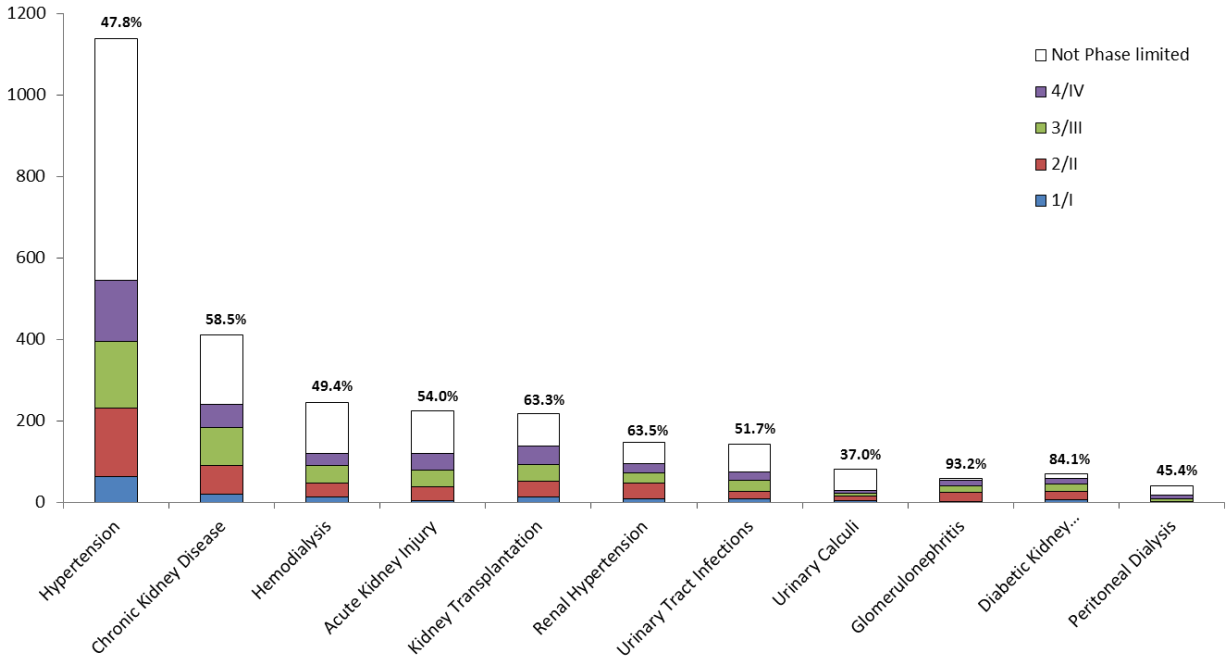


Figure 15: Total numbers and phase analysis of current clinical trials identified from clinicaltrials.gov. Each column represents the total number of trials for each field. The different bars represent the different phases. Several MeSH terms were applied to best cover each discipline as described in Methods.

In conclusion, the coverage of different disease entities within nephrology is strongly biased towards hypertension and kidney replacement therapies but AKI-related trials are now better represented among the currently ongoing trials.

3.1.7. Preclinical studies in nephrology compared with other medical disciplines

Preclinical research activity was analyzed using PubMed from 1945 to 2016. Oncology, infectious diseases, and neurology have reported the most studies since the 1990s, whereas kidney disease–related studies, in narrow and expanded definitions, remain at the low end among the medical disciplines since 1945 (Figure 16A). The average slope of additional preclinical studies reported each year from 1945 to 2003 was 95.0 ± 60.2 for all disciplines, and the average slopes were 26.7 and 30.5 for kidney diseases and expanded kidney diseases (excluding UTI), respectively (both P values versus all disciplines < 0.001). Since the last evaluation in 2003 (years 2004–2014), the slope increased to 313.8 ± 217.0 for all disciplines, indicating a profound increase in number and spread among the disciplines in annual preclinical study reporting. In the same period, studies on kidney diseases and their expanded definition increased to 88.5 and 89.3, respectively (both P values versus all disciplines < 0.001). Over the entire period, all disciplines display an annual increase of reported clinical trials of 133.6 ± 85.1, whereas kidney diseases display an annual increase of reported clinical trials of 37.8 and expanded kidney diseases display an annual increase of reported clinical trials of 40.5 (both P values versus all disciplines < 0.001) [1].

Again, even with the inclusion of the term UTI in the expanded definition of nephrology there was no big increase in the annual increase of trials, with the values increasing from 30.5 to 31.8 for the years 1945-2003, to 92.8 from 89.3 for the years 2004-2014 and to 42.2 from 40.5 for the whole period analysed (Figure 16B). As explained already in the corresponding analysis on clinical trials, the years from 2015 on were excluded from this analysis due to delays in MeSH term indexing within the PubMed database.

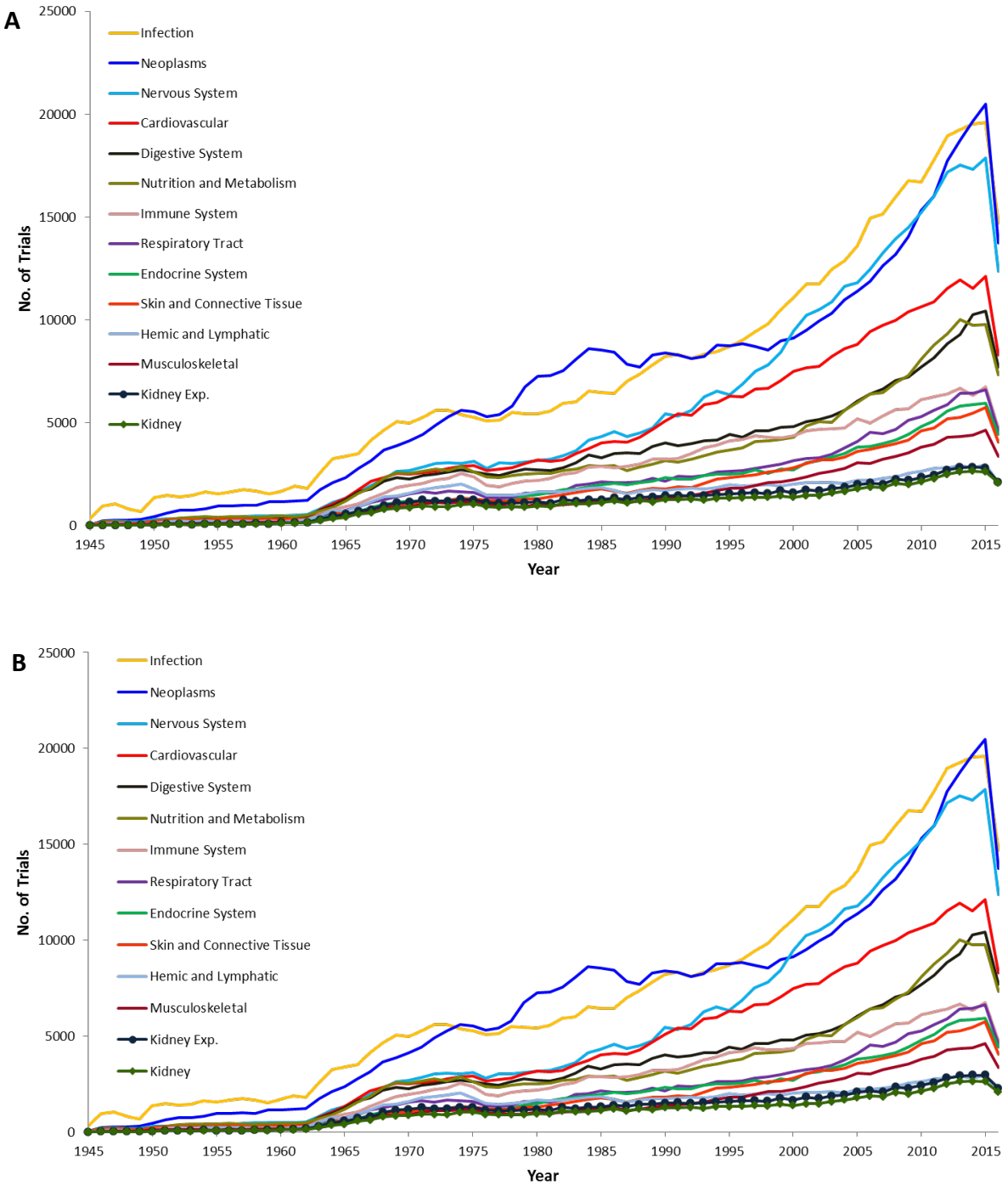


Figure 16: Quantitative analysis of preclinical studies in medical disciplines. Several MeSH terms were applied to best cover each discipline as described in Methods. Nephrology ("Kidney") is represented by the MeSH term "kidney diseases". (A) Annual numbers of preclinical studies per discipline identified from Pubmed. Expanded (Exp.) nephrology ("Kidney Exp.") covers the MeSH term "RRT". (B) Annual numbers of preclinical studies per discipline identified from Pubmed. Expanded (Exp.) nephrology this time covers the MeSH terms "RRT" and "Urinary Tract Infections". The sudden decline in numbers in the years 2015–2016 should relate to delays in data inclusion.

Thus, although increasing in number, the count of kidney-related preclinical studies was again found to lag behind other disciplines.

3.1.8. Preclinical study coverage of different kidney disease entities

Studies focusing on hypertension again by far outweigh all other kidney disease entities and preclinical research as well (Figure 17A), but preclinical kidney research topics covered a broader range of topics than seen in clinical trials (Figure 17B). Whereas studies on kidney transplantation revealed an early peak in the mid-1960s, preclinical research activity on GN and hypertensive nephropathy substantially increased starting from the early 1980s (Figure 17B) [1].

As a more recent trend, studies addressing AKI, CKD, and diabetic nephropathy have become by far the most popular preclinical research topics within the last decade (Figure 17B), with GN maintaining the levels of research activity since its peak, while areas such as PD or Kidney Calculi show the least research activity through the entire timeline examined [1].

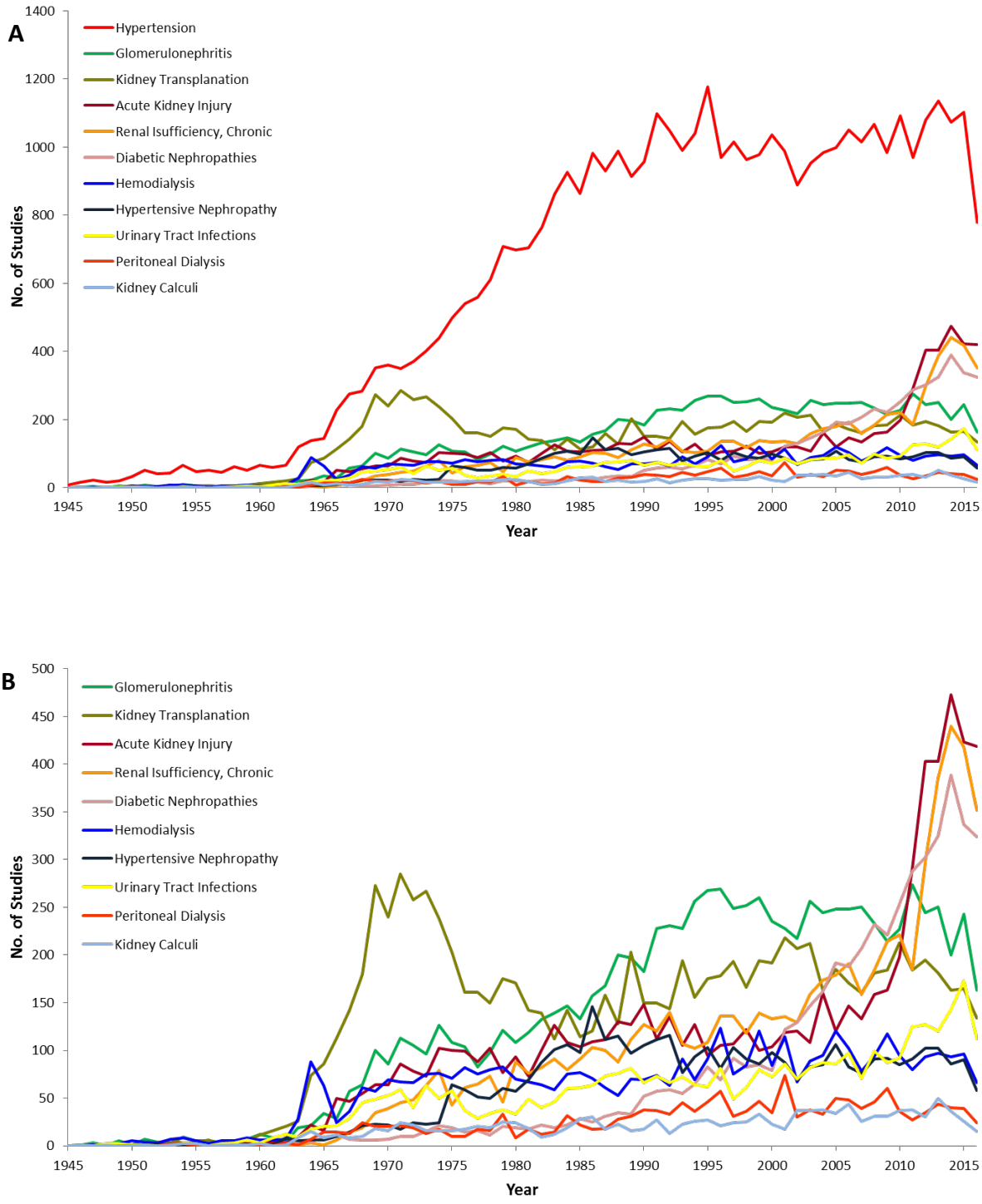


Figure 17: **Topic coverage of preclinical studies in the nephrology domain.** Several MeSH terms were applied to best cover each discipline as described in Methods. (A) Annual numbers of the major areas of nephrology identified from the Pubmed database from 1945 to 2016 (B) "Hypertension" is excluded, in order to provide a better overview of the other nephrological areas. The sudden decline in numbers in the years 2015–2016 should relate to delays in data inclusion.

3.2. Qualitative Analyses

3.2.1. Quality of clinical trial reporting in kidney research

To assess the quality of trial reporting, we selected 125 publications from top medical and nephrology journals as listed in Figure 18. Seven had to be deleted for invalidity criteria (two prospective trials, one observational trial, one non-randomized trial, and three non-original articles).

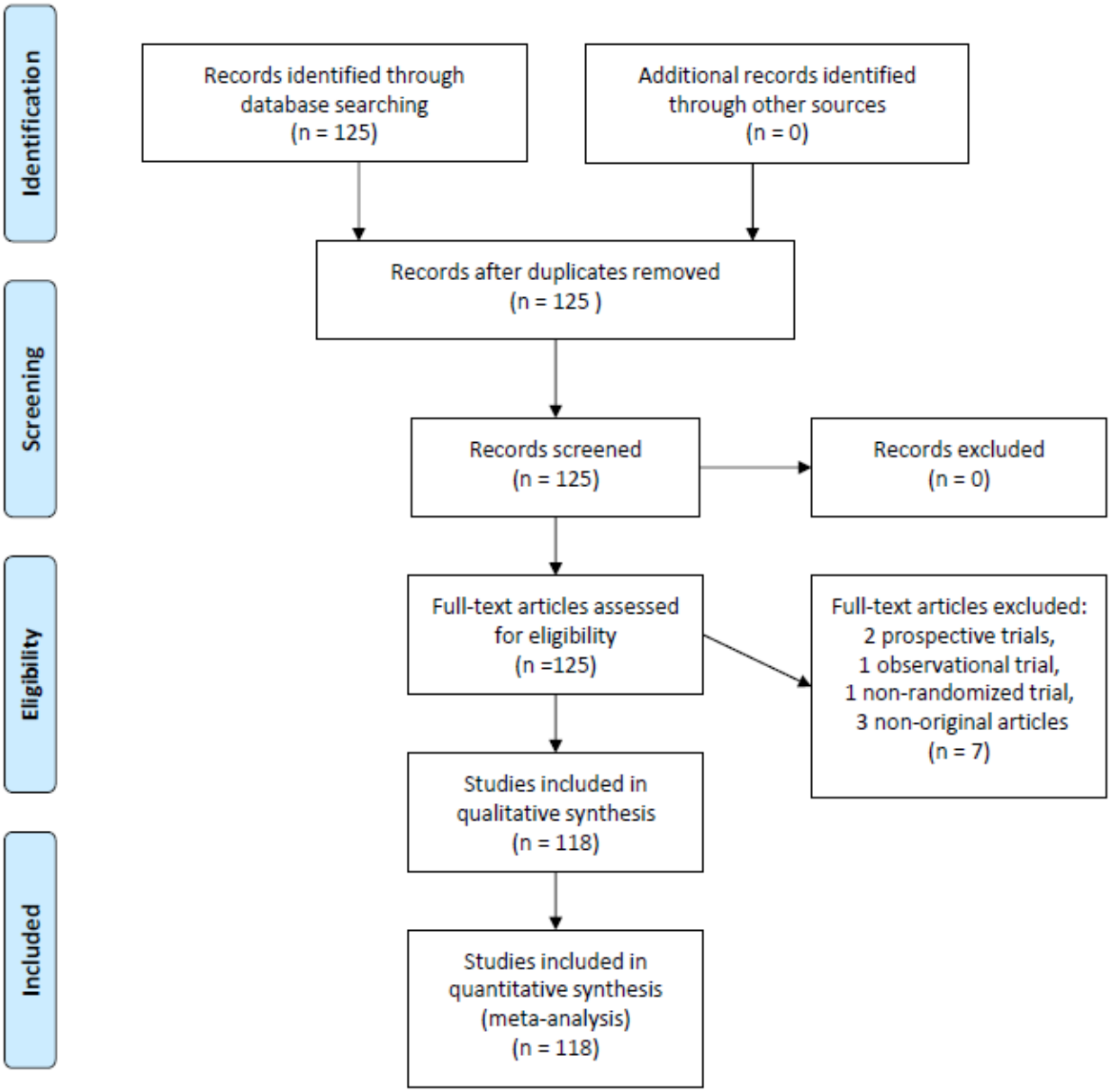


Figure 18: Flow chart illustrating the identification and selection of clinical trial report papers for the quality analysis.

The main bodies of the remaining 118 papers were scored for the modified CONSORT criteria as not reported, insufficiently reported, or sufficiently reported as listed in Table 5.

The title did not identify studies as RCTs in 69.5%. Abstracts provided a structured summary of the trial design in 51.7% (Table 7). The introduction named the objectives and a clear hypothesis in 82.2%, while 93.2% of the trials sufficiently explained their rationale. The precise trial design, including allocation ratio of participants was missing in 40.7% of the papers. Eligibility criteria, including inclusion and exclusion points, were reported in around four fifths of the papers. More than half also reported settings and location of trial conduction. A precise description of how and when the intervention was administered, in order to allow replication, was reported in 66.9% of the studies. A precise definition of the primary and secondary outcomes was reported in 60.2% of the trials. Information about sample size calculation was lacking in more than half the articles. The modes of randomization, such as sequence generation, the mechanisms of allocation concealment and implementation, were reported only in 35.6%, 19.5%, and 14.4%, respectively. Less than one third of articles reported double-blinding, whereas the statistical methods used for group comparisons on primary and secondary outcomes were mostly reported sufficiently (90.7%). Exactly half the papers specified the number of participants who were randomized, who received the intended treatment and who were analyzed regarding the primary outcome, and even less than half included a participant flow diagram. Three fourths of studies reported baseline data, including demographic and clinical characteristics for each group, and around the same percentage specified the numbers of participants included in each analysis, while an adequate intention-to-treat analysis regarding the primary end point was performed in only less than half (45.8%) of the studies. Adverse events of the intervention were reported in a little more than half the time [1].

Analyzing trends over time revealed linear improvements from 1996 to 2016 in reporting trial nature in the title, structuring abstracts, explanation of rationale, trial design, settings and location of the trials, clearly declaring primary and secondary outcomes, sample size calculations and double blinding of trials, statistical methods, presenting flow diagrams with participants and specifying reason for exclusion after randomization, defining periods of recruitment and follow-up, presenting baseline data and number of participants for each analysis, conducting ITT analysis and side effects (Table 7, Figure 19A). Reverse trends were

importantly found for describing precisely how and when the interventions were performed, while randomization procedures including random allocation sequence were either minimally improved, stale or trending backwards [1].

Among the leading journals reporting kidney-related clinical trials, a great diversity of matching CONSORT quality criteria was found. Only The Lancet identified trials as randomized in the title in more than half the papers examined, and the same journal along with the NEJM and AJKD provided structured abstracts, whereas Kidney International and JASN did not (Table 7, Figure 19B). In all the journals most of the time the scientific rationale was sufficiently explained and hypotheses and objectives were clearly stated. Trial design on the other hand was generally described insufficiently. Information on randomization procedures were clearly lacking in the JASN, while also in the other journals they were more often absent than present, while sample size calculations were also less frequent in the JASN than in other journals. The Lancet was the journal with the higher percentage of double-blinded studies, while explanations of the blinding procedures were lacking across all journals. Statistical methods were sufficiently reported almost universally. A flow diagram was included in four fifths of The Lancet's articles but was rare otherwise. Baseline data were included in more than 60% of articles in all journals and number of participants was presented for each analysis in more than three fourths in all the journals other than the JASN, with the NEJM being the most reliable in both categories. Clinical trials reported in JASN also more frequently lacked an ITT analysis compared with those of other journals, with NEJM again topping the category, and unlike NEJM, the other journals insufficiently reported the statistical methods. Only The Lancet reported less than half the time side effects of the interventions [1].

Table 7: Quality assessment of clinical trials according to modified CONSORT criteria

Sample Size: 125, Invalid: 7, Valid: 118		0 : Not reported		1 : Insufficiently reported / Unclear		2 : Sufficiently Reported		2016 --> 36 2006 --> 54 1996 --> 28	0 : Not reported		1 : Insufficiently reported / Unclear		2 : Sufficiently Reported		JASN: 26 NEJM: 19 Lancet: 5 Kidney Int.: 26 AJKD: 42	0 : Not reported		1 : Insufficiently reported / Unclear		2 : Sufficiently Reported	
Title	*Identified as a randomized trial in the title*	82	69.5%	8	6.8%	28	23.7%	1996	23	82.1%	1	3.6%	4	14.3%	JASN	23	88.5%	0	0.0%	3	11.5%
															NEJM	19	100.0%	0	0.0%	0	0.0%
								2006	38	70.4%	4	7.4%	12	22.2%	Lancet	2	40.0%	0	0.0%	3	60.0%
								2016	21	58.3%	3	8.3%	12	33.3%	Kidney Int.	22	84.6%	1	3.8%	3	11.5%
															AJKD	16	38.1%	7	16.7%	19	45.2%
Abstract	*Structured summary of trial design, methods, results, and conclusions*	57	48.3%	0	0.0%	61	51.7%	1996	24	85.7%	0	0.0%	4	14.3%	JASN	26	100.0%	0	0.0%	0	0.0%
															NEJM	0	0.0%	0	0.0%	19	100.0%
								2006	22	40.7%	0	0.0%	32	59.3%	Lancet	0	0.0%	0	0.0%	5	100.0%
								2016	11	30.6%	0	0.0%	25	69.4%	Kidney Int.	26	100.0%	0	0.0%	0	0.0%
															AJKD	5	11.9%	0	0.0%	37	88.1%
Background	*Scientific background and explanation of rationale*	0	0.0%	8	6.8%	110	93.2%	1996	0	0.0%	4	14.3%	24	85.7%	JASN	0	0.0%	3	11.5%	23	88.5%
															NEJM	0	0.0%	0	0.0%	19	100.0%
								2006	0	0.0%	3	5.6%	51	94.4%	Lancet	0	0.0%	3	60.0%	2	40.0%
								2016	0	0.0%	1	2.8%	35	97.2%	Kidney Int.	0	0.0%	1	3.8%	25	96.2%
															AJKD	0	0.0%	1	2.4%	41	97.6%
	Specific objectives or hypotheses clearly stated	6	5.1%	15	12.7%	97	82.2%	1996	3	10.7%	4	14.3%	21	75.0%	JASN	1	3.8%	4	15.4%	21	80.8%
															NEJM	2	10.5%	4	21.1%	13	68.4%
								2006	3	5.6%	3	5.6%	48	88.9%	Lancet	0	0.0%	1	20.0%	4	80.0%
								2016	0	0.0%	8	22.2%	28	77.8%	Kidney Int.	2	7.7%	5	19.2%	19	73.1%
															AJKD	1	2.4%	1	2.4%	40	95.2%
Trial Design	*Trial design (such as **parallel, factorial**) including allocation ratio.*	48	40.7%	49	41.5%	21	17.8%	1996	15	53.6%	10	35.7%	3	10.7%	JASN	11	42.3%	8	30.8%	7	26.9%
															NEJM	9	47.4%	6	31.6%	4	21.1%
								2006	25	46.3%	23	42.6%	6	11.1%	Lancet	3	60.0%	1	20.0%	1	20.0%
								2016	8	22.2%	16	44.4%	12	33.3%	Kidney Int.	8	30.8%	15	57.7%	3	11.5%
															AJKD	17	40.5%	19	45.2%	6	14.3%
	*Important changes to methods after trial commencement (such as **eligibility criteria**), with reasons.*	115	97.5%	1	0.8%	2	1.7%	1996	27	96.4%	1	3.6%	0	0.0%	JASN	25	96.2%	1	3.8%	0	0.0%
															NEJM	19	100.0%	0	0.0%	0	0.0%
								2006	53	98.1%	0	0.0%	1	1.9%	Lancet	4	80.0%	0	0.0%	1	20.0%
								2016	35	97.2%	0	0.0%	1	2.8%	Kidney Int.	26	100.0%	0	0.0%	0	0.0%
															AJKD	41	97.6%	0	0.0%	1	2.4%
Participats	***Eligibility criteria** for participants*	10	8.5%	12	10.2%	96	81.4%	1996	5	17.9%	6	21.4%	17	60.7%	JASN	3	11.5%	3	11.5%	20	76.9%
															NEJM	0	0.0%	1	5.3%	18	94.7%
								2006	4	7.4%	2	3.7%	48	88.9%	Lancet	1	20.0%	2	40.0%	2	40.0%
								2016	1	2.8%	4	11.1%	31	86.1%	Kidney Int.	4	15.4%	2	7.7%	20	76.9%
															AJKD	2	4.8%	4	9.5%	36	85.7%
	***Settings and locations** where the **data** were collected.*	24	20.3%	31	26.3%	63	53.4%	1996	9	32.1%	8	28.6%	11	39.3%	JASN	8	30.8%	8	30.8%	10	38.5%
															NEJM	1	5.3%	3	15.8%	15	78.9%
								2006	11	20.4%	15	27.8%	28	51.9%	Lancet	2	40.0%	1	20.0%	2	40.0%
								2016	4	11.1%	8	22.2%	24	66.7%	Kidney Int.	8	30.8%	3	11.5%	15	57.7%
															AJKD	5	11.9%	16	38.1%	21	50.0%
Interventions	*The **interventions** for each group with sufficient details to allow replication, including **how** and **when** they were actually administered.*	12	10.2%	27	22.9%	79	66.9%	1996	1	3.6%	7	25.0%	20	71.4%	JASN	4	15.4%	7	26.9%	15	57.7%
															NEJM	3	15.8%	4	21.1%	12	63.2%
								2006	4	7.4%	11	20.4%	39	72.2%	Lancet	1	20.0%	2	40.0%	2	40.0%
								2016	7	19.4%	9	25.0%	20	55.6%	Kidney Int.	0	0.0%	6	23.1%	20	76.9%
															AJKD	4	9.5%	8	19.0%	30	71.4%
Outcomes	*Completely defined pre-specified **primary** and **secondary outcome measures**, including how and when they were assessed*	36	30.5%	11	9.3%	71	60.2%	1996	17	60.7%	4	14.3%	7	25.0%	JASN	10	38.5%	5	19.2%	11	42.3%
															NEJM	0	0.0%	1	5.3%	18	94.7%
								2006	17	31.5%	4	7.4%	33	61.1%	Lancet	3	60.0%	0	0.0%	2	40.0%
								2016	2	5.6%	3	8.3%	31	86.1%	Kidney Int.	12	46.2%	1	3.8%	13	50.0%
															AJKD	11	26.2%	4	9.5%	27	64.3%
	*Any **changes** to trial outcomes after the trial commenced, with reasons.*	117	99.2%	0	0.0%	1	0.8%	1996	28	100.0%	0	0.0%	0	0.0%	JASN	26	100.0%	0	0.0%	0	0.0%
															NEJM	18	94.7%	0	0.0%	1	5.3%
								2006	53	98.1%	0	0.0%	1	1.9%	Lancet	5	100.0%	0	0.0%	0	0.0%
								2016	36	100.0%	0	0.0%	0	0.0%	Kidney Int.	26	100.0%	0	0.0%	0	0.0%
															AJKD	42	100.0%	0	0.0%	0	0.0%

Table 7: Quality assessment of clinical trials according to modified CONSORT criteria

Sample Size	*How sample size was determined*		61	51.7%	1	0.8%	56	47.5%	1996	24	85.7%	0	0.0%	4	14.3%	JASN	22	84.6%	0	0.0%	4	15.4%
																NEJM	5	26.3%	0	0.0%	14	73.7%
									2006	25	46.3%	0	0.0%	29	53.7%	Lancet	2	40.0%	0	0.0%	3	60.0%
									2016	12	33.3%	1	2.8%	25	69.4%	Kidney Int.	13	50.0%	0	0.0%	13	50.0%
																AJKD	19	45.2%	1	2.4%	22	52.4%
	Explanation of any interim analyses and stopping guidelines.		103	87.3%	1	0.8%	14	11.9%	1996	25	89.3%	0	0.0%	3	10.7%	JASN	22	84.6%	0	0.0%	4	15.4%
																NEJM	13	68.4%	1	5.3%	5	26.3%
									2006	47	87.0%	0	0.0%	7	13.0%	Lancet	2	40.0%	0	0.0%	3	60.0%
									2016	31	86.1%	1	2.8%	4	11.1%	Kidney Int.	25	96.2%	0	0.0%	1	3.8%
																AJKD	41	97.6%	0	0.0%	1	2.4%
Randomization	***Sequence generation***	*Method used to generate the random allocation sequence*	75	63.6%	1	0.8%	42	35.6%	1996	26	92.9%	0	0.0%	2	7.1%	JASN	24	92.3%	0	0.0%	2	7.7%
																NEJM	12	63.2%	1	5.3%	6	31.6%
									2006	27	50.0%	0	0.0%	27	50.0%	Lancet	3	60.0%	0	0.0%	2	40.0%
									2016	22	61.1%	1	2.8%	13	36.1%	Kidney Int.	15	57.7%	0	0.0%	11	42.3%
																AJKD	21	50.0%	0	0.0%	21	50.0%
		Type of randomization; details of any restriction (such as blocking and block size).	79	66.9%	1	0.8%	38	32.2%	1996	21	75.0%	0	0.0%	7	25.0%	JASN	23	88.5%	0	0.0%	3	11.5%
																NEJM	7	36.8%	0	0.0%	12	63.2%
									2006	35	64.8%	1	1.9%	18	33.3%	Lancet	4	80.0%	0	0.0%	1	20.0%
									2016	23	63.9%	0	0.0%	13	36.1%	Kidney Int.	21	80.8%	0	0.0%	5	19.2%
																AJKD	24	57.1%	1	2.4%	17	40.5%
	Allocation concealment mechanism	*Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned.*	92	78.0%	3	2.5%	23	19.5%	1996	25	89.3%	2	7.1%	1	3.6%	JASN	25	96.2%	0	0.0%	1	3.8%
																NEJM	15	78.9%	0	0.0%	4	21.1%
									2006	28	51.9%	1	1.9%	15	27.8%	Lancet	3	60.0%	0	0.0%	2	40.0%
									2016	29	80.6%	0	0.0%	7	19.4%	Kidney Int.	17	65.4%	3	11.5%	6	23.1%
																AJKD	32	76.2%	0	0.0%	10	23.8%
	Implementation	*Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions*	99	83.9%	2	1.7%	17	14.4%	1996	28	100.0%	0	0.0%	0	0.0%	JASN	25	96.2%	0	0.0%	1	3.8%
																NEJM	18	94.7%	0	0.0%	1	5.3%
									2006	43	79.6%	1	1.9%	10	18.5%	Lancet	3	60.0%	0	0.0%	2	40.0%
									2016	28	77.8%	1	2.8%	7	19.4%	Kidney Int.	21	80.8%	1	3.8%	4	15.4%
																AJKD	32	76.2%	1	2.4%	9	21.4%
Blinding	*Status*		75	63.6%	7	5.9%	36	30.5%	1996	21	75.0%	0	0.0%	7	25.0%	JASN	21	80.8%	1	3.8%	4	15.4%
																NEJM	10	52.6%	2	10.5%	7	36.8%
									2006	34	63.0%	3	5.6%	17	31.5%	Lancet	2	40.0%	0	0.0%	3	60.0%
									2016	20	55.6%	4	11.1%	12	33.3%	Kidney Int.	15	57.7%	2	7.7%	9	34.6%
																AJKD	27	64.3%	2	4.8%	13	31.0%
	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes).		96	81.4%	6	5.1%	16	13.6%	1996	27	96.4%	0	0.0%	1	3.6%	JASN	19	73.1%	6	23.1%	1	3.8%
																NEJM	14	73.7%	5	26.3%	0	0.0%
									2006	44	81.5%	7	13.0%	3	5.6%	Lancet	3	60.0%	1	20.0%	1	20.0%
									2016	25	69.4%	9	25.0%	2	5.6%	Kidney Int.	24	92.3%	1	3.8%	1	3.8%
																AJKD	36	85.7%	3	7.1%	3	7.1%
	If relevant, description of the similarity of interventions.		104	88.1%	3	2.5%	11	9.3%	1996	27	96.4%	0	0.0%	1	3.6%	JASN	24	92.3%	1	3.8%	1	3.8%
																NEJM	17	89.5%	0	0.0%	2	10.5%
									2006	49	90.7%	2	3.7%	3	5.6%	Lancet	4	80.0%	0	0.0%	1	20.0%
									2016	28	77.8%	1	2.8%	7	19.4%	Kidney Int.	25	96.2%	0	0.0%	1	3.8%
																AJKD	34	81.0%	2	4.8%	6	14.3%
Statistical Methods	*Statistical methods used to compare groups for primary and secondary outcomes.*		3	2.5%	8	6.8%	107	90.7%	1996	2	7.1%	2	7.1%	24	85.7%	JASN	1	3.8%	1	3.8%	24	92.3%
																NEJM	0	0.0%	0	0.0%	19	100.0%
									2006	1	1.9%	5	9.3%	48	88.9%	Lancet	1	20.0%	1	20.0%	3	60.0%
									2016	0	0.0%	1	2.8%	35	97.2%	Kidney Int.	1	3.8%	3	11.5%	22	84.6%
																AJKD	0	0.0%	3	7.1%	39	92.9%
	Methods for additional analyses, such as subgroup analyses and adjusted analyses.		53	44.9%	10	8.5%	55	46.6%	1996	18	64.3%	2	7.1%	8	28.6%	JASN	15	57.7%	2	7.7%	9	34.6%
																NEJM	3	15.8%	2	10.5%	14	73.7%
									2006	26	48.1%	5	9.3%	23	42.6%	Lancet	3	60.0%	0	0.0%	2	40.0%
									2016	9	25.0%	3	8.3%	24	66.7%	Kidney Int.	13	50.0%	1	3.8%	12	46.2%
																AJKD	19	45.2%	5	11.9%	18	42.9%

Table 7: Quality assessment of clinical trials according to modified CONSORT criteria

Participant flow	*Diagramm*	72	61.0%	0	0.0%	46	39.0%	1996	26	92.9%	0	0.0%	2	7.1%	JASN	21	80.8%	0	0.0%	5	19.2%
															NEJM	10	52.6%	0	0.0%	9	47.4%
								2006	30	55.6%	0	0.0%	24	44.4%	Lancet	1	20.0%	0	0.0%	4	80.0%
								2016	16	44.4%	0	0.0%	20	55.6%	Kidney Int.	19	73.1%	0	0.0%	7	26.9%
															AJKD	21	50.0%	0	0.0%	21	50.0%
	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	22	18.6%	37	31.4%	59	50.0%	1996	12	42.9%	11	39.3%	5	17.9%	JASN	10	38.5%	10	38.5%	6	23.1%
															NEJM	1	5.3%	4	21.1%	14	73.7%
								2006	7	13.0%	17	31.5%	30	55.6%	Lancet	1	20.0%	0	0.0%	4	80.0%
								2016	3	8.3%	9	25.0%	24	66.7%	Kidney Int.	5	19.2%	9	34.6%	12	46.2%
															AJKD	5	11.9%	14	33.3%	23	54.8%
	For each group, losses and exclusions after randomization, together with reasons.	41	34.7%	13	11.0%	64	54.2%	1996	14	50.0%	4	14.3%	10	35.7%	JASN	12	46.2%	2	7.7%	12	46.2%
															NEJM	6	31.6%	0	0.0%	13	68.4%
								2006	15	27.8%	7	13.0%	32	59.3%	Lancet	1	20.0%	0	0.0%	4	80.0%
								2016	12	33.3%	2	5.6%	22	61.1%	Kidney Int.	10	38.5%	3	11.5%	13	50.0%
															AJKD	12	28.6%	8	19.0%	22	52.4%
Recruitment	*Dates defining the periods of recruitment and follow-up*	18	15.3%	57	48.3%	43	36.4%	1996	7	25.0%	18	64.3%	3	10.7%	JASN	5	19.2%	17	65.4%	4	15.4%
															NEJM	1	5.3%	3	15.8%	15	78.9%
								2006	10	18.5%	24	44.4%	20	37.0%	Lancet	2	40.0%	2	40.0%	1	20.0%
								2016	1	2.8%	15	41.7%	20	55.6%	Kidney Int.	7	26.9%	14	53.8%	5	19.2%
															AJKD	3	7.1%	21	50.0%	18	42.9%
	Why the trial ended or was stopped.	104	88.1%	5	4.2%	9	7.6%	1996	24	85.7%	2	7.1%	2	7.1%	JASN	23	88.5%	0	0.0%	3	11.5%
															NEJM	14	73.7%	1	5.3%	4	21.1%
								2006	48	88.9%	0	0.0%	6	11.1%	Lancet	4	80.0%	0	0.0%	1	20.0%
								2016	32	88.9%	3	8.3%	1	2.8%	Kidney Int.	24	92.3%	2	7.7%	0	0.0%
															AJKD	39	92.9%	2	4.8%	1	2.4%
Baseline Data	*A table showing baseline demographic and clinical characteristics for each group.*	10	8.5%	16	13.6%	92	78.0%	1996	5	17.9%	9	32.1%	14	50.0%	JASN	4	15.4%	5	19.2%	17	65.4%
															NEJM	2	10.5%	0	0.0%	17	89.5%
								2006	2	3.7%	7	13.0%	45	83.3%	Lancet	0	0.0%	2	40.0%	3	60.0%
								2016	3	8.3%	0	0.0%	33	91.7%	Kidney Int.	2	7.7%	4	15.4%	20	76.9%
															AJKD	2	4.8%	5	11.9%	35	83.3%
Numbers Analyzed	*For each group, number of participants (denominator) included in each analysis .*	10	8.5%	17	14.4%	91	77.1%	1996	5	17.9%	8	28.6%	15	53.6%	JASN	3	11.5%	6	23.1%	17	65.4%
															NEJM	1	5.3%	0	0.0%	18	94.7%
								2006	5	9.3%	9	16.7%	40	74.1%	Lancet	1	20.0%	0	0.0%	4	80.0%
								2016	0	0.0%	0	0.0%	36	100.0%	Kidney Int.	2	7.7%	4	15.4%	20	76.9%
															AJKD	3	7.1%	7	16.7%	32	76.2%
Intention-to-treat	*regarding the primary endpoint*	51	43.2%	13	11.0%	54	45,8%	1996	18	64.3%	5	17.9%	5	17.9%	JASN	18	69.2%	3	11.5%	5	19.2%
															NEJM	2	10.5%	2	10.5%	15	78.9%
								2006	22	40.7%	5	9.3%	27	50.0%	Lancet	2	40.0%	0	0.0%	3	60.0%
								2016	13	36.1%	1	2.8%	22	61.1%	Kidney Int.	13	50.0%	0	0.0%	13	50.0%
															AJKD	17	40.5%	7	16.7%	18	42.9%
Loss - to - Analysis	*(n randomly assigned -n in analysis)/ n randomly assigned*	8,79 % all papers, 19,04 with Calculable L-t-A						1996	8.3% all papers, 25.7% w. Calculabe L-t-A						JASN	10.6% all papers, 21.3% w. Calculable L-t-A						
															NEJM	0.0% all papers, 0.4% w. Caluclable L-t-A						
								2006	6.0% all papers, 18.1% w. Calculable L-t-A						Lancet	12,2% all papers, 30,5% w. Calcuclable L-t-A						
								2016	6.8% all papers, 22.1% w. Calculable L-t-A						Kidney Int.	6.5% all papers, 21.2% w. Calculable L-t-A						
															AJKD	7.3% all papars, 20.6% w. Calculable L-t-A						
Outcomes & Estimation	*For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval).*	0	0.0%	52	44.1%	66	55.9%	1996	0	0.0%	25	89.3%	3	10.7%	JASN	0	0.0%	15	57.7%	11	42.3%
															NEJM	0	0.0%	2	10.5%	17	89.5%
								2006	0	0.0%	23	42.6%	31	57.4%	Lancet	0	0.0%	3	60.0%	2	40.0%
								2016	0	0.0%	4	11.1%	32	88.9%	Kidney Int.	0	0.0%	16	61.5%	10	38.5%
															AJKD	0	0.0%	16	38.1%	26	61.9%
	For binary outcomes, presentation of both absolute and relative effect sizes.	71	60.2%	10	8.5%	37	31.4%	1996	24	85.7%	2	7.1%	2	7.1%	JASN	20	76.9%	2	7.7%	4	15.4%
															NEJM	3	15.8%	3	15.8%	13	68.4%
								2006	33	61.1%	3	5.6%	18	33.3%	Lancet	2	40.0%	0	0.0%	3	60.0%
								2016	14	38.9%	5	13.9%	17	47.2%	Kidney Int.	20	76.9%	1	3.8%	5	19.2%
															AJKD	26	61.9%	4	9.5%	12	28.6%

Table 7: Quality assessment of clinical trials according to modified CONSORT criteria

Ancillary Analyses	*Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory.*	43	36.4%	17	14.4%	58	49.2%	1996	15	53.6%	5	17.9%	8	28.6%	JASN	14	53.8%	3	11.5%	9	34.6%
															NEJM	4	21.1%	1	5.3%	14	73.7%
								2006	20	37.0%	8	14.8%	26	48.1%	Lancet	2	40.0%	1	20.0%	2	40.0%
								2016	8	22.2%	3	8.3%	24	66.7%	Kidney Int.	9	34.6%	4	15.4%	13	50.0%
															AJKD	14	33.3%	8	19.0%	20	47.6%
Harms	*All important harms or unintended effects in each group.*	40	33.9%	12	10.2%	66	55.9%	1996	18	64.3%	3	10.7%	7	25.0%	JASN	12	46.2%	1	3.8%	13	50.0%
															NEJM	1	5.3%	5	26.3%	13	68.4%
								2006	16	29.6%	6	11.1%	32	59.3%	Lancet	3	60.0%	0	0.0%	2	40.0%
								2016	6	16.7%	3	8.3%	27	75.0%	Kidney Int.	11	42.3%	1	3.8%	14	53.8%
															AJKD	13	31.0%	5	11.9%	24	57.1%

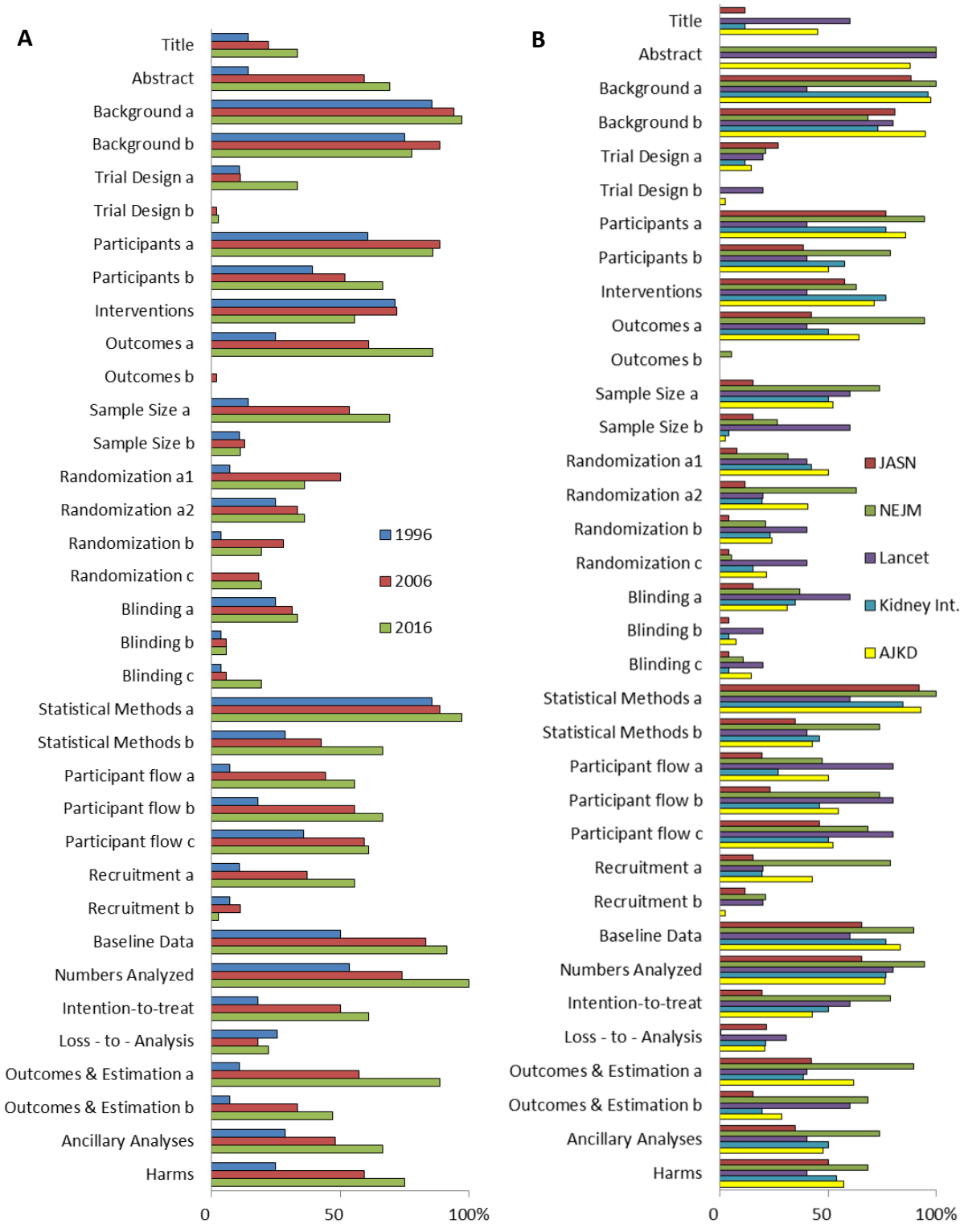


Figure 19: Quality assessment of reporting clinical trials in the main final paper according to CONSORT criteria. Each of the CONSORT criteria was assessed in representative samples selected from The NEJM, The Lancet, JASN, AJKD, and Kidney International of the years 1996, 2006, and 2016. Shown are the percentages of papers fulfilling the criterion "sufficiently reported" for (A) all journals in each of the 3 years to detect changes over time or (B) each of the journals across all time points.

3.2.2. Quality of preclinical trial reporting in kidney research

For quality assessment of preclinical studies, we selected 209 publications from JASN, Kidney International, and NDT. Seventy-four had to be deleted for invalidity criteria as shown in Figure 20 (3 articles not found, 4 only in vitro studies, 7 articles proved to be clinical trials, 1 belonged to the "Nephrology Image" category, 59 were non-original articles).

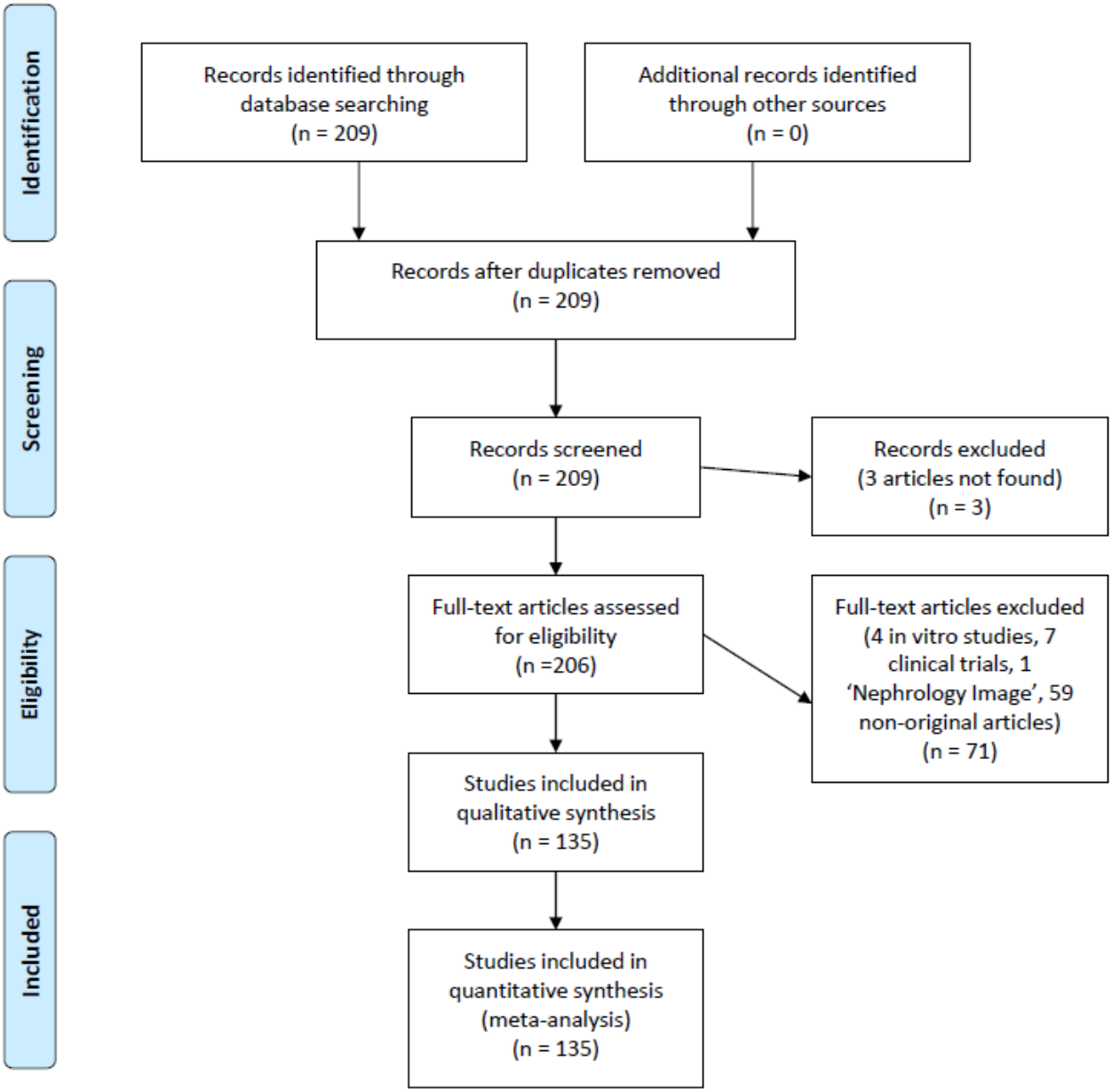


Figure 20: Flow chart illustrating the identification and selection of preclinical study reports papers for the quality analysis.

The remaining 135 papers were graded for the modified ARRIVE criteria as specified in Methods and in Table 6.

The experimental rationales were almost always sufficiently explained, while any form of explanation of why the specific animal model was used or the study's relevance to human biology was completely absent in more than half the articles (Table 8). Objectives or a hypothesis were specified in the introduction in 73%. The methods specified a detailed ethical statement in 81% and clearly defined the number or type of experimental groups in 65%. However, details on randomization, details on blinding, and a timeline diagram were scarce, being provided in only 17%, 1%, and 12%, respectively. Experimental procedures and specifics on the type of animals used were generally well described (98% and 97%, respectively), although adequate information on housing and husbandry were largely lacking (34%, in 41.5% no mention at all). Information on sample size calculation was always absent (0%), and also, numbers of independent replications were rare (19%), while almost in two fifths of the articles no mention of the number of animals in the experiments was made. More than three fourths of the articles provided no information regarding allocation method of the animals. Only a minority of studies (13%) specified the primary and secondary outcomes. Regarding statistical methods, the types of tests were almost always reported (95%), but the unit of analysis for each dataset and whether the data met the pre-specified assumptions of the statistical approach were not reported (0%). Baseline data were reported in only 12% of the studies, and the numbers analyzed for each test were thoroughly reported in only a third of the time. Adverse events were hardly ever reported (2%) [1].

Analyzing trends over time revealed linear improvements from 1996 to 2016 in reporting the relevance of the animal model to the human biology, ethical statements, blinding, experimental procedures and timeline diagrams (Figure 21A, Table 8). Reverse trends were found for describing the primary and secondary objectives or a research hypothesis and defining primary or secondary outcomes. Completely neglected across the entire study period was reporting details on group size calculations and whether the data obtained met the assumptions of the statistical approach. Importantly, any form of randomization, the method of allocation concealment and the number of animal in analysis were rarely reported and even showed a reverse trend from 2006 to 2016 (Table 8, Figure 21A) [1].

Table 8: Quality assessment of preclinical studies according to modified ARRIVE criteria

Total 209, 74 invalid, valid **135**		***0 : Not reported***		***1: Unclear / Insufficiently Reported***		***2: Sufficiently Reported***		1997 --> 30 2006 --> 61 2016 --> 44	***0 : Not reported***		***1: Unclear / Insufficiently Reported***		***2: Sufficiently Reported***		JASN: 50 Kidney Int.: 56 NDT: 29	***0 : Not reported***		***1: Unclear / Insufficiently Reported***		***2: Sufficiently Reported***	
1. Title	*Provide as accurate and concise a description of the content of the article as possible*	Subjective, not examined by the researchers						1996 2006 2016	Subjective, not examined by the researchers						JASN Kidney Int. NDT	Subjective, not examined by the researchers					
2. Abstract	*Provide an accurate summary of the backround, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusion of the study*	Subjective, not examined by the researchers						1996 2006 2016	Subjective, not examined by the researchers						JASN Kidney Int. NDT	Subjective, not examined by the researchers					
3. Background	*a. Study context and* ***experimental rationale***	0	0.0%	4	3.0%	131	97.0%	1996	0	0.0%	3	10.0%	27	90.0%	JASN	0	0.0%	1	2.0%	49	98.0%
								2006	0	0.0%	0	0.0%	61	100.0%	Kidney Int.	0	0.0%	1	1.8%	55	98.2%
								2016	0	0.0%	1	2.3%	43	97.7%	NDT	0	0.0%	2	6.9%	27	93.1%
	How and why animal ***species*** *and models being* ***used adress the objectives****, study's* ***relevance to human*** *biology*	72	53.3%	29	21.5%	34	25.0%	1996	13	43.3%	10	33.3%	7	23.3%	JASN	29	58.0%	10	20.0%	11	22.0%
								2006	30	49.2%	16	26.2%	15	24.6%	Kidney Int.	28	50.0%	14	25.0%	14	25.0%
								2016	29	65.9%	3	6.8%	12	27.3%	NDT	15	51.7%	5	17.2%	9	31.0%
4. Objectives	*Primary and any secondary objectives or hypotheses*	0	0.0%	37	27.4%	98	72.6%	1996	0	0.0%	5	16.7%	25	83.3%	JASN	0	0.0%	19	38.0%	31	62.0%
								2006	0	0.0%	14	23.0%	47	77.0%	Kidney Int.	0	0.0%	15	26.8%	41	73.2%
								2016	0	0.0%	18	40.9%	26	59.1%	NDT	0	0.0%	3	10.3%	26	89.7%
5. Ethical statement	*Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.*	26	19.3%	0	0.0%	109	80.7%	1996	23	76.7%	7	23.3%	7	23.3%	JASN	1	2.0%	0	0.0%	49	98.0%
								2006	2	3.3%	0	0.0%	59	96.7%	Kidney Int.	15	26.8%	0	0.0%	41	73.2%
								2016	1	2.3%	0	0.0%	43	97.7%	NDT	10	34.5%	0	0.0%	19	65.5%
6. Study design	*a. The number of* ***experimental and control groups***	2	1.5%	45	33.3%	88	65.2%	1996	1	3.3%	13	43.3%	16	53.3%	JASN	0	0.0%	17	34.0%	33	66.0%
								2006	0	0.0%	10	16.4%	51	83.6%	Kidney Int.	2	3.6%	23	41.1%	31	55.4%
								2016	1	2.3%	22	50.0%	21	47.7%	NDT	0	0.0%	5	17.2%	24	82.8%
	b,c. ***Randomization*** *and details of the experimental unit*	108	80.0%	4	3.0%	23	17.0%	1996	26	86.7%	1	3.3%	3	10.0%	JASN	39	78.0%	3	6.0%	8	16.0%
								2006	44	72.1%	2	3.3%	15	24.6%	Kidney Int.	49	87.5%	1	1.8%	6	10.7%
								2016	38	86.4%	1	2.3%	5	11.4%	NDT	20	69.0%	0	0.0%	9	31.0%
	b. ***Blinding*** *performed*	97	71.9%	36	26.7%	2	1.5%	1996	27	90.0%	3	10.0%	0	0.0%	JASN	34	68.0%	14	28.0%	2	4.0%
								2006	41	67.2%	20	32.8%	0	0.0%	Kidney Int.	42	75.0%	14	25.0%	0	0.0%
								2016	29	65.9%	1	2.3%	14	31.8%	NDT	21	72.4%	8	27.6%	0	0.0%
	d. A time-line diagram or ***flow chart***	119	88.1%	0	0.0%	16	11.9%	1996	30	100.0%	0	0.0%	0	0.0%	JASN	43	86.0%	0	0.0%	7	14.0%
								2006	54	88.5%	0	0.0%	7	11.5%	Kidney Int.	49	87.5%	0	0.0%	7	12.5%
								2016	35	79.5%	0	0.0%	9	20.5%	NDT	27	93.1%	0	0.0%	2	6.9%
7. Experimental procedures	*For each experiment and each experimental group, including controls, provide precise details of all procedures carried out.*	0	0.0%	3	2.2%	132	97.8%	1996	0	0.0%	3	10.0%	27	90.0%	JASN	0	0.0%	0	0.0%	50	100.0%
								2006	0	0.0%	0	0.0%	61	100.0%	Kidney Int.	0	0.0%	0	0.0%	56	100.0%
								2016	0	0.0%	0	0.0%	44	100.0%	NDT	0	0.0%	3	10.3%	26	89.7%
8. Experimental animals	*a,b. Provide details of the animals used, including* ***species****, strain,* ***sex****, developmental stage,* ***weight*** *and other relevant inforamtion(e.g.* ***Source****, genetic modification status)*	4	3.0%	17	12.6%	114	84.4%	1996	2	6.7%	4	13.3%	24	80.0%	JASN	2	4.0%	6	12.0%	42	84.0%
								2006	1	1.6%	4	6.6%	56	91.8%	Kidney Int.	2	3.6%	8	14.3%	46	82.1%
								2016	1	2.3%	9	20.5%	34	77.3%	NDT	0	0.0%	3	10.3%	26	89.7%
9. Housing and husbandry	*Housing, husbandry and welfare-related assessments*	56	41.5%	33	24.4%	46	34.1%	1996	14	46.7%	9	30.0%	7	23.3%	JASN	21	42.0%	16	32.0%	13	26.0%
								2006	25	41.0%	9	14.8%	27	44.3%	Kidney Int.	24	42.9%	11	19.6%	21	37.5%
								2016	17	38.6%	15	34.1%	12	27.3%	NDT	11	37.9%	6	20.7%	12	41.4%

Table 8: Quality assessment of preclinical studies according to modified ARRIVE criteria

10. Sample size	*a. Specify the **total number of animals** used in each experiment, and the **number of animals** in each experimental group.*	53	39.3%	27	20.0%	55	40.7%	1996	14	46.7%	7	23.3%	9	30.0%	JASN	19	38.0%	11	22.0%	20	40.0%
								2006	16	26.2%	13	21.3%	32	52.5%	Kidney Int.	29	51.8%	9	16.1%	18	32.1%
								2016	23	52.3%	7	15.9%	14	31.8%	NDT	5	17.2%	7	24.1%	17	58.6%
	*b. Explain how the number of animals was arrived at. Provide details of any **sample size calculation** used.*	135	100.0%	0	0.0%	0	0.0%	1996	30	100.0%	0	0.0%	0	0.0%	JASN	50	100.0%	0	0.0%	0	0.0%
								2006	61	100.0%	0	0.0%	0	0.0%	Kidney Int.	56	100.0%	0	0.0%	0	0.0%
								2016	44	100.0%	0	0.0%	0	0.0%	NDT	29	100.0%	0	0.0%	0	0.0%
	*c. Indicate the number of independent **replications** of each experiment, if relevant.*	93	68.9%	16	11.9%	26	19.3%	1996	22	73.3%	2	6.7%	6	20.0%	JASN	31	62.0%	7	14.0%	12	24.0%
								2006	45	73.8%	8	13.1%	8	13.1%	Kidney Int.	39	69.6%	6	10.7%	11	19.6%
								2016	26	59.1%	6	13.6%	12	27.3%	NDT	23	79.3%	3	10.3%	3	10.3%
11. Allocating animals to experimental groups	*a,b. Details of allocation method*	104	77.0%	6	4.4%	25	18.5%	1996	26	86.7%	1	3.3%	3	10.0%	JASN	37	74.0%	5	10.0%	8	16.0%
								2006	41	67.2%	2	3.3%	18	29.5%	Kidney Int.	49	87.5%	0	0.0%	7	12.5%
								2016	37	84.1%	3	6.8%	4	9.1%	NDT	18	62.1%	1	3.4%	10	34.5%
12. Experimental outcomes	*Primary and secondary experimental outcomes assessed*	94	69.6%	24	17.8%	17	12.6%	1996	18	60.0%	8	26.7%	4	13.3%	JASN	31	62.0%	10	20.0%	9	18.0%
								2006	39	63.9%	13	21.3%	9	14.8%	Kidney Int.	45	80.4%	5	8.9%	6	10.7%
								2016	37	84.1%	3	6.8%	4	9.1%	NDT	18	62.1%	9	31.0%	2	6.9%
13. Statistical methods	*a. Provide details of the **statistical methods used** for each analysis.*	6	4.4%	1	0.7%	128	94.8%	1996	4	13.3%	0	0.0%	26	86.7%	JASN	1	2.0%	1	2.0%	48	96.0%
								2006	1	1.6%	0	0.0%	60	98.4%	Kidney Int.	3	5.4%	0	0.0%	53	94.6%
								2016	1	2.3%	1	2.3%	42	95.5%	NDT	2	6.9%	0	0.0%	27	93.1%
	*b. Specify **the unit of analysis** for each dataset (e.g. **single animal, group of animals, single neuron**).*	117	86.7%	14	10.4%	4	3.0%	1996	25	83.3%	5	16.7%	0	0.0%	JASN	47	94.0%	2	4.0%	1	2.0%
								2006	56	91.8%	4	6.6%	1	1.6%	Kidney Int.	47	83.9%	8	14.3%	1	1.8%
								2016	36	81.8%	5	11.4%	3	6.8%	NDT	23	79.3%	4	13.8%	2	6.9%
	*c. Describe any methods used to assess **whether the data met the assumptions of the statistical approach**.*	134	99.3%	1	0.7%	0	0.0%	1996	30	100.0%	0	0.0%	0	0.0%	JASN	50	100.0%	0	0.0%	0	0.0%
								2006	60	98.4%	1	1.6%	0	0.0%	Kidney Int.	55	98.2%	1	1.8%	0	0.0%
								2016	44	100.0%	0	0.0%	0	0.0%	NDT	29	100.0%	0	0.0%	0	0.0%
14. Baseline data	*For each experimental group, relevant characteristics and health status of animals prior to treatment or testing.*	95	24.0%	24	17.8%	16	11.9%	1996	22	73.3%	5	16.7%	3	10.0%	JASN	34	68.0%	11	22.0%	5	10.0%
								2006	38	62.3%	14	23.0%	9	14.8%	Kidney Int.	41	73.2%	8	14.3%	7	12.5%
								2016	35	79.5%	5	11.4%	4	9.1%	NDT	20	69.0%	5	17.2%	4	13.8%
15. Numbers analysed	*Numbers analysed (included numbers of animals not included and why)*	18	13.3%	73	54.1%	44	32.6%	1996	7	23.3%	18	60.0%	5	16.7%	JASN	2	4.0%	29	58.0%	19	38.0%
								2006	6	9.8%	28	45.9%	27	44.3%	Kidney Int.	7	12.5%	33	58.9%	16	28.6%
								2016	5	11.4%	27	61.4%	12	27.3%	NDT	9	31.0%	11	37.9%	9	31.0%
16. Outcomes and estimation	*Report the results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval).*	5	3.7%	3	2.2%	127	94.1%	1996	3	10.0%	0	0.0%	27	90.0%	JASN	1	2.0%	3	6.0%	46	92.0%
								2006	1	1.6%	1	1.6%	59	96.7%	Kidney Int.	2	3.6%	0	0.0%	54	96.4%
								2016	1	2.3%	2	4.5%	41	93.2%	NDT	2	6.9%	0	0.0%	27	93.1%
17. Adverse events	*Details of all important adverse events and modifications*	131	97.0%	1	0.7%	3	2.2%	1996	30	100.0%	0	0.0%	0	0.0%	JASN	48	96.0%	1	2.0%	1	2.0%
								2006	59	96.7%	0	0.0%	2	3.3%	Kidney Int.	54	96.4%	0	0.0%	2	3.6%
								2016	42	95.5%	1	2.3%	1	2.3%	NDT	29	100.0%	0	0.0%	0	0.0%

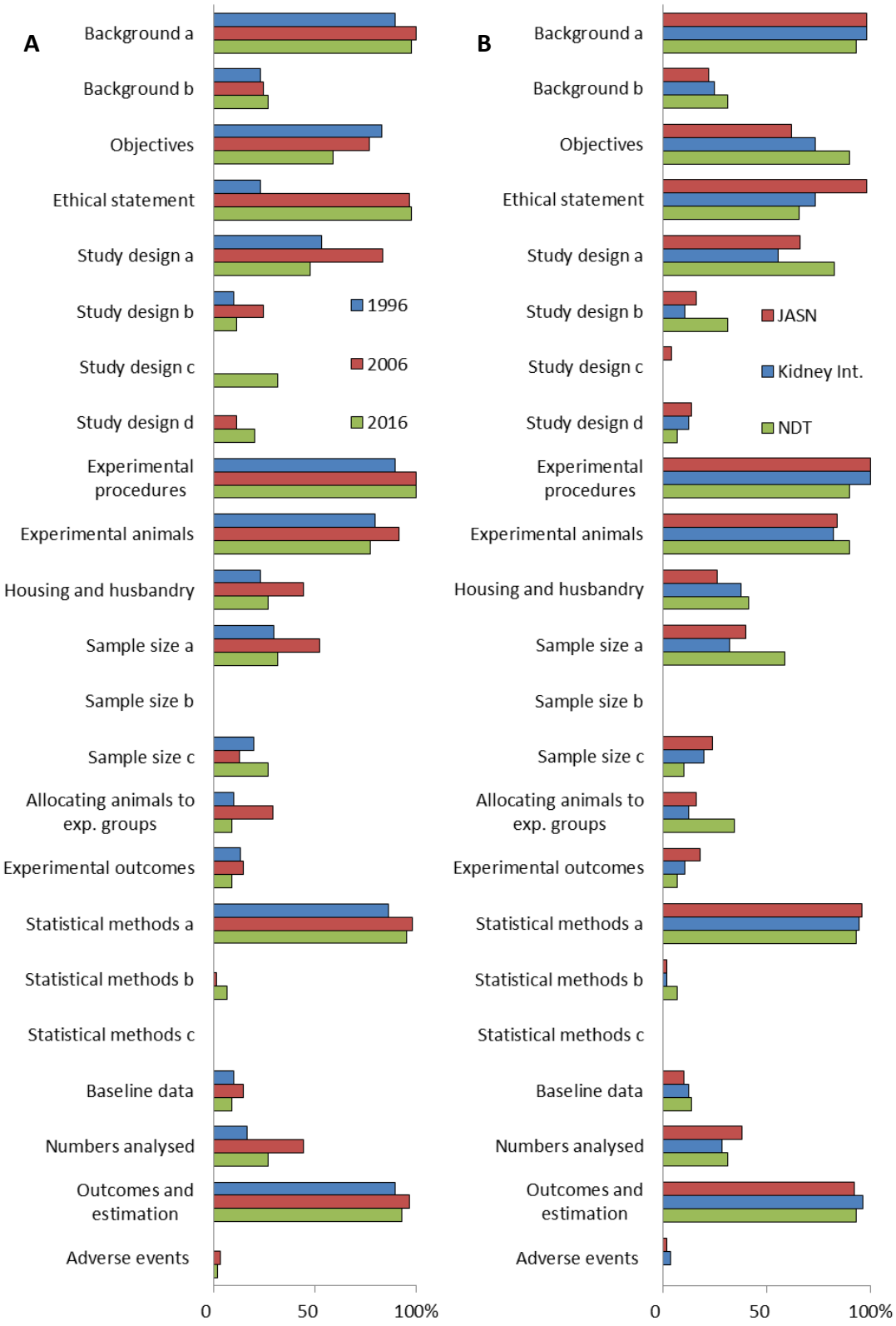


Figure 21: Quality assessment of reporting preclinical studies in the main paper according to the ARRIVE criteria. Each of the ARRIVE criteria was assessed in representative samples selected from JASN, Kidney International and NDT of the years 1996, 2006, and 2016. Shown are the percentages of papers fulfilling the criterion "sufficiently reported" for (A) all journals in each of the 3 years to detect changes over time or (B) each of the journals across all time points.

Instead, rationale, experimental procedures, statistical methods, and outcomes were generally well reported.

Among the evaluated journals (JASN, Kidney International, and NDT), reporting of preclinical studies according to the ARRIVE quality criteria revealed some but no profound differences (Figure 21B, Table 8). JASN scored higher on ethics statement reporting and numbers of analysis. NDT reported objectives, number of groups and their allocation methods and randomization procedures better. Kidney International did not stand out compared to the other two journals in any category. All journals rarely reported details on group size calculations, whether the data obtained met the assumptions of the statistical approach, blinding, the unit of the analysis, baseline data and adverse events [1].

3.2.3. Reproducibility analysis

In order to assess the reproducibility of our review and to define interobserver variability, the two independent investigators were in total agreement on 542/600. This represents an interobserver analytical coherence of 90.3%, corresponding to an interobserver variability of 9.67%. When analysing the discrepant cases, we did not find a systematic error or a repeated misinterpretation of a criterion, rather isolated differences of opinions or human errors from the two investigators.

3.2.4. Registration analysis

We tried to define the percentage of nephrological RCTs registered in a public trials registry, according to the ICJME recommendation for clinical trials, which applies to all clinical trials that started enrolment after July 1, 2005 [361]. From the initial sample of 100 clinical papers, six articles, from which no Registration Number could be identified, referred to trials concluded before the ICMJE recommendation for registration. One article was a purely observational RCT, which according to the recommendation does not require registration. From the remaining 93 articles, 65 referred to trials registered in a public registry (69.8%). If we limit results to articles published after 2015, in order to examine the more recent status of registration, the percentage of registered trials improves to 73.5% (25/34).

We also checked the frequency of kidney trial registration before enrolment of the first participant, a request by the ICMJE since 2005. We then tried to identify the trials, which not only had a registration number, but were already registered prior to enrolment of the first participant, by comparing the 'First Submitted Date' with the 'Study Start Date'. Trials that had already started enrolment before July 1, 2005 and were registered were graded positively in this category regardless of submission date. 52 out of the 65 registered trials were registered prospectively (80%), which means that 55.9% (52/93) of the whole sample of trials were registered before the start of the study. Limiting results to articles published after 2015, the percentage of registered trials prior to first patient enrolment is 61.8%.

3.2.5. Trial design vs. trial reporting

We tried to assess whether the results of the current study could also have a meaningful translation to design quality and not only study reporting.

12 articles from the original 125 RCT analyzed were sampled. For 6 of the 12 articles examined, no registration number or further information about the trials could be found (3 articles originally published in 2006, 3 in 1996).

For 3 trials (2 articles published in 2016, 1 in 2006) we could identify a registration number but no other protocols or previous published articles providing information about study design. For one of them further information about trial location could be found, for another more detailed criteria about inclusion and exclusion of patients and for two of the trials in question further information about trial design (such as parallel, factorial and allocation ratio).

Regarding the 3 remaining trials of the subgroup analysis, 2 of them had registration information, and all 3 of them had other articles or protocols published, from which many additional data about study design could be extracted, significantly improving grading in many key categories, such as: Trial Design, Eligibility Criteria, Settings & Locations, Interventions, Outcomes, Sample Size Determination, Randomization Criteria (Sequence generation, Allocation concealment mechanism, Implementation), Blinding (Who was

blinded, Similarity of interventions), Methods for Additional Analyses, Participant Flow, Recruitment , Ancillary Analysis and Harms.

In conclusion, the results of this subgroup analysis showed that for some of the articles examined, the qualitative score for trial reporting was matching the quality of the study's design, since no further information about the trial in question could be found. On the other hand, for half of the sample examined, important information regarding study design and trial conduction could be extracted, and in the case of 3 of the articles examined, significantly altering the original grading. Thus, our analysis is only valid for the main paper published and not for previous or subsequent publications reporting additional details.

4. Discussion

We had hypothesized that the numbers of kidney-related clinical trials would have increased within the last 15 years, maybe even compared with other medical disciplines. We had further speculated that reporting quality should have improved since the introduction of reporting guidelines for clinical trials such as the CONSORT Statement and that both assumptions also apply to preclinical studies of nephrology, something that to our knowledge had not been assessed before [1].

4.1. The amount of nephrological trials and studies remains low

In 2004, Strippoli, *et al.* [34] documented the low quantity of kidney disease–related clinical trials among the other medical disciplines, which raised some disappointment in the field. Other than updating their findings, we also tried to exclude that this could have been a false negative result due to omitting trials on RRTs and UTI by introducing “expanded nephrology” definitions, adding the above terms in all other kidney related diseases. This, however, did not substantially change the outcome [1].

The analysis on the quantity of preclinical studies provided similar findings, again showing that research activity in nephrology compares negatively to all other fields of internal medicine, both currently and through the last half century. Expanding the nephrology-related MeSH term also did not result in a relevant increase in study numbers. Nephrology lacks the profound increases in published preclinical studies reported from other medical disciplines in the given timeframe [1].

Among the kidney trials themselves, research activity was biased towards hypertension and RRTs. One possible explanation could be that these topics of research allow trial conduction with specified end points being able to be evaluated within a short timeframe, allowing shorter trials and quicker outcome evaluation. In contrast, some disease entities such as CKD not only require a trial design spanning over many years to accurately observe outcomes regarding for example ESKD, but also come with limitations of sufficiently identifying trials

outcomes that can predict ESKD. This can also be tied with industry activity. Clinical trials with budgets of hundreds of million dollars need financial support, i.e. frequently industry support. Trials on disease entities more likely to produce instant profitable results may benefit from stronger financial support, while at the same time disciplines with strong publication output also enjoy more frequent funding, creating a vicious cycle that leaves clinically significant disease entities such as AKI, CKD or GN on the edge of the research activity and interest, while favouring more marketable diseases and interventions such as hypertension or RRT.

While hypertension remained the main research subject in preclinical studies, we observed a more equal distribution among the rest of the disease entities, mirroring major trends in nephrology through the years, such as the implementation of kidney transplantation in the 1960's, novel classifications for AKI and CKD, and the evolving global epidemic of type 2 diabetes [1].

Be it because of lack of interventional questions asked, as Strippoli, *et al* [34] suggested based on their findings, or the block in the translation from basic science to human studies, as other have hypothesized [23], [27], [452] the fact is that the lack of evidence-based medical interventions, and especially in specific fields such as GN or AKI, can have a negative impact on the treatment of concerned patients and stands for improvement.

4.2. RCT reporting quality has improved but further advancements are needed

Firstly, it is important to note, as will be explained in detail below, that our main analysis did not include supplementary information or previously published study protocols, and does not refer to or grade the design of the trials examined, rather the reporting. At this point, it is of interest to compare the results of the current study to those of previous similar reviews, both regarding the reporting quality of kidney trials but also analyses of other medical disciplines, so as to see if our results are in line with those of previous publications, but also to examine whether the problems identified here are also prevalent in other medical fields. In the parenthesis are presented the results of our study for comparative reasons.

Zheng, *et al.* conducted a study aiming to systematically identify RCTs from 1996-2015 investigating the efficacy of pharmacological therapies in heart failure with preserved ejection fraction and to assess the quality of reporting using the CONSORT 2010 statement [453]. In the 33 RCTs included, eligibility criteria for participants were adequately reported in 97% of the studies (81.4%), precise mention of interventions in 78.8% (67%), prespecified primary outcomes in 66.7% (60.2%), determination of sample size in 69.7% (47.5%). The method of allocation was sufficient in 33.3% (35.6%), the type of randomization in 33.3% (32.2%), the mechanism used to implement the random allocation in 12.1% (19.5%), who generated the random allocation sequence, who enrolled participants and who assigned participants to interventions in 21.2% (14.4%), mention of blinding in 32.3% (13.6%), statistical methods in 97.0% (90.7%). Baseline data were reported in 90.9% (78.0%) and number of participants included in each analysis and whether the analysis was by original assigned groups in 54.5% (77.1%). Another study aiming to examine the reporting guidelines and trial registration policies within cardiac and cardiovascular-system journals in 2016 showed that, of the trials surveyed, 42.8% (39%) published a CONSORT diagram in their manuscript, while 80.8% (69.8% in our analysis, 73.5% for articles published after 2015) published a trial registry number [454].

There are a lot of similarities in the quality of items examined between the studies. It is important to note that in 11 of the 14 items presented above, reporting quality of RCTs in cardiology compare favorably to our analysis of clinical kidney studies. Despite of that fact, the authors of the above studies both concluded that “cardiac and cardiovascular system journals infrequently require, recommend or enforce the use of reporting guidelines” and that “there remains a considerable variation in reporting quality, with many important aspects relating to trial methodology and results consistently under reported”.

Liu, *et al*. performed a study aiming to assess to what extent reports of RCTs in solid organ transplantation adhere to the 2010 CONSORT statement, analyzing 290 RCTs published between 2007 and 2009. The authors found that 98% of reports provided an adequate description of the scientific background (93%) and 97% of specific objectives and hypotheses (82%). 17% of reports described the trial design, such as parallel or factorial (18%). 52% of trials prespecified primary outcomes (60%). Sample size calculation was described in 40% of reports (48%), 32% included a flow chart of participants at each study stage (39%). 36% of

trials described an appropriate method to generate the randomization sequence (36%) and 18% described a double-blinded study (31%). The authors concluded that the analysis showed “considerable poor compliance to the CONSORT statement” and that the “the reporting of the Methods, Results and Discussion domains were substandard” [455].

An evaluation published in 2018 of the adherence to the CONSORT checklist from 2011-2014 of 182 RCTs on Otolaryngology – Head and Neck Surgery (ORL-HNS) showed that only 6.5% of RCTs described the individual responsible for enrolling and assigning subjects and method of randomization (14.4%). 58.6% described the method used to generate the random allocation sequence (35.6%), 24.7% mentioned the type of randomization (32.2%), 62.1% described the mechanism used to implement the random allocation sequence (19.5%), 59.7% reported who was blinded and how (13.6%), 32.4% reported the estimated effect size and precision (55.9%) and 40.6% reported a sample size calculation (47.5%). Eligibility criteria of participants were adequately reported in 92.3% (81.4%), 99.5% provided sufficient details of interventions (66.9%), 42.3% pre-specified primary outcomes (60.2%), and 96.7% specified statistical methods (90.7%) [456].

A study published in 2009 evaluating the quality of reporting internal and external validity data in published reports of RCTs from 2003 to 2008 on stents for percutaneous coronary interventions found that the generation of the allocation sequence was adequate in 58.3% of the reports (35.6%). Adequate blinding was reported in one-fifth of the reports (30.5%) and an intention-to-treat analysis was described in 79.5% (45.8%) [457]. Another study examining one hundred fifty published surgical RCTs of the same year concluded that the overall reporting quality was low, with only 55% of CONSORT items addressed and with 45% of trials describing adequate methods for sample size calculation (47.5%), 43% random sequence generation (35.6%), 45% allocation concealment (19.5%), and 37% blinding (30.5%) [458].

A neurological study of 2019 assessing the reporting quality of 44 published RCTs from 1998 to 2017 on the restless legs syndrome, based on a checklist arising from the CONSORT, shows that only 14 of the 38 checklist items (36.8%) were addressed in 75% or more of the studies examined and found that the reporting of RLS-related RCTs is suboptimal [459].

While of course differences can be observed between the studies presented, not only due to the different medical fields examined, but also due to the varied methodological procedures of each study, the different years of publication and the different timelines of the trials, many important items of trial quality remain underreported irrespective of the medical discipline. Reporting of prespecified outcomes, information on randomization procedures and allocation method, blinding, calculation of sample size, and method of analysis are essential elements to the reproducibility and reliability of a trial and were universally suboptimal, irrespective of the medical field. This enhances our belief that the current findings of this study regarding reporting quality refer to problems not only prevalent in kidney trials, but can be generalized to other medical domains.

But also previous works on kidney trials produced similar results to ours. Deo, *et al.* conducted an evaluation of RCTs published in 2007 and 2008 in patients with CKD [33]. 57% of the studies included a flow diagram (39%) as requested by the CONSORT guidelines, 27% did not clearly describe a primary outcome (40 %), 42% included all participants randomly assigned in the primary outcome analysis (46%) and 54% claimed to have done an ITT analysis (56%), but in 56% of these, the primary outcome analysis did not include all randomly assigned participants. Median loss to analysis in those with loss to analysis was 10% (19%).

In their qualitative analysis Strippoli, *et al.* found that 89% of the clinical trials examined lacked clear allocation concealment, while more than half did not report double blinding. An ITT analysis was only performed 30% of the time [34]. Our study seems to verify the above results, with unclear or complete lack of reporting regarding allocation methods in 80% of the trials examined, lack of double-blinding in 64% of the trials and clear and adequate ITT analysis conducted in 46% of the trials. Examining trends over time, while Strippoli, *et al.* concluded that there has been little variation over the years in the quality domains of blinding, ITT analysis and only a small but statistically significant decrease in the proportion of trials with unclear allocation concealment, our analysis could show upward trends for the quality domains in question, with clear improvement in the reporting of allocation concealment, double-blinding and ITT analysis. It is important to note that the timelines examined for the studies differ, as the timeline of the analysis of Strippoli, *et al.* spans from

1966 to 2002, while our study shows trends from 1996 to 2016, so these results can be interpreted as a positive step in the reporting quality of kidney studies.

Furthermore, we observed a steady and clear improvement regarding the quality of reporting of clinical trials not only in the domains above, but to most items of quality reporting in the current study. Our study seems to verify findings also of other previous publications on other medical disciplines, which also have found a clear improvement of reporting quality in RCTs over time [453]. The CONSORT checklist and the underlying rationale have become increasingly familiar to clinical trialists, and there appears to be buy-in to these standards. Also further evidence on the effectiveness of the adoption of the CONSORT guidelines has accumulated the last years [455]. After an analysis in 2006 showed that journal adoption of CONSORT is associated with improved reporting of RCTs, a review with similar findings in 2013 demonstrate that "despite the general inadequacies of reporting of RCTs, journal endorsement of the CONSORT Statement may beneficially influence the completeness of reporting of trials published in medical journals" [460][461].

4.3. Preclinical reporting quality analysis overts no improvements with time

The quality assessment of preclinical studies from kidney journals raises additional concerns. Around 5 years ago started a debate regarding the lack of reproducibility of preclinical results, potentially wasting millions of dollars on resulting clinical trials on inappropriate drug targets or candidates [14]. The increasing awareness on the lack of proper reporting and reproducibility of preclinical studies [13][17][21] lead to a general acknowledgment of the problem [462] and to concerns about the reliability of preclinical research as a predictor of human outcomes as a whole. Ironically, nephrology may have initially escaped the backlash of this crisis due to lack of quantity in both clinical and preclinical studies. To this aim, the ARRIVE guidelines on reporting of preclinical studies were published in 2010 [28]. The hope was that such guidelines would help improve the reporting of preclinical studies, resulting in more thorough reviews on publication of animal experiments, and so lead to an improvement of the design, conduction and finally reproducibility, reliability and translation of preclinical study results.

We conducted this qualitative analysis assessing animal studies both before and after the publication of these guidelines in nephrological articles from kidney specific journals. The rationale for assessing compliance with these guidelines even before their publications, i.e. the years 1996 and 2006, as the ARRIVE guidelines were originally published in 2010, is that we thought that a comparison of the time before and after their publication can provide information on their effect. Of course quality criteria existed even before the establishment of these guidelines, their creation was needed to endorse adherence, and hopefully such an analysis helps to identify areas of improvement and progress and areas that are lagging behind.

Our analysis revealed significant deficiencies in adhering to these guidelines not only before, but also after this date. In particular, providing precise information on animal sub strains and housing conditions, naming the assumptions for group size calculations, randomization, defining primary end points that are also relevant for human disease in animal studies, reporting of baseline data for the animals used such as gender, age or comorbidities [20] are important deficits that can have a major impact on the reproducibility and the reliability of a study's result [21] [1].

Across the kidney journals included in the study, differences were minimal, with various strengths and deficiencies identified between JASN, Kidney International and NDT. In the core issues identified in the 'reproducibility' discussion, these journals collectively earn a failing grade. It would have been interesting to also analyse other important journals, such as Journal of Clinical Investigation, Nature Medicine, Nature, Science, JCI Insight, etc., but these multidisciplinary journals publish kidney-related preclinical studies less frequently and only in low numbers within the set time periods [1].

At this point, it would also be interesting to compare the results of this current study to those of previous publications assessing the quality of reporting both on animal research as a whole and on animal research of other medical disciplines, so as to see if the problems identified here can also be generalized beyond the scope of kidney research. Another point of interest is to examine if other fields have observed an improvement in the reporting quality over time, and especially since the publication of the ARRIVE guidelines, something that our analysis did not indicate. The results of our analysis are presented in the parentheses for comparative reasons.

One of the largest and most comprehensive reviews of published animal research, commissioned by the NC3Rs, which resulted in the introduction of the ARRIVE guidelines, found that only 59% of the 271 articles assessed stated the hypothesis or objective of the study, and characteristics of the animals (72.6% and 84.4% respectively in our study). 87% of the articles did not report using randomisation (80.0%) and 86% (71.9%) had no mention of blinding [17].

Vesterinen, *et al.* examined 156 publication to assess the study design, statistical analyses, and reporting of cerebrovascular research during the year 2008 [463]. They found that 27% of the animal studies clearly stated the primary research hypothesis (72.6%), 22% adequately reported randomization procedures (17%), 8% mentioned any forms of allocation concealment (18.5%), 15% reported a blinded assessment of the outcomes (1.5%) and only 1% of the articles mentioned any form of sample size calculation (0.0%).

A more recent study from Ting, *et al.*, investigating the quality of reporting of 41 published interventional animal studies in experimental rheumatology in 2012, found that an ethical statement was not reported in 22% (19.3%) [464]. 65.9% clearly described an objective or stated a hypothesis (72.6%). Reporting of randomization and assessor blinding occurred in 17.1% and 29.3%, respectively (17.0% and 1.5%, respectively in our study). None of the studies reported sample size calculation or details of allocation method (0% and 18.5%, respectively). Details of animal strain and species were reported in 53.7% (84.4%), and housing and husbandry reported in only 4.9% (34.1%). 61% failed to clearly define experimental outcomes (69.6%). 75.6% adequately reported statistical methods (94.8%) and 9.8% of papers reported important adverse events (2.2%).

We can see that while differences between the fields can be found, with kidney studies for example better defining objectives or hypotheses and giving more precise information on the animals used and their environment, important deficiencies on design traits can be identified universally. The authors of the above studies concluded that the reporting quality in their respective fields exhibits “poor reporting of key design principles” and that “a number of factors should be addressed if the quality of research in basic and translational biomedicine is to be improved”, while strongly endorsing the adoption and the widespread implementation of the ARRIVE statement.

The hope was that enforcing adherence to the ARRIVE standards and reporting methods and results accordingly may help to improve what has been labelled the “reproducibility crisis” in preclinical research. Assuring proper group size calculations, randomization, a blinded analysis and considering sex disparities in experimental animals should be important in this context. But these guidelines have shown little evidence of resulting in any major improvement in reporting quality until now. In our analysis, only the reporting of the relevance of the animal model to the human biology, ethical statements, blinding, and timeline diagrams improved over time, whereas many other criteria did not. A number of important traits essential to a robust design of a preclinical study [18] [19] even showed a negative tendency, with investigators more likely to neglect information in 2016 rather than in 2006 on primary objectives and hypothesis, numbers of groups examined and numbers included in the analysis, any details on or if randomization occurred or any details on other forms of allocation methods between groups, details on the animals used and their housing and husbandry or information on their baseline data, definition on primary and secondary outcomes assessed.

This seems to verify results of other previous publications on this topic. An analysis of papers published in PLOS and Nature journals indicates that there had been very little improvement in reporting standards two years after the endorsement of the ARRIVE guidelines by all Nature and PLOS journals [465]. Baker, *et al*. evaluated key areas of reporting and found that the percentage of studies reporting blinding and randomization in their experimental design was similar to that in past surveys, leading the authors to state that “despite their endorsement by these journals, the guidelines have had little impact on reporting standards in published papers, at least in the neuroimmunological field, but the problem is likely to be more widespread”. Another review from 2015 on 83 publications on Chagas disease preclinical drug research showed similar results when examining quality items before and after the ARRIVE publication, with the authors stating that “publication of ARRIVE guidelines did not seem to enhance reporting quality, compared to papers appeared before ARRIVE publication” [466]. Other reviews examining their effect also in other fields of medicine have provided similarly disappointing results [467] [468].

Why these guidelines have largely proven to be unsuccessful is up for debate, but their implementation appears to be more difficult for journals and editors compared to guidelines

such as CONSORT. Problems may arise from the varied nature of preclinical studies, since exploratory studies in initial hypothesis generating phase of research should be allowed to have greater flexibility both in their pre-specification of outcomes and in general design than validation studies aiming to test a preformed hypothesis or clinical trials. At a practical level, for some journals the length of this checklist with 20 items may have caused problems in implementation, especially since traditionally preclinical studies are more bound to include ancillary experimental analyses, which can make application of the ARRIVE guidelines for each of them burdensome [469].

But even journal-requested completion of an ARRIVE checklist does not appear do have major effect on the quality of reporting. A randomized controlled trial by Hair, *et al.* aiming to assess the effect of an email request to authors to complete an ARRIVE checklist on compliance with the ARRIVE guidelines, showed that details of animal husbandry was the only item to show improvements in reporting and that simply requesting completion of an ARRIVE checklist at submission does not significantly increase adherence to the ARRIVE guidelines [470]. Other approaches, such as more stringent editorial policies, editorial checks of compliance, a targeted approach on key quality items and further measures to mandate checklist completion may be required to see improvements in quality, measures that in reviews of other specialties have resulted in an increase of reporting quality [468].

4.4. Further perspectives

The results of our analysis, both regarding the number of trials and studies published in nephrology but also concerning their quality, make clear that improvements are needed in order to overcome the deficits we highlighted. There needs to be an understanding of why the amount and the quality of published articles in nephrology is lacking and an urgency to try and find solutions to increase research activity on kidney diseases and ensure more robust reporting and reliable results.

The relatively low number of clinical and preclinical studies in the field of nephrology may reflect the low levels of funding from governmental agencies, industry and non-profits, relative to other fields that are included in the analyses. A fact sheet from the American Society of Nephrology (https://www.asn-online.org/policy/webdocs/FactSheet-Unbalanced.pdf) recently published highlighted the fact, that the U.S. government invests

what equals to less than 1% of Medicare kidney care costs in kidney research. Of course pharmaceutical companies and governmental authorities would prefer to allocate money in diseases with more immediate profit and more marketing power. Even so, an increase in funding of research on kidney diseases could help to most importantly improve the treatment outlook and the quality of life of many kidney patients, but also would probably be profitable on the level of health care costs of nephrological diseases.

Even the US government and the White House recently acknowledged the problem, publishing an executive order in July of 2019, which among others stated that “the state of care for patients with CKD and ESKD is unacceptable: too many at-risk patients progress to late-stage kidney failure; the mortality rate is too high; current treatment options are expensive and do not produce an acceptable quality of life”, while pledging to “support research regarding preventing, treating, and slowing progression of kidney disease” in order to “prevent kidney failure whenever possible through better diagnosis, treatment, and incentives for preventive care” [3]. The hope is that this will boost kidney research and ESKD management in the next years.

But even if kidney research activity improves, it would not alleviate the fact that the quality of the manuscripts published on the field overts major deficiencies. New strategies are needed in order to ensure that the articles being printed and published reach a high standard of quality, ensuring the reliability and reproducibility of their results. Changes in editorial and review policies, with more strict and mandatory requirements for the guidelines, rather than simple endorsement or support from the journals, can be one of many steps in the right direction. This applies for both clinical trials and most importantly animal studies, since they are the ones presenting a substantially lower quality of reporting and no significant improvement could be observed since the introduction of reporting guidelines both in our analysis and previous reviews of other fields [468][465][470].

Already some journals included in our study have taken important steps to tackle the problems highlighted, with JASN for example making changes to their editorial procedures for preclinical studies, requiring now a structured abstract as a mandatory prerequisite, eliminating word limits in the Methods section, highlighting its importance in the Information for Authors, moving it to a more prominent position after the Introduction, and

paying closer attention and more thoroughly reviewing the reporting of the statistical analysis [469].

Another possible solution which has been suggested before and has also been analyzed in the current study comes in the form of study registration [8]. Since 2005 the International Committee of Medical Journal Editors (ICMJE) requests the registration of clinical trials prior to the enrolment of the first participant [361][362]. Simultaneously, there are some journals that require a protocol before publication. The rationale is that if a study is registered prior to its conduction, its progress can more easily be followed; their primary and secondary end points and outcomes can be prespecified before conduction or analysis, thus avoiding the publication of trials with different primary end points than those originally identified because the originally hypothesis was disproved. Also, there is a logic pattern suggesting that trials already registered are more likely to be published even if their results are disappointing, thus contributing to the solution of the problem of publication bias, which refers to trials producing positive or significant results heavily circulating in journals, while studies with disproved or null results almost never getting published, creating a distorted view of the scientific status and neglecting the importance of recognizing disproved hypotheses.

The analysis we conducted on trial registration showed that almost 70% of the trials examined were registered, while this number climbs to 73.5% if limited to trials published from 2015 on. When analyzing the same fact but with stricter criteria, meaning registration before enrollment of the first participants, these numbers fell to 56% and 62% respectively. It becomes thus evident that even after the recommendations for trial registration and despite the endorsement of various journals, many trials remain unregistered. Of course, in order to allow a comparison of the analytical data after trial commencement and the design protocol before patient enrolment, not only a registration number is required, but even more design characteristics should be noted and registered, which in reality is not always the case. A study from Ross, *et al.* found that reporting of optional data elements varied and publication rates among completed trials registered within ClinicalTrials.gov were low, while advocating for greater attention to reporting of all data elements [471]. Rasmussen, *et al.* concluded, after comparing the prevalence of favorable results of registered and unregistered randomized controlled trials in oncology, that trial registration alone, without a

requirement for full reporting of research results, does not appear to reduce a bias, while the authors support “the inclusion of full results reporting in trial registers, as well as protocols to allow assessment of whether results have been completely reported” [472].

But the above described measures are meant to tackle reporting problems in the field of clinical research and are not applied or focused on basic science. It is possible that measures like study registration with accompanied reporting of data elements also for animal research would have positive effects on reporting transparency or publication bias, similar to the desired effect of clinical trial registration. By registering before the start of the experiment, selective reporting of results can be minimized and reviewers and readers can be allowed to compare the initial study plan to the final publications. Of course, avoiding duplication of preclinical studies has also important ethical parameters and can improve the welfare of animals. Furthermore, study registration of animal experiments requiring a pre-planned design and coming with specific requirements could also help substantially improve the implementation of reporting guidelines like the ARRIVE, which up to now has proved to be challenging [469][468].

Such efforts have slowly started to arise. In April of 2018 the site *https://preclinicaltrials.eu* launched, an international register of preclinical trial protocols, and since January 7, 2019 the Animal Study Registry is in function and can be used worldwide for registration of preclinical studies. The latter is an initiative of The German Federal Institute for Risk Assessment (BfR), a scientifically independent research institution and it provides a freely accessible platform, with its main purpose to register animal experiments with detailed information on methods as well as the statistical planning, working hypotheses and biometric planning prior to the start of the study [473], hoping to improve transparency, quality and reproducibility of animal experiments [474].

Of course it is clear that such initiatives are doomed, if they are not met with support from the scientific community, but more importantly if they are not endorsed in a journalistic level and become essential elements of the publication process, which in the end is what most members of the research field are interested in. A mandatory registration and protocol requirements, along with mandatory adherence to the respective guidelines for reporting would be great steps in the direction of improved and adequate reporting quality of both clinical trials and preclinical studies.

4.5. Study limitations

One important limitation of our study is that our analysis could not distinguish between true trial design deficits or simply underreporting. It is important to clarify that the main analysis conducted and the criteria selected and developed are for trial reporting, and specifically for important information in the main body of a manuscript, without even considering the Supplementary Material or previously published study protocols, hence our results do not necessarily question and are not meant to examine the quality of trial or study design or conduction but mostly, question underreporting in the main body of the final paper, which may be hampered by space or other reporting limitations. As the results of our subgroup analysis examining on this fact showed, sometimes the qualitative score for trial reporting was matching the quality of the study's design, since no further information about the trial in question could be found, but also, for some of the studies assessed, important differences could be found between our assessment of the main body of the paper published and the assessment of the design methods. However, many of the items assessed for quality reporting, such as details of randomization, blinding, precise definitions of pre-specified end points and performing an intention-to-treat analysis are essential to avoid erroneous conclusions and these important aspects should always be reported in the main body of the final paper.

A detailed and careful analysis of study design deficits could of course be very informative and would help to further examine the qualitative status of trials in the nephrological field. Such an analysis would require specific criteria and protocol and is unfortunately beyond the scope of this study. The qualitative analysis of our study, both for the RCTs and the preclinical trials, refers to the quality of trial reporting, and is not to be interpreted as grading of study design or trial conduction.

Another point to be discussed regarding the numbers analysis of nephrological studies is that a lot of trials assess kidney outcomes as secondary outcomes. For example, type 2 diabetes may define the primary outcome as mortality, but secondary outcomes may include kidney endpoints. Unfortunately, no sufficient way to address that in the database analysis was found. To do so would have required looking at all existing literature one by one to check that, and this not only for the kidney domain but also for all other domains, which would have been tens of thousands of trial reports. Defining robust criteria for this would

have been impossible. Finally, as the same argument will apply to all other disciplines (also cardiovascular complications are secondary endpoints in kidney trials) we do not think this point would significantly affect our conclusions.

Another important limitation of our study refers to the phase analysis conducted for the RCT trials using the Cochrane Library. While the phase-analysis using the clinicaltrials.gov database was carried out using integrated limits of the database itself, in the phase-analysis form the CENTRAL database the terms “Phase 1/2/3/4”or “Phase I/II/III/IV” were added manually. This fact raises the question as to whether the results are truly phase-specified trials or not. To add to the concerns regarding this fact, a test using the term “Phase 5” also brought back results, although fewer in comparison to phases 0-4, although no phase 5 clinical trials exist. Due to this fact, the phase categorization of the total number of trials both for the specialties and for the coverage inside nephrology should be looked upon with a critical eye.

As illustrated in the flow chart of the clinical analysis (Figure 18), seven out of 127 papers (5.6%) during our quality analysis had to be excluded for not being true interventional trials. It is likely that there is a similar rate of misclassified articles in the quantitative analysis. We do not see how this error can be avoided without reading all the thousands articles published one by one. However, as this rate should distribute in a random manner equally among all the disciplines or kidney disease entities, it should not affect the conclusions of the analyses.

Regarding the preclinical part of the manuscript, many papers were omitted from the qualitative analysis of the preclinical studies, because we limited inclusion criteria to apply only to original articles of in vivo animal experiments, so as to be compatible with the ARRIVE criteria, upon which the qualitative analysis was based. This should again not be concerning regarding misclassification of trials in the quantitative analysis, the aim of which was to show preclinical animal research activity in the various fields, so the inclusion of non-original articles such as editorials or reviews should not be counted as a limiting factor of the analysis. Of course a misclassification of articles is possible, but as it would spread randomly among the fields, it should not bias the conclusions.

A bigger point of discussion and subsequently a limitation of our study could be the lack of reliable databases and methods to navigate and search through records of preclinical studies. The only reliable method which could be identified by the researchers was the use of the Limits: animals in the Pubmed database, the sensitivity and reliability of which can be questioned, as evident by the amount of studies misclassified in our analysis. Further efforts should be made for the construction of reliable preclinical databases, similar to efforts such as the Cochrane Library and the CENTRAL system or clinicaltrials.gov, in order to improve the research quality of preclinical fields. This could also have an impact on the problems mentioned above regarding the translation of preclinical studies to clinical trials and applications, as a reliable and easy way for researchers to navigate through and access preclinical studies could of course help the availability of preclinical studies, thus allowing important preclinical information to circulate more reliably among the scientific community, avoiding unneeded replication of dead end studies or allowing replication when needed and in the end helping the formulation of more specific, concrete questions and the conduction of more clinic relevant studies.

Finally, another limitation of our study could be the fact that only a single investigator conducted the analysis of the manuscripts, thus making it more vulnerable to possible bias. In order to tackle this problem and to examine the reproducibility of our study, we conducted an analysis of a subgroup of papers, explained and described in detail above, which resulted in an interobserver coherence of 90.3%. Furthermore, we did not find a systematic error or a repeated misinterpretation of a criterion, and we are thus confident in the reproducibility and reliability of our results.

4.6. Conclusion

In summary, the numbers of clinical and preclinical research papers in nephrology have remained low compared to those of other medical disciplines. While currently improved research activity in a broader area of the nephrological scope could be identified, important disease entities are neglected compared to more profitable diseases. The quality of data reporting in the main body of papers presenting clinical trials keeps improving but is still suboptimal in many ways. The quality of data reporting of preclinical studies is still in its infancy and may contribute to reproducibility problems and problems of translation.

Efforts at all levels are needed to overcome these deficits in the future. Given the central role of kidney disease–related morbidity and mortality, as well as health care costs, greater investments in kidney research are needed in order to improve research activity and further progress the treatments and interventions of kidney patients.

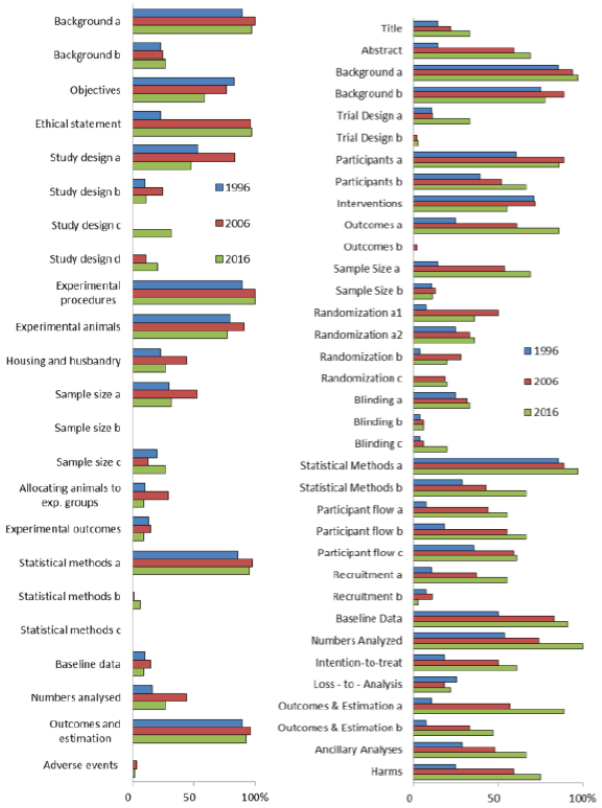
Of equal importance are further efforts to ensure that the quality of clinical trials on kidney diseases keeps trending upwards and that nephrological preclinical studies finally start to show improvement in major areas of reporting affecting reproducibility, reliability and transparency. In order to reach these goals, more thorough editorial and review procedures during the publication process, a renewed focus on the methods of the experiments and on reporting guidelines and finally, registration of studies and preplanned design and statistical analysis prior to conduction could potentially prove to be important steps in the right direction.

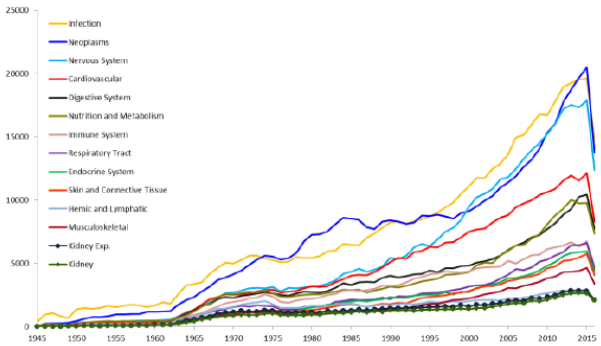
Quantity and Reporting Quality of Kidney Research

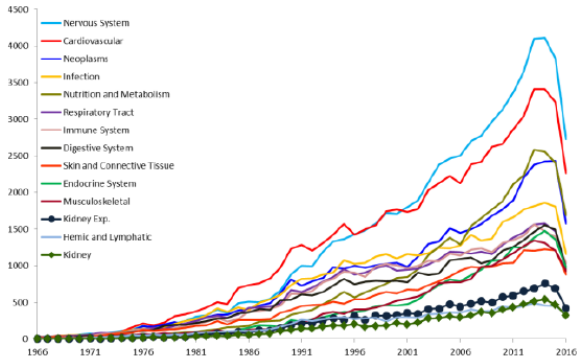
Systematic Analysis of Quantity of:

- Human RCT (1966-2016)
- animal studies (1945-2016)

Reporting Quality in main body of final paper according to modified CONSORT/ARRIVE Criteria







- Nephrology ranks at or near the bottom in human RCTs and animal research compared to other medical disciplines

- Reporting Quality in human RCTs improved over time but important items are still neglected

-Reporting quality of animal studies has not improved and remains low

CONCLUSION

Both the Quantity and the Reporting Quality of kidney research can and should be further improved.

Figure 22: Visual summary of the results and conclusion of this study

Bibliography

[1] M. K. Tomidis Chatzimanouil, L. Wilkens, and H. Anders, "Quantity and Reporting Quality of Kidney Research," *J. Am. Soc. Nephrol.*, vol. 30, no. 1, pp. 13–22, Jan. 2019.

[2] "Kidney - Wikipedia." [Online]. Available: https://en.wikipedia.org/wiki/Kidney. [Accessed: 29-Feb-2020].

[3] "Executive Order on Advancing American Kidney Health | The White House." [Online]. Available: https://www.whitehouse.gov/presidential-actions/executive-order-advancing-american-kidney-health/. [Accessed: 02-Feb-2020].

[4] "Phases of clinical research - Wikipedia." [Online]. Available: https://en.wikipedia.org/wiki/Phases_of_clinical_research. [Accessed: 22-Mar-2020].

[5] "Phases of clinical trials." [Online]. Available: https://www.nccn.org/patients/resources/clinical_trials/phases.aspx. [Accessed: 22-Mar-2020].

[6] K. F. Schulz, D. G. Altman, and D. Moher, "CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials," *BMJ*, vol. 340, no. mar23 1, pp. c332–c332, Mar. 2010.

[7] J. A. Samuels and D. A. Molony, "Randomized Controlled Trials in Nephrology: State of the Evidence and Critiquing the Evidence," *Adv. Chronic Kidney Dis.*, vol. 19, no. 1, pp. 40–46, 2012.

[8] S. C. Palmer, M. Sciancalepore, and G. F. M. Strippoli, "Trial quality in nephrology: How are we measuring up?," *Am. J. Kidney Dis.*, vol. 58, no. 3, pp. 335–337, 2011.

[9] J. M. Kendall, "Designing a research project: randomised controlled trials and their principles.," *Emerg. Med. J.*, vol. 20, no. 2, pp. 164–8, Mar. 2003.

[10] C. Gluud, "Trials and errors in clinical research," *Lancet*, vol. 354, no. 9196 SUPPL., p. SIV59, Dec. 1999.

[11] D. Moher *et al.*, "CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials," *BMJ*, vol. 340, no. mar23 1, pp. c869–c869, Mar. 2010.

[12] M. Kabisch, C. Ruckes, M. Seibert-Grafe, and M. Blettner, "Randomized controlled trials: part 17 of a series on evaluation of scientific publications.," *Dtsch. Arztebl. Int.*, vol. 108, no. 39, pp. 663–8, Sep. 2011.

[13] C. G. Begley and L. M. Ellis, "Raise standards for preclinical cancer research," *Nature*, vol. 483, no. 7391, pp. 531–533, Mar. 2012.

[14] F. Prinz, T. Schlange, and K. Asadullah, "Believe it or not: how much can we rely on published data on potential drug targets?," *Nat. Rev. Drug Discov.*, vol. 10, no. 9, pp. 712–712, Sep. 2011.

[15] L. P. Freedman, I. M. Cockburn, and T. S. Simcoe, "The Economics of Reproducibility in Preclinical Research.," *PLoS Biol.*, vol. 13, no. 6, p. e1002165, Jun. 2015.

[16] N. A. Vasilevsky *et al.*, "On the reproducibility of science: unique identification of research resources in the biomedical literature," *PeerJ*, vol. 1, p. e148, Sep. 2013.

[17] C. Kilkenny *et al.*, "Survey of the Quality of Experimental Design, Statistical Analysis and Reporting of Research Using Animals," *PLoS One*, vol. 4, no. 11, 2009.

[18] N. A. Crossley *et al.*, "Empirical Evidence of Bias in the Design of Experimental Stroke Studies," *Stroke*, vol. 39, no. 3, pp. 929–934, Mar. 2008.

[19] J. A. Hirst *et al.*, "The Need for Randomization in Animal Trials: An Overview of Systematic Reviews," *PLoS One*, vol. 9, no. 6, p. e98856, Jun. 2014.

[20] K. R. Hess, "Statistical Design Considerations in Animal Studies Published Recently in Cancer Research," *Cancer Res.*, vol. 71, no. 2, pp. 625–625, Jan. 2011.

[21] T. Hsieh, M. H. Vaickus, and D. G. Remick, "Enhancing Scientific Foundations to Ensure

Reproducibility: A New Paradigm," *Am. J. Pathol.*, vol. 188, no. 1, pp. 6–10, 2018.
[22] H. J. Anders, D. R. W. Jayne, and B. H. Rovin, "Hurdles to the introduction of new therapies for immune-mediated kidney diseases," *Nat. Rev. Nephrol.*, vol. 12, no. 4, pp. 205–216, 2016.
[23] H. B. van der Worp *et al.*, "Can Animal Models of Disease Reliably Inform Human Studies?," *PLoS Med.*, vol. 7, no. 3, p. e1000245, Mar. 2010.
[24] I. Zucker and A. K. Beery, "Males still dominate animal studies.," *Nature*, vol. 465, no. 7299, p. 690, Jun. 2010.
[25] L. R. Miller *et al.*, "Considering sex as a biological variable in preclinical research," *FASEB J.*, vol. 31, no. 1, pp. 29–34, 2017.
[26] K. Shah, C. E. McCormack, and N. A. Bradbury, "Do you know the sex of your cells?," *AJP Cell Physiol.*, vol. 306, no. 1, pp. C3–C18, 2014.
[27] M. de Caestecker *et al.*, "Bridging Translation by Improving Preclinical Study Design in AKI," *J. Am. Soc. Nephrol.*, vol. 26, no. 12, pp. 2905–2916, 2015.
[28] C. Kilkenny, W. J. Browne, I. C. Cuthill, M. Emerson, and D. G. Altman, "Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research," *PLoS Biol.*, vol. 8, no. 6, p. e1000412, Jun. 2010.
[29] A. Holderied and H. J. Anders, "Animal models of kidney inflammation in translational medicine," *Drug Discov. Today Dis. Model.*, vol. 11, pp. 19–27, 2014.
[30] C. Baigent *et al.*, "Challenges in conducting clinical trials in nephrology: conclusions from a Kidney Disease—Improving Global Outcomes (KDIGO) Controversies Conference," *Kidney Int.*, vol. 92, no. 2, pp. 297–305, 2017.
[31] K. A. Nath, "Models of Human AKI: Resemblance, Reproducibility, and Return on Investment," *J. Am. Soc. Nephrol.*, vol. 26, no. 12, pp. 2891–2893, 2015.
[32] M. K. Campbell *et al.*, "Evidence-based medicine in nephrology: identifying and critically appraising the literature," *Nephrol. Dial. Transplant.*, vol. 15, no. 12, pp. 1950–1955, Dec. 2000.
[33] A. Deo, C. H. Schmid, A. Earley, J. Lau, and K. Uhlig, "Loss to analysis in randomized controlled trials in CKD," *Am. J. Kidney Dis.*, vol. 58, no. 3, pp. 349–355, 2011.
[34] G. F. M. Strippoli, J. C. Craig, and F. P. Schena, "The Number, Quality, and Coverage of Randomized Controlled Trials in Nephrology," *J. Am. Soc. Nephrol.*, vol. 15, no. 2, pp. 411–419, 2004.
[35] "Cochrane Controlled Register of Trials (CENTRAL) | Cochrane Library." [Online]. Available: https://www.cochranelibrary.com/central/about-central. [Accessed: 13-Nov-2019].
[36] T. B. Drüeke *et al.*, "Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia," *N. Engl. J. Med.*, vol. 355, no. 20, pp. 2071–2084, 2006.
[37] A. K. Singh *et al.*, "Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease," *N. Engl. J. Med.*, vol. 355, no. 20, pp. 2085–2098, 2006.
[38] Z. Zheng *et al.*, "Perioperative Rosuvastatin in Cardiac Surgery," *N. Engl. J. Med.*, vol. 374, no. 18, pp. 1744–1753, May 2016.
[39] G. Maschio *et al.*, "Effect of the Angiotensin-Converting–Enzyme Inhibitor Benazepril on the Progression of Chronic Renal Insufficiency," *N. Engl. J. Med.*, vol. 334, no. 15, pp. 939–945, Apr. 1996.
[40] Strategies for Management of Antiretroviral Therapy (SMART) Study Group *et al.*, "CD4+ count-guided interruption of antiretroviral treatment.," *N. Engl. J. Med.*, vol. 355, no. 22, pp. 2283–96, Nov. 2006.
[41] C. Wanner *et al.*, "Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes," *N. Engl. J. Med.*, vol. 375, no. 4, pp. 323–334, Jul. 2016.
[42] N. Arber *et al.*, "Celecoxib for the Prevention of Colorectal Adenomatous Polyps," *N. Engl. J. Med.*, vol. 355, no. 9, pp. 885–895, 2006.
[43] S. P. Marso *et al.*, "Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes," *N. Engl. J. Med.*, vol. 375, no. 19, pp. 1834–1844, 2016.
[44] R. D. Jackson *et al.*, "Calcium plus Vitamin D Supplementation and the Risk of Fractures\r10.1056/NEJMoa055218," *N. Engl. J. Med.*, vol. 354, no. 7, pp. 669–683, 2006.

[45] A. Ravaud, R. Motzer, and H. et al Pandha, “Adjuvant Sunitinib in High-risk Renal-cell Carcinoma After Nephrectomy,” *N. Engl. J. Med.*, vol. 375, no. 23, pp. 2246–2254, 2016.
[46] F. Vincenti *et al.*, “Belatacept and Long-Term Outcomes in Kidney Transplantation,” *N. Engl. J. Med.*, vol. 374, no. 4, pp. 333–343, Jan. 2016.
[47] A. Lamy *et al.*, “Five-Year Outcomes after Off-Pump or On-Pump Coronary-Artery Bypass Grafting,” *N. Engl. J. Med.*, vol. 375, no. 24, pp. 2359–2368, 2016.
[48] T. Dreischulte, P. Donnan, A. Grant, A. Hapca, C. McCowan, and B. Guthrie, “Safer Prescribing — A Trial of Education, Informatics, and Financial Incentives,” *N. Engl. J. Med.*, vol. 374, no. 11, pp. 1053–1064, 2016.
[49] G. Marenzi *et al.*, “*N* -Acetylcysteine and Contrast-Induced Nephropathy in Primary Angioplasty,” *N. Engl. J. Med.*, vol. 354, no. 26, pp. 2773–2782, 2006.
[50] F. F. Hou *et al.*, “Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency,” *N. Engl. J. Med.*, vol. 354, no. 2, pp. 131–140, 2006.
[51] S. Gaudry *et al.*, “Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit,” *N. Engl. J. Med.*, vol. 375, no. 2, pp. 122–133, 2016.
[52] M. M. Bertagnolli *et al.*, “Celecoxib for the Prevention of Sporadic Colorectal Adenomas,” *N. Engl. J. Med.*, vol. 355, no. 9, pp. 873–884, 2006.
[53] S. E. Nissen *et al.*, “Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis,” *N. Engl. J. Med.*, vol. 375, no. 26, pp. 2519–2529, Dec. 2016.
[54] G. Van den Berghe *et al.*, “Intensive Insulin Therapy in the Medical ICU,” *N. Engl. J. Med.*, vol. 354, no. 5, pp. 449–461, Feb. 2006.
[55] G. G. Van Essen *et al.*, “Association between angiotensin-converting-enzyme gene polymorphism and failure of renoprotective therapy,” *Lancet*, vol. 347, no. 8994, pp. 94–95, 1996.
[56] N. B. Haas *et al.*, “Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): A double-blind, placebo-controlled, randomised, phase 3 trial,” *Lancet*, vol. 387, no. 10032, pp. 2008–2016, 2016.
[57] C. M.L., L. I., L. Ch., M. C., R. B., and C. P., “Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients,” *Lancet*, vol. 348, no. 9042, pp. 1620–1622, 1996.
[58] G. Peer *et al.*, “Randomised crossover trial of naitrexone in uraemic pruritus,” *Lancet*, vol. 348, no. 9041, pp. 1552–1554, 1996.
[59] C. Vinsonneau *et al.*, “Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial,” *Lancet*, vol. 368, no. 9533, pp. 379–385, 2006.
[60] A. K. Saxena *et al.*, “Tunneled catheters’ outcome optimization among diabetics on dialysis through antibiotic-lock placement,” *Kidney Int.*, vol. 70, no. 9, pp. 1629–1635, 2006.
[61] R. N. Fine, E. Kohaut, D. Brown, J. Kuntze, and K. M. Attie, “Long-term treatment of growth retarded children with chronic renal insufficiency, with recombinant human growth hormone,” *Kidney International*, vol. 49, no. 3. pp. 781–785, 1996.
[62] A. Lauschke, U. Teichgräber, U. Frei, and K. U. Eckardt, “‘Low-dose’ dopamine worsens renal perfusion in patients with acute renal failure,” *Kidney Int.*, vol. 69, no. 9, pp. 1669–1674, 2006.
[63] J. A. Delmez, J. Kelber, K. Y. Norword, K. S. Giles, and E. Slatopolsky, “Magnesium carbonate as a phosphorus binder: A prospective, controlled, crossover study,” *Kidney Int.*, vol. 49, no. 1, pp. 163–167, 1996.
[64] J. Gossmann *et al.*, “Mechanism of angiotensin converting enzyme inhibitor-related anemia in renal transplant recipients,” *Kidney Int.*, vol. 50, no. 3, pp. 973–978, 1996.
[65] S. Bianchi, R. Bigazzi, and V. M. Campese, “Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease,” *Kidney Int.*, vol. 70, no. 12, pp. 2116–2123, 2006.
[66] F. Zannad *et al.*, “Prevention of cardiovascular events in end-stage renal disease: Results of a randomized trial of fosinopril and implications for future studies,” *Kidney Int.*, vol. 70, no. 7, pp. 1318–1324, 2006.

[67] J. A. Breyer *et al.*, “Predictors of the progression of renal insufficiency in patients with insulin-dependent diabetes and overt diabetic nephropathy,” *Kidney Int.*, vol. 50, no. 5, pp. 1651–1658, 1996.
[68] A. G. Bostom *et al.*, “High dose B-vitamin treatment of hyperhomocysteinemia in dialysis patients,” *Kidney Int.*, vol. 49, no. 1, pp. 147–152, 1996.
[69] V. Krane *et al.*, “Long-term effects following 4 years of randomized treatment with atorvastatin in patients with type 2 diabetes mellitus on hemodialysis,” *Kidney Int.*, vol. 89, no. 6, pp. 1380–1387, 2016.
[70] P. E. Pergola, B. S. Spinowitz, C. S. Hartman, B. J. Maroni, and V. H. Haase, “Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease,” *Kidney Int.*, vol. 90, no. 5, pp. 1115–1122, 2016.
[71] B. Redaelli *et al.*, “Effect of a new model of hemodialysis potassium removal on the control of ventricular arrhythmias,” *Kidney Int.*, vol. 50, no. 2, pp. 609–617, 1996.
[72] I. C. Macdougall, B. Tucker, J. Thompson, C. R. V. Tomson, L. R. I. Baker, and A. E. G. Raine, “A randomized controlled study of iron supplementation in patients treated with erythropoietin.,” *Kidney Int.*, vol. 50, no. 5, pp. 1694–9, Nov. 1996.
[73] M. R. Weir *et al.*, “Treatment with patiromer decreases aldosterone in patients with chronic kidney disease and hyperkalemia on renin-angiotensin system inhibitors,” *Kidney Int.*, vol. 90, no. 3, pp. 696–704, 2016.
[74] C. C. Yang, S. P. Hsu, M. S. Wu, S. M. Hsu, and C. T. Chien, “Effects of vitamin C infusion and vitamin E-coated membrane on hemodialysis-induced oxidative stress,” *Kidney Int.*, vol. 69, no. 4, pp. 706–714, 2006.
[75] J. S. Cho, J. K. Shim, S. Soh, M. K. Kim, and Y. L. Kwak, “Perioperative dexmedetomidine reduces the incidence and severity of acute kidney injury following valvular heart surgery,” *Kidney Int.*, vol. 89, no. 3, pp. 693–700, 2016.
[76] A. Haris, D. J. Sherrard, and G. Hercz, “Reversal of adynamic bone disease by lowering of dialysate calcium,” *Kidney Int.*, vol. 70, no. 5, pp. 931–937, 2006.
[77] C. Grootscholten *et al.*, “Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial,” *Kidney Int.*, vol. 70, no. 4, pp. 732–742, 2006.
[78] S. Aslam, T. Santha, A. Leone, and C. Wilcox, “Effects of amlodipine and valsartan on oxidative stress and plasma methylarginines in end-stage renal disease patients on hemodialysis,” *Kidney Int.*, vol. 70, no. 12, pp. 2109–2115, 2006.
[79] P. Alaupovic, P. O. Attman, C. Knight-Gibson, H. Mulec, L. Weiss, and O. Samuelsson, “Effect of fluvastatin on apolipoprotein-defined lipoprotein subclasses in patients with chronic renal insufficiency,” *Kidney Int.*, vol. 69, no. 10, pp. 1865–1871, 2006.
[80] G. L. Bakris, J. B. Copley, N. Vicknair, R. Sadler, and S. Leurgans, “Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy.,” *Kidney Int.*, vol. 50, no. 5, pp. 1641–50, Nov. 1996.
[81] D. Demetriou, A. Habicht, M. Schillinger, W. H. Hörl, and A. Vychytil, “Adequacy of automated peritoneal dialysis with and without manual daytime exchange: A randomized controlled trial,” *Kidney Int.*, vol. 70, no. 9, pp. 1649–1655, 2006.
[82] M. Rathi *et al.*, “Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis,” *Kidney Int.*, vol. 89, no. 1, pp. 235–242, 2016.
[83] S. Klahr, “Role of dietary protein and blood pressure in the progression of renal disease,” *Kidney Int.*, vol. 49, no. 6, pp. 1783–1786, 1996.
[84] P. Saudan *et al.*, “Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure,” *Kidney Int.*, vol. 70, no. 7, pp. 1312–1317, 2006.
[85] J. L. Lin, D. T. Lin-Tan, C. C. Yu, Y. J. Li, Y. Y. Huang, and K. L. Li, “Environmental exposure to lead and progressive diabetic nephropathy in patients with type II diabetes,” *Kidney Int.*, vol. 69, no. 11, pp. 2049–2056, 2006.
[86] K. J. Schjoedt *et al.*, “Beneficial impact of spironolactone on nephrotic range albuminuria in

diabetic nephropathy," *Kidney Int.*, vol. 70, no. 3, pp. 536–542, 2006.
[87] M. J. Janssen *et al.*, "Citrate compared to low molecular weight heparin anticoagulation in chronic hemodialysis patients.," *Kidney Int.*, vol. 49, no. 3, pp. 806–13, Mar. 1996.
[88] K. V Lieberman and A. Tejani, "A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children.," *J. Am. Soc. Nephrol.*, vol. 7, no. 1, pp. 56–63, Jan. 1996.
[89] C. Ponticelli *et al.*, "Randomized study with cyclosporine in kidney transplantation: 10-year follow-up.," *J. Am. Soc. Nephrol.*, vol. 7, no. 5, pp. 792–7, May 1996.
[90] P. F. Hoyer and J. Brodeh, "Initial treatment of idiopathic nephrotic syndrome in children: prednisone versus prednisone plus cyclosporine A: a prospective, randomized trial.," *J. Am. Soc. Nephrol.*, vol. 17, no. 4, pp. 1151–7, Apr. 2006.
[91] W. Scheele *et al.*, "Phosphodiesterase Type 5 Inhibition Reduces Albuminuria in Subjects with Overt Diabetic Nephropathy," *J. Am. Soc. Nephrol.*, vol. 27, no. 11, pp. 3459–3468, 2016.
[92] F. Locatelli, L. Del Vecchio, and P. Pozzoni, "Anemia and cardiovascular risk: the lesson of the CREATE Trial.," *J. Am. Soc. Nephrol.*, vol. 17, no. 12 Suppl 3, pp. S262-6, Dec. 2006.
[93] P. Jose *et al.*, "Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction.," *J. Am. Soc. Nephrol.*, vol. 17, no. 10, pp. 2886–91, Oct. 2006.
[94] R. Ouseph, J. D. Leiser, and S. M. Moe, "Calcitriol and the parathyroid hormone-ionized calcium curve: a comparison of methodologic approaches.," *J. Am. Soc. Nephrol.*, vol. 7, no. 3, pp. 497–505, Mar. 1996.
[95] A. Barnett, "Preventing renal complications in type 2 diabetes: results of the diabetics exposed to telmisartan and enalapril trial.," *J. Am. Soc. Nephrol.*, vol. 17, no. 4 Suppl 2, pp. S132-5, Apr. 2006.
[96] M. Goicoechea *et al.*, "Effects of Atorvastatin on Inflammatory and Fibrinolytic Parameters in Patients with Chronic Kidney Disease," *J. Am. Soc. Nephrol.*, vol. 17, no. 12_suppl_3, pp. S231–S235, 2006.
[97] X. Wang, J. Lewis, and L. J. Appel et al., "Validation of Creatinine-Based Estimates of GFR When Evaluating Risk Factors in Longitudinal Studies of Kidney Disease," *J. Am. Soc. Nephrol.*, vol. 17, no. 10, pp. 2900–2909, 2006.
[98] R. A. F. de Lind van Wijngaarden *et al.*, "Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: A prospective analysis of 100 patients with severe renal involvement.," *J. Am. Soc. Nephrol.*, vol. 17, no. 8, pp. 2264–74, Aug. 2006.
[99] B. M. Robinson, M. M. Joffe, R. L. Pisoni, F. K. Port, and H. I. Feldman, "Revisiting survival differences by race and ethnicity among hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study.," *J. Am. Soc. Nephrol.*, vol. 17, no. 10, pp. 2910–8, Oct. 2006.
[100] W. L. Henrich, R. L. Clark, and J. P. Kelly et al., "Non-Contrast-Enhanced Computerized Tomography and Analgesic-Related Kidney Disease: Report of the National Analgesic Nephropathy Study," *J. Am. Soc. Nephrol.*, vol. 17, no. 5, pp. 1472–1480, 2006.
[101] T. A. Depner *et al.*, "Multicenter clinical validation of an on-line monitor of dialysis adequacy.," *J. Am. Soc. Nephrol.*, vol. 7, no. 3, pp. 464–71, Mar. 1996.
[102] L. Garneata, A. Stancu, D. Dragomir, G. Stefan, and G. Mircescu, "Ketoanalogue-Supplemented Vegetarian Very Low-Protein Diet and CKD Progression," *J. Am. Soc. Nephrol.*, vol. 27, no. 7, pp. 2164–2176, 2016.
[103] S. Ambalavanan, J. P. Fauvel, R. K. Sibley, and B. D. Myers, "Mechanism of the antiproteinuric effect of cyclosporine in membranous nephropathy.," *J. Am. Soc. Nephrol.*, vol. 7, no. 2, pp. 290–8, Feb. 1996.
[104] M. A. Cameron, N. M. Maalouf, B. Adams-Huet, O. W. Moe, and K. Sakhaee, "Urine composition in type 2 diabetes: predisposition to uric acid nephrolithiasis.," *J. Am. Soc. Nephrol.*, vol. 17, no. 5, pp. 1422–8, May 2006.
[105] B. S. Levine and M. Song, "Pharmacokinetics and efficacy of pulse oral versus intravenous calcitriol in hemodialysis patients.," *J. Am. Soc. Nephrol.*, vol. 7, no. 3, pp. 488–96, Mar. 1996.
[106] M. Chonchol, T. Greene, Y. Zhang, A. N. Hoofnagle, and A. K. Cheung, "Low Vitamin D and

High Fibroblast Growth Factor 23 Serum Levels Associate with Infectious and Cardiac Deaths in the HEMO Study," *J. Am. Soc. Nephrol.*, vol. 27, no. 1, pp. 227–237, 2016.

[107] S. Levey *et al.*, "Effects of diet and antihypertensive therapy on creatinine clearance and serum creatinine concentration in the Modification of Diet in Renal Disease Study.," *J. Am. Soc. Nephrol.*, vol. 7, no. 4, pp. 556–66, Apr. 1996.

[108] M. Polenakovic and A. Sikole, "Is erythropoietin a survival factor for red blood cells?," *J. Am. Soc. Nephrol.*, vol. 7, no. 8, pp. 1178–82, Aug. 1996.

[109] S. Levey *et al.*, "Effects of dietary protein restriction on the progression of moderate renal disease in the Modification of Diet in Renal Disease Study.," *J. Am. Soc. Nephrol.*, vol. 7, no. 12, pp. 2616–26, Dec. 1996.

[110] A. Ishani *et al.*, "Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial.," *J. Am. Soc. Nephrol.*, vol. 17, no. 5, pp. 1444–52, May 2006.

[111] G. M. Chertow *et al.*, "Long-Term Effects of Frequent In-Center Hemodialysis," *J. Am. Soc. Nephrol.*, vol. 27, no. 6, pp. 1830–1836, 2016.

[112] E. Ok *et al.*, "Reduction of Dialysate Calcium Level Reduces Progression of Coronary Artery Calcification and Improves Low Bone Turnover in Patients on Hemodialysis," *J. Am. Soc. Nephrol.*, vol. 27, no. 8, pp. 2475–2486, 2016.

[113] A. S. Levey *et al.*, "Short-term effects of protein intake, blood pressure, and antihypertensive therapy on glomerular filtration rate in the Modification of Diet in Renal Disease Study.," *J. Am. Soc. Nephrol.*, vol. 7, no. 10, pp. 2097–109, Oct. 1996.

[114] L. Holdstock *et al.*, "Four-Week Studies of Oral Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor GSK1278863 for Treatment of Anemia," *J. Am. Soc. Nephrol.*, vol. 27, no. 4, pp. 1234–1244, 2016.

[115] R. M. Hakim, R. L. Wingard, L. Husni, R. A. Parker, and T. F. Parker, "The effect of membrane biocompatibility on plasma beta 2-microglobulin levels in chronic hemodialysis patients.," *J. Am. Soc. Nephrol.*, vol. 7, no. 3, pp. 472–8, Mar. 1996.

[116] K. C. Norris *et al.*, "Baseline predictors of renal disease progression in the African American Study of Hypertension and Kidney Disease.," *J. Am. Soc. Nephrol.*, vol. 17, no. 10, pp. 2928–36, Oct. 2006.

[117] T. Dad *et al.*, "Aspirin Use and Incident Cardiovascular Disease, Kidney Failure, and Death in Stable Kidney Transplant Recipients: A Post Hoc Analysis of the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) Trial," *Am. J. Kidney Dis.*, vol. 68, no. 2, pp. 277–286, 2016.

[118] J. T. Park *et al.*, "High-Dose Versus Conventional-Dose Continuous Venovenous Hemodiafiltration and Patient and Kidney Survival and Cytokine Removal in Sepsis-Associated Acute Kidney Injury: A Randomized Controlled Trial," *Am. J. Kidney Dis.*, vol. 68, no. 4, pp. 599–608, 2016.

[119] D. Coyne *et al.*, "Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD," *Am. J. Kidney Dis.*, vol. 47, no. 2, pp. 263–276, 2006.

[120] C. M. Arce *et al.*, "Kidney Function and Cardiovascular Events in Postmenopausal Women: The Impact of Race and Ethnicity in the Women's Health Initiative," *Am. J. Kidney Dis.*, vol. 67, no. 2, pp. 198–208, 2016.

[121] M. A. Roberts *et al.*, "The β-Blocker to Lower Cardiovascular Dialysis Events (BLOCADE) feasibility study: A randomized controlled trial," *Am. J. Kidney Dis.*, vol. 67, no. 6, pp. 902–911, 2016.

[122] D. Fischer, K. Cline, M. A. Plone, M. Dillon, S. K. Burke, and A. T. Blair, "Results of a Randomized Crossover Study Comparing Once-Daily and Thrice-Daily Sevelamer Dosing," *Am. J. Kidney Dis.*, vol. 48, no. 3, pp. 437–444, 2006.

[123] R. D. Toto, B. Adams-Huet, A. Z. Fenves, H. C. Mitchell, W. Mulcahy, and R. D. Smith, "Effect of ramipril on blood pressure and protein excretion rate in normotensive nondiabetic patients with proteinuria," *Am. J. Kidney Dis.*, vol. 28, no. 6, pp. 832–840, 1996.

[124] Y. P. Siu, K. T. Leung, M. K. H. Tong, and T. H. Kwan, “Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level,” *Am. J. Kidney Dis.*, vol. 47, no. 1, pp. 51–59, 2006.
[125] R. K. Sharma, N. Prasad, A. Gupta, and R. Kapoor, “Treatment of Erectile Dysfunction With Sildenafil Citrate in Renal Allograft Recipients: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial,” *Am. J. Kidney Dis.*, vol. 48, no. 1, pp. 128–133, 2006.
[126] R. A. Brigandi *et al.*, “A novel hypoxia-inducible factor-prolyl hydroxylase inhibitor (GSK1278863) for anemia in CKD: A 28-day, phase 2A randomized trial,” *Am. J. Kidney Dis.*, vol. 67, no. 6, pp. 861–871, 2016.
[127] N. Attallah, Y. Osman-Malik, S. Frinak, and A. Besarab, “Effect of intravenous ascorbic acid in hemodialysis patients with EPO-hyporesponsive anemia and hyperferritinemia,” *Am. J. Kidney Dis.*, vol. 47, no. 4, pp. 644–654, 2006.
[128] M. E *et al.*, “A prospective comparison of bicarbonate dialysis, hemodiafiltration, and acetate-free biofiltration in the elderly,” *Am. J. kidney Dis.*, vol. 27, no. 4, pp. 541–547, 1996.
[129] P. K. T. Li *et al.*, “Hong Kong Study Using Valsartan in IgA Nephropathy (HKVIN): A Double-Blind, Randomized, Placebo-Controlled Study,” *Am. J. Kidney Dis.*, vol. 47, no. 5, pp. 751–760, 2006.
[130] J. Rossert *et al.*, “Effect of Early Correction of Anemia on the Progression of CKD,” *Am. J. Kidney Dis.*, vol. 47, no. 5, pp. 738–750, 2006.
[131] M. O. Kaisar *et al.*, “A Randomized Controlled Trial of Fludrocortisone for the Treatment of Hyperkalemia in Hemodialysis Patients,” *Am. J. Kidney Dis.*, vol. 47, no. 5, pp. 809–814, 2006.
[132] G. Schulman, R. Agarwal, M. Acharya, T. Berl, S. Blumenthal, and N. Kopyt, “A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study of AST-120 (Kremezin) in patients with moderate to severe CKD,” *Am. J. Kidney Dis.*, vol. 47, no. 4, pp. 565–577, 2006.
[133] K. C. Siamopoulos *et al.*, “Long-Term Treatment With EPO Increases Serum Levels of High-Density Lipoprotein in Patients With CKD,” *Am. J. Kidney Dis.*, vol. 48, no. 2, pp. 242–249, 2006.
[134] A. S. Levey *et al.*, “Effects of Dietary Protein Restriction on the Progression of Moderate Renal Disease in the Modification of Diet in Renal Disease Study,” *Am. J. Kidney Dis.*, vol. 27, no. 5, pp. 652–663, 1996.
[135] K. L. Ho, P. A. Rutherford, T. H. Thomas, and R. Wilkinson, “Abnormal sodium-lithium countertransport kinetics in immunoglobulin A nephropathy patients and their families: Association with hypertension,” *Am. J. Kidney Dis.*, vol. 27, no. 3, pp. 334–340, 1996.
[136] R. L. Morton *et al.*, “Impact of Educational Attainment on Health Outcomes in Moderate to Severe CKD,” *Am. J. Kidney Dis.*, vol. 67, no. 1, pp. 31–39, 2016.
[137] Y. Dauvilliers *et al.*, “Rotigotine in Hemodialysis-Associated Restless Legs Syndrome: A Randomized Controlled Trial,” *Am. J. Kidney Dis.*, vol. 68, no. 3, pp. 434–443, 2016.
[138] P. Giannattasio *et al.*, “Effects of Efficiency and Length of Acetate-Free Biofiltration Session on Postdialysis Solute Rebound,” *Am. J. Kidney Dis.*, vol. 47, no. 6, pp. 1045–1054, 2006.
[139] M. Sangill and E. B. Pedersen, “The effect of glucose added to the dialysis fluid on blood pressure, blood glucose, and quality of life in hemodialysis patients: A placebo-controlled crossover study,” *Am. J. Kidney Dis.*, vol. 47, no. 4, pp. 636–643, 2006.
[140] B. Mihaylova *et al.*, “Cost-effectiveness of simvastatin plus ezetimibe for cardiovascular prevention in CKD: Results of the study of heart and renal protection (SHARP),” *Am. J. Kidney Dis.*, vol. 67, no. 4, pp. 576–584, 2016.
[141] F. R. Mc Causland *et al.*, “C-Reactive Protein and Risk of ESRD: Results From the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT),” *Am. J. Kidney Dis.*, vol. 68, no. 6, pp. 873–881, 2016.
[142] Y. C. Chen, W. T. Chiu, and M. S. Wu, “Therapeutic Effect of Topical Gamma-Linolenic Acid on Refractory Uremic Pruritus,” *Am. J. Kidney Dis.*, vol. 48, no. 1, pp. 69–76, 2006.
[143] B. U. Ihle, J. A. Whitworth, S. Shahinfar, A. Cnaan, P. S. Kincaid-Smith, and G. J. Becker, “Angiotensin-converting enzyme inhibition in nondiabetic progressive renal insufficiency: A controlled double-blind trial,” *Am. J. Kidney Dis.*, vol. 27, no. 4, pp. 489–495, 1996.

[144] A. K. Pieper *et al.*, “A randomized crossover trial comparing sevelamer with calcium acetate in children with CKD,” *Am. J. Kidney Dis.*, vol. 47, no. 4, pp. 625–635, 2006.
[145] C. Ponticelli *et al.*, “A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotropic hormone in idiopathic membranous nephropathy,” *Am. J. Kidney Dis.*, vol. 47, no. 2, pp. 233–240, 2006.
[146] A. Ishani *et al.*, “Telehealth by an Interprofessional Team in Patients with CKD: A Randomized Controlled Trial,” *Am. J. Kidney Dis.*, vol. 68, no. 1, pp. 41–49, 2016.
[147] M. Landray *et al.*, “The second United Kingdom Heart and Renal Protection (UK-HARP-II) study: A randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD,” *Am. J. Kidney Dis.*, vol. 47, no. 3, pp. 385–395, 2006.
[148] T. Higuchi *et al.*, “Levocarnitine Improves Cardiac Function in Hemodialysis Patients with Left Ventricular Hypertrophy: A Randomized Controlled Trial,” *Am. J. Kidney Dis.*, vol. 67, no. 2, pp. 260–270, 2016.
[149] J. P. Lash *et al.*, “Quality of Life in the African American Study of Kidney Disease and Hypertension: Effects of Blood Pressure Management,” *Am. J. Kidney Dis.*, vol. 47, no. 6, pp. 956–964, 2006.
[150] B. Rutkowski *et al.*, “Low-Sodium Versus Standard-Sodium Peritoneal Dialysis Solution in Hypertensive Patients: A Randomized Controlled Trial,” *Am. J. Kidney Dis.*, vol. 67, no. 5, pp. 753–761, 2016.
[151] G. Mircescu *et al.*, “Once-Every-2-Weeks and Once-Weekly Epoetin Beta Regimens: Equivalency in Hemodialyzed Patients,” *Am. J. Kidney Dis.*, vol. 48, no. 3, pp. 445–455, 2006.
[152] A. T. Brockenbrough, M. O. Dittrich, S. T. Page, T. Smith, J. C. Stivelman, and W. J. Bremner, “Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease,” *Am. J. Kidney Dis.*, vol. 47, no. 2, pp. 251–262, 2006.
[153] A. S. Levey *et al.*, “Effect of Dietary Protein Restriction on the Progression of Kidney Disease: Long-Term Follow-Up of the Modification of Diet in Renal Disease (MDRD) Study,” *Am. J. Kidney Dis.*, vol. 48, no. 6, pp. 879–888, 2006.
[154] K. Y. Chan *et al.*, “Enhanced psychosocial support for caregiver burden for patients with chronic kidney failure choosing not to be treated by dialysis or transplantation: A pilot randomized controlled trial,” *Am. J. Kidney Dis.*, vol. 67, no. 4, pp. 585–592, 2016.
[155] A. L. Kamper, N.-H. Holstein-Rathlou, P. P. Leyssac, and S. Strandgaard, “The Influence of Angiotensin-Converting Enzyme Inhibition on Renal Tubular Function in Progressive Chronic Nephropathy,” *Am. J. Kidney Dis.*, vol. 28, no. 6, pp. 822–831, 1996.
[156] K. Norris *et al.*, “Cardiovascular Outcomes in the African American Study of Kidney Disease and Hypertension (AASK) Trial,” *Am. J. Kidney Dis.*, vol. 48, no. 5, pp. 739–751, 2006.
[157] R. Provenzano *et al.*, “Roxadustat (FG-4592) versus epoetin alfa for anemia in patients receiving maintenance hemodialysis: A phase 2, randomized, 6- to 19-week, open-label, active-comparator, dose-ranging, safety and exploratory efficacy study,” *Am. J. Kidney Dis.*, vol. 67, no. 6, pp. 912–924, 2016.
[158] N. M. Selby, S. H. Lambie, P. G. Camici, C. S. Baker, and C. W. McIntyre, “Occurrence of Regional Left Ventricular Dysfunction in Patients Undergoing Standard and Biofeedback Dialysis,” *Am. J. Kidney Dis.*, vol. 47, no. 5, pp. 830–841, 2006.
[159] O. W. Amro, J. K. Paulus, F. Noubary, and R. D. Perrone, “Low-Osmolar Diet and Adjusted Water Intake for Vasopressin Reduction in Autosomal Dominant Polycystic Kidney Disease: A Pilot Randomized Controlled Trial,” *Am. J. Kidney Dis.*, vol. 68, no. 6, pp. 882–891, 2016.
[160] Z. Sohrabi, M. H. Eftekhari, M. H. Eskandari, A. Rezaianzadeh, and M. M. Sagheb, “Intradialytic Oral Protein Supplementation and Nutritional and Inflammation Outcomes in Hemodialysis: A Randomized Controlled Trial,” *Am. J. Kidney Dis.*, vol. 68, no. 1, pp. 122–130, 2016.
[161] K. Susztak and E. P. Böttinger, “Diabetic nephropathy: a frontier for personalized medicine.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 2, pp. 361–7, Feb. 2006.
[162] F. Madore, J. M. Lazarus, and H. R. Brady, “Therapeutic plasma exchange in renal diseases.,” *J. Am. Soc. Nephrol.*, vol. 7, no. 3, pp. 367–86, Mar. 1996.

[163] L. R. Willis, A. P. Evan, B. A. Connors, R. K. Handa, P. M. Blomgren, and J. E. Lingeman, "Prevention of lithotripsy-induced renal injury by pretreating kidneys with low-energy shock waves.," *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 663–73, Mar. 2006.
[164] W. D. Paulson, C. N. Torres-Rivera, L. Gray, and P. Tso, "Intestinal lipid absorption in the nephrotic rat.," *J. Am. Soc. Nephrol.*, vol. 7, no. 3, pp. 431–6, Mar. 1996.
[165] Y. Wang *et al.*, "LDL Receptor-Related Protein 6 Modulates Ret Proto-Oncogene Signaling in Renal Development and Cystic Dysplasia," *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 417–427, 2016.
[166] K. M. A. Rouschop, N. Claessen, S. T. Pals, J. J. Weening, and S. Florquin, "CD44 disruption prevents degeneration of the capillary network in obstructive nephropathy via reduction of TGF-beta1-induced apoptosis.," *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 746–53, Mar. 2006.
[167] H. Matsuda *et al.*, "Development of gene silencing pyrrole-imidazole polyamide targeting the TGF-beta1 promoter for treatment of progressive renal diseases.," *J. Am. Soc. Nephrol.*, vol. 17, no. 2, pp. 422–32, Feb. 2006.
[168] J. R. Timoshanko, A. R. Kitching, T. J. Semple, P. G. Tipping, and S. R. Holdsworth, "A pathogenetic role for mast cells in experimental crescentic glomerulonephritis.," *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 150–9, Jan. 2006.
[169] P.-Y. Gan, D. S. Y. Tan, J. D. Ooi, M. A. Alikhan, A. R. Kitching, and S. R. Holdsworth, "Myeloperoxidase Peptide-Based Nasal Tolerance in Experimental ANCA-Associated GN," *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 385–391, 2016.
[170] M. Schwartzman *et al.*, "Podocyte-Specific Deletion of Yes-Associated Protein Causes FSGS and Progressive Renal Failure," *J. Am. Soc. Nephrol.*, vol. 27, no. 1, pp. 216–226, 2016.
[171] L. D. Dworkin, J. A. Benstein, E. Tolbert, and H. D. Feiner, "Salt restriction inhibits renal growth and stabilizes injury in rats with established renal disease.," *J. Am. Soc. Nephrol.*, vol. 7, no. 3, pp. 437–42, Mar. 1996.
[172] M. P. Madaio and M. J. Shlomchik, "Emerging concepts regarding B cells and autoantibodies in murine lupus nephritis. B cells have multiple roles; all autoantibodies are not equal.," *J. Am. Soc. Nephrol.*, vol. 7, no. 3, pp. 387–96, Mar. 1996.
[173] M. Nangaku, "Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure.," *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 17–25, Jan. 2006.
[174] J. P. Vora, S. M. Zimsen, D. C. Houghton, and S. Anderson, "Evolution of metabolic and renal changes in the ZDF/Drt-fa rat model of type II diabetes.," *J. Am. Soc. Nephrol.*, vol. 7, no. 1, pp. 113–7, Jan. 1996.
[175] R. Mohamed *et al.*, "Low-Dose IL-17 Therapy Prevents and Reverses Diabetic Nephropathy, Metabolic Syndrome, and Associated Organ Fibrosis," *J. Am. Soc. Nephrol.*, vol. 27, no. 3, pp. 745–765, 2016.
[176] J. M. Thurman *et al.*, "Treatment with an inhibitory monoclonal antibody to mouse factor B protects mice from induction of apoptosis and renal ischemia/reperfusion injury.," *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 707–15, Mar. 2006.
[177] I. Mami *et al.*, "Angiogenin Mediates Cell-Autonomous Translational Control under Endoplasmic Reticulum Stress and Attenuates Kidney Injury," *J. Am. Soc. Nephrol.*, vol. 27, no. 3, pp. 863–876, 2016.
[178] D. P. Basile *et al.*, "Progression after AKI: Understanding Maladaptive Repair Processes to Predict and Identify Therapeutic Treatments," *J. Am. Soc. Nephrol.*, vol. 27, no. 3, pp. 687–697, 2016.
[179] M. Omata *et al.*, "N-acetyl-seryl-aspartyl-lysyl-proline ameliorates the progression of renal dysfunction and fibrosis in WKY rats with established anti-glomerular basement membrane nephritis.," *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 674–85, Mar. 2006.
[180] S. H. Han *et al.*, "Deletion of Lkb1 in Renal Tubular Epithelial Cells Leads to CKD by Altering Metabolism," *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 439–453, 2016.
[181] U. Panzer *et al.*, "Compartment-specific expression and function of the chemokine IP-10/CXCL10 in a model of renal endothelial microvascular injury.," *J. Am. Soc. Nephrol.*, vol. 17, no. 2, pp. 454–64, Feb. 2006.

[182] N. S. Sheerin, K. Abe, P. Risley, and S. H. Sacks, “Accumulation of immune complexes in glomerular disease is independent of locally synthesized c3.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 686–96, Mar. 2006.
[183] M. Hara-Chikuma and A. S. Verkman, “Aquaporin-1 facilitates epithelial cell migration in kidney proximal tubule.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 39–45, Jan. 2006.
[184] R. D. Pawar *et al.*, “Toll-like receptor-7 modulates immune complex glomerulonephritis.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 141–9, Jan. 2006.
[185] S. X. Zhang, J. J. Wang, K. Lu, R. Mott, R. Longeras, and J.-X. Ma, “Therapeutic potential of angiostatin in diabetic nephropathy.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 2, pp. 475–86, Feb. 2006.
[186] E. P. Rhee, “NADPH Oxidase 4 at the Nexus of Diabetes, Reactive Oxygen Species, and Renal Metabolism.,” *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 337–9, 2016.
[187] M. A. Kluger *et al.*, “ROR t+Foxp3+ Cells are an Independent Bifunctional Regulatory T Cell Lineage and Mediate Crescentic GN,” *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 454–465, 2016.
[188] D. Houamel *et al.*, “Hepcidin as a Major Component of Renal Antibacterial Defenses against Uropathogenic Escherichia coli,” *J. Am. Soc. Nephrol.*, vol. 27, no. 3, pp. 835–846, 2016.
[189] R. Takeda *et al.*, “Ghrelin improves renal function in mice with ischemic acute renal failure.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 113–21, Jan. 2006.
[190] C. Henique *et al.*, “Nuclear Factor Erythroid 2-Related Factor 2 Drives Podocyte-Specific Expression of Peroxisome Proliferator-Activated Receptor Essential for Resistance to Crescentic GN,” *J. Am. Soc. Nephrol.*, vol. 27, no. 1, pp. 172–188, 2016.
[191] P. Fiorina *et al.*, “Role of CXC chemokine receptor 3 pathway in renal ischemic injury.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 716–23, Mar. 2006.
[192] L. S. K. Walker and M. von Herrath, “CD4 T cell differentiation in type 1 diabetes,” *Clin. Exp. Immunol.*, vol. 183, no. 1, pp. 16–29, 2016.
[193] J. Ehling *et al.*, “Quantitative Micro-Computed Tomography Imaging of Vascular Dysfunction in Progressive Kidney Diseases,” *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 520–532, 2016.
[194] M. M. Ruseva *et al.*, “Efficacy of Targeted Complement Inhibition in Experimental C3 Glomerulopathy,” *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 405–416, 2016.
[195] I. Lopez *et al.*, “Calcimimetic R-568 decreases extraosseous calcifications in uremic rats treated with calcitriol.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 795–804, Mar. 2006.
[196] M. Józsi *et al.*, “Factor H and atypical hemolytic uremic syndrome: mutations in the C-terminus cause structural changes and defective recognition functions.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 170–177, Jan. 2006.
[197] Y.-H. You, T. Quach, R. Saito, J. Pham, and K. Sharma, “Metabolomics Reveals a Key Role for Fumarate in Mediating the Effects of NADPH Oxidase 4 in Diabetic Kidney Disease.,” *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 466–81, 2016.
[198] Y. M. Wang *et al.*, “Foxp3-transduced polyclonal regulatory T cells protect against chronic renal injury from adriamycin.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 697–706, Mar. 2006.
[199] G. D. Han *et al.*, “IFN-inducible protein-10 plays a pivotal role in maintaining slit-diaphragm function by regulating podocyte cell-cycle balance.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 2, pp. 442–53, Feb. 2006.
[200] J. J. T. H. Roelofs *et al.*, “Tissue-type plasminogen activator modulates inflammatory responses and renal function in ischemia reperfusion injury.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 131–40, Jan. 2006.
[201] G. C. Zeller, J. Hirahashi, A. Schwarting, A. H. Sharpe, and V. R. Kelley, “Inducible co-stimulator null MRL-Faslpr mice: uncoupling of autoantibodies and T cell responses in lupus.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 122–30, Jan. 2006.
[202] C. Roufosse *et al.*, “Bone marrow-derived cells do not contribute significantly to collagen I synthesis in a murine model of renal fibrosis.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 775–82, Mar. 2006.
[203] H. Rabb *et al.*, “Inflammation in AKI: Current Understanding, Key Questions, and Knowledge Gaps,” *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 371–379, 2016.

[204] B. G. Chousterman *et al.*, “Ly6Chigh Monocytes Protect against Kidney Damage during Sepsis via a CX3CR1-Dependent Adhesion Mechanism,” *J. Am. Soc. Nephrol.*, vol. 27, no. 3, pp. 792–803, 2016.
[205] A. R. Chade, “Vascular Endothelial Growth Factor Therapy for the Kidney: Are We There Yet?,” *J. Am. Soc. Nephrol.*, vol. 27, no. 1, pp. 1–3, 2016.
[206] H. Rabb, “Immune modulation of acute kidney injury.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 604–6, Mar. 2006.
[207] E. Suganuma *et al.*, “Antiatherogenic effects of angiotensin receptor antagonism in mild renal dysfunction.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 2, pp. 433–41, Feb. 2006.
[208] M. A. Alikhan *et al.*, “Endogenous Toll-Like Receptor 9 Regulates AKI by Promoting Regulatory T Cell Recruitment,” *J. Am. Soc. Nephrol.*, vol. 27, no. 3, pp. 706–714, 2016.
[209] H. Peng *et al.*, “CKD Stimulates Muscle Protein Loss Via Rho-associated Protein Kinase 1 Activation,” *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 509–519, 2016.
[210] M. A. Little *et al.*, “Therapeutic effect of anti-TNF-alpha antibodies in an experimental model of anti-neutrophil cytoplasm antibody-associated systemic vasculitis.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 160–9, Jan. 2006.
[211] D. R. Abrahamson and B. M. Steenhard, “Renal therapy by stem cells: outsource or in-house?,” *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 12–4, Jan. 2006.
[212] T. Odenwald *et al.*, “Acute blood pressure effects and chronic hypotensive action of calcimimetics in uremic rats.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 655–62, Mar. 2006.
[213] G. Zheng *et al.*, “DNA vaccination with CCL2 DNA modified by the addition of an adjuvant epitope protects against ‘nonimmune’ toxic renal injury.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 2, pp. 465–74, Feb. 2006.
[214] M. P. Cohen and F. N. Ziyadeh, “Role of Amadori-modified nonenzymatically glycated serum proteins in the pathogenesis of diabetic nephropathy.,” *J. Am. Soc. Nephrol.*, vol. 7, no. 2, pp. 183–90, Feb. 1996.
[215] J. L. Huang *et al.*, “Vascular Endothelial Growth Factor C for Polycystic Kidney Diseases,” *J. Am. Soc. Nephrol.*, vol. 27, no. 1, pp. 69–77, 2016.
[216] S. Panizo *et al.*, “MicroRNAs 29b, 133b, and 211 Regulate Vascular Smooth Muscle Calcification Mediated by High Phosphorus,” *J. Am. Soc. Nephrol.*, vol. 27, no. 3, pp. 824–834, 2016.
[217] R. Fukuda *et al.*, “Podocyte p53 Limits the Severity of Experimental Alport Syndrome,” *J. Am. Soc. Nephrol.*, vol. 27, no. 1, pp. 144–157, 2016.
[218] T. Chiba *et al.*, “Retinoic Acid Signaling Coordinates Macrophage-Dependent Injury and Repair after AKI,” *J. Am. Soc. Nephrol.*, vol. 27, no. 2, pp. 495–508, 2016.
[219] M. D. Okusa, M. H. Rosner, J. A. Kellum, and C. Ronco, “Therapeutic Targets of Human AKI: Harmonizing Human and Animal AKI,” *J. Am. Soc. Nephrol.*, vol. 27, no. 1, pp. 44–48, 2016.
[220] A. Remuzzi *et al.*, “Regression of Renal Disease by Angiotensin II Antagonism Is Caused by Regeneration of Kidney Vasculature,” *J. Am. Soc. Nephrol.*, vol. 27, no. 3, pp. 699–705, 2016.
[221] G. S. Braun *et al.*, “IL-6 Trans-Signaling Drives Murine Crescentic GN.,” *J. Am. Soc. Nephrol.*, vol. 27, no. 1, pp. 132–42, Jan. 2016.
[222] M. Liu *et al.*, “A pathophysiologic role for T lymphocytes in murine acute cisplatin nephrotoxicity.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 3, pp. 765–74, Mar. 2006.
[223] J. A. Shayman, “Sphingolipids: their role in intracellular signaling and renal growth.,” *J. Am. Soc. Nephrol.*, vol. 7, no. 2, pp. 171–82, Feb. 1996.
[224] R. Levi *et al.*, “Increased parathyroid hormone gene expression in secondary hyperparathyroidism of experimental uremia is reversed by calcimimetics: correlation with posttranslational modification of the trans acting factor AUF1.,” *J. Am. Soc. Nephrol.*, vol. 17, no. 1, pp. 107–12, Jan. 2006.
[225] R. Zent and A. Pozzi, “Antiangiogenic Therapy in Diabetic Nephropathy,” *J. Am. Soc. Nephrol.*, vol. 17, no. 2, pp. 325–327, Feb. 2006.
[226] S. Kondo *et al.*, “Addition of the antioxidant probucol to angiotensin II type I receptor antagonist arrests progressive mesangioproliferative glomerulonephritis in the rat.,” *J. Am.*

Soc. Nephrol., vol. 17, no. 3, pp. 783–94, Mar. 2006.
[227] M. C. Menon and M. J. Ross, "Epithelial-to-mesenchymal transition of tubular epithelial cells in renal fibrosis: A new twist on an old tale," *Kidney Int.*, vol. 89, no. 2, pp. 263–266, 2016.
[228] Y. De Marinis *et al.*, "Epigenetic regulation of the thioredoxin-interacting protein (TXNIP) gene by hyperglycemia in kidney," *Kidney Int.*, vol. 89, no. 2, pp. 342–353, 2016.
[229] D. Unnersjö-Jess, L. Scott, H. Blom, and H. Brismar, "Super-resolution stimulated emission depletion imaging of slit diaphragm proteins in optically cleared kidney tissue," *Kidney Int.*, vol. 89, no. 1, pp. 243–247, 2016.
[230] H. C. Tillmann *et al.*, "Efficacy and immunogenicity of novel erythropoietic agents and conventional rhEPO in rats with renal insufficiency," *Kidney Int.*, vol. 69, no. 1, pp. 60–67, 2006.
[231] M. Porst *et al.*, "Fibrillin-1 regulates mesangial cell attachment, spreading, migration and proliferation," *Kidney Int.*, vol. 69, no. 3, pp. 450–456, 2006.
[232] S. Riazi, C. Maric, and C. A. Ecelbarger, "17-β Estradiol attenuates streptozotocin-induced diabetes and regulates the expression of renal sodium transporters," *Kidney Int.*, vol. 69, no. 3, pp. 471–480, 2006.
[233] M. A. Kluger *et al.*, "Treg17 cells are programmed by Stat3 to suppress Th17 responses in systemic lupus," *Kidney Int.*, vol. 89, no. 1, pp. 158–166, 2016.
[234] D. Katagiri *et al.*, "Interstitial renal fibrosis due to multiple cisplatin treatments is ameliorated by semicarbazide-sensitive amine oxidase inhibition," *Kidney Int.*, vol. 89, no. 2, pp. 374–385, 2016.
[235] N. Maril, R. Margalit, S. Rosen, S. N. Heyman, and H. Degani, "Detection of evolving acute tubular necrosis with renal 23Na MRI: Studies in rats," *Kidney Int.*, vol. 69, no. 4, pp. 765–768, 2006.
[236] C. A. Amador *et al.*, "Deletion of mineralocorticoid receptors in smooth muscle cells blunts renal vascular resistance following acute cyclosporine administration," *Kidney Int.*, vol. 89, no. 2, pp. 354–362, 2016.
[237] S. C. Hung *et al.*, "Indoxyl sulfate suppresses endothelial progenitor cell-mediated neovascularization," *Kidney Int.*, vol. 89, no. 3, pp. 574–585, 2016.
[238] V. David *et al.*, "Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production," *Kidney Int.*, vol. 89, no. 1, pp. 135–146, 2016.
[239] T. J. Hsieh *et al.*, "Upregulation of osteopontin gene expression in diabetic rat proximal tubular cells revealed by microarray profiling," *Kidney Int.*, vol. 69, no. 6, pp. 1005–1015, 2006.
[240] L. Schaefer *et al.*, "Tubular gelatinase A (MMP-2) and its tissue inhibitors in polycystic kidney disease in the Han:SPRD rat," *Kidney Int.*, vol. 49, no. 1, pp. 75–81, 1996.
[241] W. H. Yiu *et al.*, "Kallistatin protects against diabetic nephropathy in db/db mice by suppressing AGE-RAGE-induced oxidative stress," *Kidney Int.*, vol. 89, no. 2, pp. 386–398, 2016.
[242] T. Irifuku *et al.*, "Inhibition of H3K9 histone methyltransferase G9a attenuates renal fibrosis and retains klotho expression," *Kidney Int.*, vol. 89, no. 1, pp. 147–157, 2016.
[243] M. Hatch, J. Cornelius, M. Allison, H. Sidhu, A. Peck, and R. W. Freel, "Oxalobacter sp. reduces urinary oxalate excretion by promoting enteric oxalate secretion," *Kidney Int.*, vol. 69, no. 4, pp. 691–698, 2006.
[244] J. Morinaga *et al.*, "Angiopoietin-like protein 2 increases renal fibrosis by accelerating transforming growth factor-β signaling in chronic kidney disease," *Kidney Int.*, vol. 89, no. 2, pp. 327–341, 2016.
[245] Z. G. Xu *et al.*, "Relationship between 12/15-lipoxygenase and COX-2 in mesangial cells: Potential role in diabetic nephropathy," *Kidney Int.*, vol. 69, no. 3, pp. 512–519, 2006.
[246] A. Gupta, S. Sharma, C. K. Nain, B. K. Sharma, and N. K. Ganguly, "Reactive oxygen species-mediated tissue injury in experimental ascending pyelonephritis," *Kidney Int.*, vol. 49, no. 1, pp. 26–33, 1996.
[247] N. Nagano *et al.*, "Effect of manipulating serum phosphorus with phosphate binder on

circulating PTH and FGF23 in renal failure rats," *Kidney Int.*, vol. 69, no. 3, pp. 531–537, 2006.
[248] J. Klein, J. L. Bascands, H. Mischak, and J. P. Schanstra, "The role of urinary peptidomics in kidney disease research," *Kidney Int.*, vol. 89, no. 3, pp. 539–545, 2016.
[249] O. Ruiz-Andres *et al.*, "The inflammatory cytokine TWEAK decreases PGC-1α expression and mitochondrial function in acute kidney injury," *Kidney Int.*, vol. 89, no. 2, pp. 399–410, 2016.
[250] M. Taniguchi, M. Tokumoto, D. Matsuo, K. Tsuruya, H. Hirakata, and M. Iida, "Parathyroid growth and regression in experimental uremia," *Kidney Int.*, vol. 69, no. 3, pp. 464–470, 2006.
[251] T. Naito, R. C. Griffiths, T. M. Coffman, and V. R. Kelley, "Transplant approach establishes that kidneys are responsible for serum CSF-1 but require a stimulus in MRL-lpr mice," *Kidney Int.*, vol. 49, no. 1, pp. 67–74, 1996.
[252] J. W. Dear *et al.*, "Sepsis-induced organ failure is mediated by different pathways in the kidney and liver: Acute renal failure is dependent on MyD88 but not renal cell apoptosis," *Kidney Int.*, vol. 69, no. 5, pp. 832–836, 2006.
[253] F. Vaziri-Sani *et al.*, "Phenotypic expression of factor H mutations in patients with atypical hemolytic uremic syndrome," *Kidney Int.*, vol. 69, no. 6, pp. 981–988, 2006.
[254] T. E. Hunley *et al.*, "Angiotensin converting enzyme gene polymorphism: Potential silencer motif and impact on progression in IgA nephropathy," *Kidney Int.*, vol. 49, no. 2, pp. 571–577, 1996.
[255] I. F. Schwartz *et al.*, "Arginine uptake is attenuated through modulation of cationic amino-acid transporter-1, in uremic rats," *Kidney Int.*, vol. 69, no. 2, pp. 298–303, 2006.
[256] F. A. Prins, J. A. Bruijn, and E. De Heer, "Applications in renal immunopathology of reflection contrast microscopy, a novel superior light microscopical technique," *Kidney Int.*, vol. 49, no. 1, pp. 261–266, 1996.
[257] B. Li, T. Morioka, M. Uchiyama, and T. Oite, "Bone marrow cell infusion ameliorates progressive glomerulosclerosis in an experimental rat model," *Kidney Int.*, vol. 69, no. 2, pp. 323–330, 2006.
[258] R. H. Mak, W. Cheung, R. D. Cone, and D. L. Marks, "Leptin and inflammation-associated cachexia in chronic kidney disease," *Kidney Int.*, vol. 69, no. 5, pp. 794–797, 2006.
[259] G. Seleznik *et al.*, "The lymphotoxin β receptor is a potential therapeutic target in renal inflammation," *Kidney Int.*, vol. 89, no. 1, pp. 113–126, 2016.
[260] H. Sugiyama, N. Kashihara, H. Makino, Y. Yamasaki, and Z. Ota, "Apoptosis in glomerular sclerosis," *Kidney Int.*, vol. 49, no. 1, pp. 103–111, 1996.
[261] H. Birn and E. I. Christensen, "Renal albumin absorption in physiology and pathology," *Kidney Int.*, vol. 69, no. 3, pp. 440–449, 2006.
[262] M. Tsuji *et al.*, "Microarray analysis of a reversible model and an irreversible model of anti-Thy-1 nephritis," *Kidney Int.*, vol. 69, no. 6, pp. 996–1004, 2006.
[263] F. Y. Chow, D. J. Nikolic-Paterson, E. Ozols, R. C. Atkins, B. J. Rollin, and G. H. Tesch, "Monocyte chemoattractant protein-1 promotes the development of diabetic renal injury in streptozotocin-treated mice," *Kidney Int.*, vol. 69, no. 1, pp. 73–80, 2006.
[264] G. N. Hendy, K. A. Hruska, S. Mathew, and D. Goltzman, "New insights into mineral and skeletal regulation by active forms of vitamin D," *Kidney Int.*, vol. 69, no. 2, pp. 218–223, 2006.
[265] F. G. Lakkis, F. K. Baddoura, E. N. Cruet, K. R. Parekh, M. Fukunaga, and K. A. Munger, "Anti-inflammatory lymphokine mRNA expression in antibody-induced glomerulonephritis," *Kidney Int.*, vol. 49, no. 1, pp. 117–126, 1996.
[266] A. Brahmbhatt, A. Remuzzi, M. Franzoni, and S. Misra, "The molecular mechanisms of hemodialysis vascular access failure," *Kidney Int.*, vol. 89, no. 2, pp. 303–316, 2016.
[267] P. Ranganathan, R. Hamad, R. Mohamed, C. Jayakumar, T. Muthusamy, and G. Ramesh, "Histone deacetylase-mediated silencing of AMWAP expression contributes to cisplatin nephrotoxicity," *Kidney Int.*, vol. 89, no. 2, pp. 317–326, 2016.
[268] A. R. Carpenter *et al.*, "Uroplakin 1b is critical in urinary tract development and urothelial differentiation and homeostasis," *Kidney Int.*, vol. 89, no. 3, pp. 612–614, 2016.
[269] E. Arif, A. K. Solanki, and D. Nihalani, "Adriamycin susceptibility among C57BL/6 substrains," *Kidney Int.*, vol. 89, no. 3, pp. 721–723, 2016.

[270] C. L. Newman *et al.*, “Raloxifene improves skeletal properties in an animal model of cystic chronic kidney disease,” *Kidney Int.*, vol. 89, no. 1, pp. 95–104, 2016.
[271] Y. Imanishi *et al.*, “Phosphorus intake regulates intestinal function and polyamine metabolism in uremia,” *Kidney Int.*, vol. 49, no. 2, pp. 499–505, 1996.
[272] K. Doi and H. Rabb, “Impact of acute kidney injury on distant organ function: Recent findings and potential therapeutic targets,” *Kidney Int.*, vol. 89, no. 3, pp. 555–564, 2016.
[273] R. Rodríguez-Romo *et al.*, “AT1 receptor antagonism before ischemia prevents the transition of acute kidney injury to chronic kidney disease,” *Kidney Int.*, vol. 89, no. 2, pp. 363–373, 2016.
[274] Z. Kyossev, P. D. Walker, and W. B. Reeves, “Immunolocalization of NAD-dependent 11β-hydroxysteroid dehydrogenase in human kidney and colon,” *Kidney Int.*, vol. 49, no. 1, pp. 271–281, 1996.
[275] J. Brandt *et al.*, “Role of the complement membrane attack complex (C5b-9) in mediating experimental mesangioproliferative glomerulonephritis,” *Kidney Int.*, vol. 49, no. 2, pp. 335–343, 1996.
[276] C. M. Wyatt and T. B. Drüeke, “Fibroblast growth factor receptor 4: The missing link between chronic kidney disease and FGF23-induced left ventricular hypertrophy?,” *Kidney Int.*, vol. 89, no. 1, pp. 7–9, 2016.
[277] R. Baliga, Z. Zhang, M. Baliga, and S. V. Shah, “Evidence for cytochrome P-450 as a source of catalytic iron in myoglobinuric acute renal failure,” *Kidney Int.*, vol. 49, no. 2, pp. 362–369, 1996.
[278] E. Zaragatski *et al.*, “Vitamin K antagonism aggravates chronic kidney disease-induced neointimal hyperplasia and calcification in arterialized veins: Role of Vitamin K treatment?,” *Kidney Int.*, vol. 89, no. 3, pp. 601–611, 2016.
[279] J. Ma, A. Weisberg, J. P. Griffin, D. E. Vaughan, A. B. Fogo, and N. J. Brown, “Plasminogen activator inhibitor-1 deficiency protects against aldosterone-induced glomerular injury,” *Kidney Int.*, vol. 69, no. 6, pp. 1064–1072, 2006.
[280] S. Sachetelli *et al.*, “RAS blockade decreases blood pressure and proteinuria in transgenic mice overexpressing rat angiotensinogen gene in the kidney,” *Kidney Int.*, vol. 69, no. 6, pp. 1016–1023, 2006.
[281] C. D. Schuh *et al.*, “Long wavelength multiphoton excitation is advantageous for intravital kidney imaging,” *Kidney Int.*, vol. 89, no. 3, pp. 712–719, 2016.
[282] J. R. Chang *et al.*, “Intermedin1-53 attenuates vascular calcification in rats with chronic kidney disease by upregulation of α-Klotho,” *Kidney Int.*, vol. 89, no. 3, pp. 586–600, 2016.
[283] Y. J. Jing *et al.*, “P-Cresyl sulfate is associated with carotid arteriosclerosis in hemodialysis patients and promotes atherogenesis in apoE-/- mice,” *Kidney Int.*, vol. 89, no. 2, pp. 439–449, 2016.
[284] R. Nielsen, E. I. Christensen, and H. Birn, “Megalin and cubilin in proximal tubule protein reabsorption: From experimental models to human disease,” *Kidney Int.*, vol. 89, no. 1, pp. 58–67, 2016.
[285] G. Natarajan, D. Jeyachandran, D. Thanigachalam, R. Sakthirajan, T. Balasubramaniyan, and A. A. Kurien, “Myoglobinuric renal failure after a wasp attack,” *Kidney Int.*, vol. 89, no. 3, p. 725, 2016.
[286] N. Antunes *et al.*, “Fructose-1,6 diphosphate as a protective agent for experimental ischemic acute renal failure,” *Kidney Int.*, vol. 69, no. 1, pp. 68–72, 2006.
[287] P. J. D. Winyard *et al.*, “Deregulation of cell survival in cystic and dysplastic renal development,” *Kidney Int.*, vol. 49, no. 1, pp. 135–146, 1996.
[288] M. Christensen, A. W. Su, R. W. Snyder, A. Greco, J. H. Lipschutz, and M. P. Madaio, “Simvastatin protection against acute immune-mediated glomerulonephritis in mice,” *Kidney Int.*, vol. 69, no. 3, pp. 457–463, 2006.
[289] D. Portilla and M. D. Okusa, “T cells and T-cell receptors in acute renal failure,” *Kidney Int.*, vol. 69, no. 2, pp. 208–210, 2006.
[290] N. Yagihara *et al.*, “Variants in the SCN5A Promoter Associated With Various Arrhythmia

Phenotypes," *J. Am. Heart Assoc.*, vol. 5, no. 9, pp. 15–17, 2016.
[291] L. Dou and S. Burtey, "The harmful effect of indoxyl sulfate on neovascularization in chronic kidney disease," *Kidney Int.*, vol. 89, no. 3, pp. 532–534, 2016.
[292] V. Kliem *et al.*, "Mechanisms involved in the pathogenesis of tubulointerstitial fibrosis in 5/6-nephrectomized rats," *Kidney International*, vol. 49, no. 3. pp. 666–678, 1996.
[293] R. E. Tracy, J. P. Strong, W. P. Newman, G. T. Malcom, M. C. Oalmann, and M. A. Guzman, "Renovasculopathies of nephrosclerosis in relation to atherosclerosis at ages 25 to 54 years," *Kidney Int.*, vol. 49, no. 2, pp. 564–570, 1996.
[294] W. K. Bolton, A. M. Luo, P. Fox, W. May, and J. Fox, "Goodpasture's epitope in development of experimental autoimmune glomerulonephritis in rats," *Kidney Int.*, vol. 49, no. 2, pp. 327–334, 1996.
[295] N. Ueda, R. Baliga, and S. V. Shah, "Role of 'catalytic' iron in an animal model of minimal change nephrotic syndrome," *Kidney Int.*, vol. 49, no. 2, pp. 370–373, 1996.
[296] A. Linkermann, "Nonapoptotic cell death in acute kidney injury and transplantation," *Kidney Int.*, vol. 89, no. 1, pp. 46–57, 2016.
[297] H. Nishi, "Angiopoietin-like protein 2 and kidney fibrosis: Lessons from knockout mice," *Kidney Int.*, vol. 89, no. 2, pp. 272–274, 2016.
[298] M. C. Hu, "Klotho connects intermedin1-53to suppression of vascular calcification in chronic kidney disease," *Kidney Int.*, vol. 89, no. 3, pp. 534–537, 2016.
[299] D. L. Andress, "Vitamin D in chronic kidney disease: A systemic role for selective vitamin D receptor activation," *Kidney Int.*, vol. 69, no. 1, pp. 33–43, 2006.
[300] H. J. Anders, V. Ninichuk, and D. Schlondorff, "Progression of kidney disease: Blocking leukocyte recruitment with chemokine receptor CCR1 antagonists," *Kidney Int.*, vol. 69, no. 1, pp. 29–32, 2006.
[301] R. H. Weiss and P. Y. Lin, "Kidney cancer: Identification of novel targets for therapy," *Kidney Int.*, vol. 69, no. 2, pp. 224–232, 2006.
[302] Y. Liu, "Renal fibrosis: New insights into the pathogenesis and therapeutics," *Kidney Int.*, vol. 69, no. 2, pp. 213–217, 2006.
[303] S. C. Schiavi, "Fibroblast growth factor 23: The making of a hormone," *Kidney Int.*, vol. 69, no. 3, pp. 425–427, 2006.
[304] M. G. Costigan and W. E. Lindup, "Plasma clearance in the rat of a furan dicarboxylic acid which accumulates in uremia.," *Kidney Int.*, vol. 49, no. 3, pp. 634–8, Mar. 1996.
[305] A. C. McMahon, R. U. Naqvi, M. J. Hurst, A. E. G. Raine, and K. T. MacLeod, "Diastolic dysfunction and abnormality of the Na+/Ca2+exchanger in single uremic cardiac myocytes," *Kidney Int.*, vol. 69, no. 5, pp. 846–851, 2006.
[306] I. Nissim and J. M. Weinberg, "Glycine attenuates Fanconi syndrome induced by maleate or ifosfamide in rats.," *Kidney Int.*, vol. 49, no. 3, pp. 684–95, Mar. 1996.
[307] F. W. Tam *et al.*, "Differential expression of macrophage inflammatory protein-2 and monocyte chemoattractant protein-1 in experimental glomerulonephritis.," *Kidney Int.*, vol. 49, no. 3, pp. 715–21, Mar. 1996.
[308] K. H. Liang, F. Oveisi, and N. D. Vaziri, "Gene expression of hepatic cholesterol 7 alpha-hydroxylase in the course of puromycin-induced nephrosis.," *Kidney Int.*, vol. 49, no. 3, pp. 855–60, Mar. 1996.
[309] T. Fulpius, R. Lemoine, T. Berney, Y. Pastore, S. Moll, and S. Izui, "Polymorphonuclear leukocytes play a key role in the generation of 'wire-loop' lesions induced by a murine IgG3 rheumatoid factor.," *Kidney Int.*, vol. 49, no. 3, pp. 647–55, Mar. 1996.
[310] W. Gwinner, H. Scheuer, H. Haller, R. P. Brandes, and H. J. Groene, "Pivotal role of xanthine oxidase in the initiation of tubulointerstitial renal injury in rats with hyperlipidemia," *Kidney Int.*, vol. 69, no. 3, pp. 481–487, 2006.
[311] a Fornasieri and G. D'Amico, "Type II mixed cryoglobulinaemia, hepatitis C virus infection, and glomerulonephritis.," *Nephrol. Dial. Transplant*, vol. 11 Suppl 4, no. November, pp. 25–30, 1996.
[312] S. Sugiyama *et al.*, "Nephrology Dialysis Transplantation Advanced glycation end-products in

diabetic nephropathy," *Nephrol Dial Transpl.*, vol. 11, no. November, pp. 91–94, 1996.
[313] G. Zhang and A. M. El Nahas, "Nephrology Dialysis Transplantation The effect of rhubarb extract on experimental renal fibrosis," *Nephrol. Dial. Transplant.*, vol. 20, no. November, pp. 186–190, 1996.
[314] A. Hernández, A. Torres, M. T. Concepción, and E. Salido, "Parathyroid gland calcium receptor gene expression is not regulated by increased dietary phosphorus in normal and renal failure rats.," *Nephrol. Dial. Transpl.*, vol. 11 Suppl 3, no. November, pp. 11–14, 1996.
[315] A. Yoshifuji *et al.*, "Gut Lactobacillus protects against the progression of renal damage by modulating the gut environment in rats," *Nephrol. Dial. Transplant.*, vol. 31, no. 3, pp. 401–412, 2016.
[316] R. Birck *et al.*, "15-Deoxyspergualin and cyclophosphamide, but not mycophenolate mofetil, prolong survival and attenuate renal disease in a murine model of ANCA-associated crescentic nephritis," *Nephrol. Dial. Transplant.*, vol. 21, no. 1, pp. 58–63, 2006.
[317] P. K. Datta, S. Dhupar, and E. A. Lianos, "Regulatory effects of inducible nitric oxide synthase on cyclooxygenase-2 and heme oxygenase-1 expression in experimental glomerulonephritis," *Nephrol. Dial. Transplant.*, vol. 21, no. 1, pp. 51–57, 2006.
[318] R. Pey, M. Hafner, G. Schieren, J. Bach, and N. Gretz, "In vitro formation of cysts derived from a rat model of autosomal dominant polycystic kidney disease," *Nephrol Dial Transpl.*, vol. 11 Suppl 6, no. November, pp. 58–61, 1996.
[319] A. Moscovici, J. Bernheim, M. M. Popovtzer, and D. Rubinger, "Renal osteodystrophy in rats with reduced renal mass.," *Nephrol. Dial. Transplant*, vol. 11 Suppl 3, no. 7, pp. 146–52, Jul. 1996.
[320] C. Ronco, "Cell-cycle arrest biomarkers: The light at the end of the acute kidney injury tunnel," *Nephrol. Dial. Transplant.*, vol. 31, no. 1, pp. 3–5, 2016.
[321] S. M. Ka *et al.*, "Glomerular crescent-related biomarkers in a murine model of chronic graft versus host disease," *Nephrol. Dial. Transplant.*, vol. 21, no. 2, pp. 288–298, 2006.
[322] A. Mahiout, G. Ehlerding, and R. Brunkhorst, "Advanced glycation end-products in the peritoneal fluid and in the peritoneal membrane of continuous ambulant peritoneal dialysis patients," *Nephrol Dial Transpl.*, vol. 11 Suppl 5, no. November, pp. 2–6, 1996.
[323] G. E. Striker, R. D. Eastman, and L. J. Striker, "Diabetic nephropathy: molecular analysis of extracellular matrix and clinical studies update.," *Nephrol. Dial. Transplant*, vol. 11 Suppl 5, no. November, pp. 58–61, 1996.
[324] A. Nabokov, K. Amann, J. Wagner, F. Gehlen, K. Munter, and E. Ritz, "Influence of specific and non-specific endothelin receptor antagonists on renal morphology in rats with surgical renal ablation," *Nephrol Dial Transpl.*, vol. 11, no. 3, pp. 514–520, 1996.
[325] D. Chauveau and G. Choukroun, "Bence Jones proteinuria and myeloma kidney.," *Nephrol. Dial. Transplant*, vol. 11, no. 3, pp. 413–5, 1996.
[326] J. A. Kellum and L. S. Chawla, "Cell-cycle arrest and acute kidney injury: the light and the dark sides.," *Nephrol. Dial. Transplant*, vol. 31, no. 1, pp. 16–22, Jan. 2016.
[327] Y. Fujigaki *et al.*, "Kinetics and characterization of initially regenerating proximal tubules in S3 segment in response to various degrees of acute tubular injury," *Nephrol. Dial. Transplant.*, vol. 21, no. 1, pp. 41–50, 2006.
[328] V. M. Monnier *et al.*, "Structure of advanced Maillard reaction products and their pathological role," *Nephrol. Dial. Transplant.*, vol. 11, no. supp5, pp. 20–26, 1996.
[329] J. M. Organ *et al.*, "Reduced skeletal muscle function is associated with decreased fiber cross-sectional area in the Cy/+ rat model of progressive kidney disease," *Nephrol. Dial. Transplant.*, vol. 31, no. 2, pp. 223–230, 2016.
[330] M. Zareie, E. D. Keuning, P. M. ter Wee, C. G. Schalkwijk, R. H. J. Beelen, and J. van den Born, "Improved biocompatibility of bicarbonate/lactate-buffered PDF is not related to pH," *Nephrol. Dial. Transplant.*, vol. 21, no. 1, pp. 208–216, 2006.
[331] L. J. Striker and G. E. Striker, "Administration of AGEs in vivo induces extracellular matrix gene expression.," *Nephrol. Dial. Transplant*, vol. 11 Suppl 5, no. supp5, pp. 62–5, 1996.
[332] N. Nagano, S. Miyata, M. Abe, S. Wakita, N. Kobayashi, and M. Wada, "Sevelamer

hydrochloride reverses parathyroid gland enlargement via regression of cell hypertrophy but not apoptosis in rats with chronic renal insufficiency," *Nephrol. Dial. Transplant.*, vol. 21, no. 3, pp. 634–643, 2006.

[333] A. Ticinesi, A. Nouvenne, N. M. Maalouf, L. Borghi, and T. Meschi, "Salt and nephrolithiasis," *Nephrol. Dial. Transplant.*, vol. 31, no. 1, pp. 39–45, 2016.

[334] B. F. Schrijvers, A. Flyvbjerg, R. G. Tilton, N. H. Lameire, and A. S. De Vriese, "A neutralizing VEGF antibody prevents glomerular hypertrophy in a model of obese type 2 diabetes, the Zucker diabetic fatty rat," *Nephrol. Dial. Transplant.*, vol. 21, no. 2, pp. 324–329, 2006.

[335] S. Hagiwara *et al.*, "Eicosapentaenoic acid ameliorates diabetic nephropathy of type 2 diabetic KKAy/Ta mice: Involvement of MCP-1 suppression and decreased ERK1/2 and p38 phosphorylation," *Nephrol. Dial. Transplant.*, vol. 21, no. 3, pp. 605–615, 2006.

[336] B. Sampaio-Maia, M. Moreira-Rodrigues, P. Serrão, and M. Pestana, "Blunted renal dopaminergic system activity in puromycin aminonucleoside-induced nephrotic syndrome," *Nephrol. Dial. Transplant.*, vol. 21, no. 2, pp. 314–323, 2006.

[337] K. Tamagaki *et al.*, "Severe hyperparathyroidism with bone abnormalities and metastatic calcification in rats with adenine-induced uraemia," *Nephrol. Dial. Transplant.*, vol. 21, no. 3, pp. 651–659, 2006.

[338] J. Silver, E. Moallem, R. Kilav, E. Epstein, A. Sela, and T. Naveh-Many, "New insights into the regulation of parathyroid hormone synthesis and secretion in chronic renal failure.," *Nephrol. Dial. Transplant*, vol. 11 Suppl 3, no. November, pp. 2–5, 1996.

[339] G. Schieren, R. Pey, J. Bach, M. Hafner, and N. Gretz, "Nephrology Dialysis Transplantation Murine models of polycystic kidney disease," *Nephrol. Dial. Transplant.*, vol. 11, no. November, p. 3845, 1996.

[340] E. S. Lee *et al.*, "Oleanolic acid and N-acetylcysteine ameliorate diabetic nephropathy through reduction of oxidative stress and endoplasmic reticulum stress in a type 2 diabetic rat model," *Nephrol. Dial. Transplant.*, vol. 31, no. 3, pp. 391–400, 2016.

[341] H. Zhou *et al.*, "Urinary marker for oxidative stress in kidneys in cisplatin-induced acute renal failure in rats," *Nephrol. Dial. Transplant.*, vol. 21, no. 3, pp. 616–623, 2006.

[342] B. Rodriguez-Iturbe and R. J. Johnson, "Role of inflammatory cells in the kidney in the induction and maintenance of hypertension," *Nephrol. Dial. Transplant.*, vol. 21, no. 2, pp. 260–263, 2006.

[343] S. Zschiedrich *et al.*, "Secreted frizzled-related protein 4 predicts progression of autosomal dominant polycystic kidney disease," *Nephrol. Dial. Transplant.*, vol. 31, no. 2, pp. 284–289, 2016.

[344] G. Bledsoe *et al.*, "Kallikrein/kinin protects against gentamicin-induced nephrotoxicity by inhibition of inflammation and apoptosis," *Nephrol. Dial. Transplant.*, vol. 21, no. 3, pp. 624–633, 2006.

[345] P. R. Wahl, A. L. Serra, M. Le Hir, K. D. Molle, M. N. Hall, and R. P. Wüthrich, "Inhibition of mTOR with sirolimus slows disease progression in Han:SPRD rats with autosomal dominant polycystic kidney disease (ADPKD)," *Nephrol. Dial. Transplant.*, vol. 21, no. 3, pp. 598–604, 2006.

[346] Z. Hruby, D. Wendycz, W. Kopec, L. Czerchawski, M. Jozefowiak, and J. Rabczynski, "Effect of antiproteolytic drugs: epsilon-aminocaproic acid (EACA) and aprotinin on experimental anti-GBM nephritis," *Nephrol. Dial. Transplant.*, vol. 11, no. 1, pp. 32–39, 1996.

[347] N. Gretz *et al.*, "Nephrology Dialysis Transplantation Rat models of autosomal dominant polycystic kidney disease," *Nephrol Dial Transpl.*, vol. 11, no. 6, pp. 46–51, 1996.

[348] F. Thaiss, C. Haas, U. Helmchen, U. Wenzel, and R. A. K. Stahl, "Angiotensin-converting enzyme inhibition in experimental in-situ immune complex glomerulonephritis : influence on renal function , proteinuria , and morphology," *Nephrol. Dial. Transplant.*, no. November, pp. 40–46, 1996.

[349] M. Ketteler and J. Floege, "Calcification and the usual suspect phosphate: Still guilty but there are other guys behind the scenes," *Nephrol. Dial. Transplant.*, vol. 21, no. 1, pp. 33–35, 2006.

[350] C. Tzanno-Martins *et al.*, "The role of experimental chronic renal failure and aluminium

intoxication in cellular immune response," *Nephrol. Dial. Transplant.*, vol. 11, no. 3, pp. 474–480, Mar. 1996.
[351] E. Spandou *et al.*, "Erythropoietin attenuates renal injury in experimental acute renal failure ischaemic/reperfusion model," *Nephrol. Dial. Transplant.*, vol. 21, no. 2, pp. 330–336, 2006.
[352] M. Zeisberg, "Bone morphogenic protein-7 and the kidney: Current concepts and open questions," *Nephrol. Dial. Transplant.*, vol. 21, no. 3, pp. 568–573, 2006.
[353] C. P. Streather, J. S. Owen, B. M. Hendry, and J. E. Scoble, "Incubation of porcine high-density lipoprotein with the apical surface of LLC-PK1 renal tubular cells sustains the properties of orientated monolayers," *Nephrol Dial Transpl.*, vol. 11, no. 3, pp. 431–437, 1996.
[354] H. Minakuchi *et al.*, "The role of adipose tissue asymmetric dimethylarginine/dimethylarginine dimethylaminohydrolase pathway in adipose tissue phenotype and metabolic abnormalities in subtotally nephrectomized rats," *Nephrol. Dial. Transplant.*, vol. 31, no. 3, pp. 413–423, 2016.
[355] G. Schlieper, L. Schurgers, V. Brandenburg, C. Reutelingsperger, and J. Floege, "Vascular calcification in chronic kidney disease: An update," *Nephrol. Dial. Transplant.*, vol. 31, no. 1, pp. 31–39, 2016.
[356] D. A. Ishola *et al.*, "In mice, proteinuria and renal inflammatory responses to albumin overload are strain-dependent," *Nephrol. Dial. Transplant.*, vol. 21, no. 3, pp. 591–597, 2006.
[357] A. B. Fogo, "Progression versus regression of chronic kidney disease," *Nephrol. Dial. Transplant.*, vol. 21, no. 2, pp. 281–284, 2006.
[358] M. Eikmans, J. A. Aben, K. Koop, H. J. Baelde, E. de Heer, and J. A. Bruijn, "Genetic factors in progressive renal disease: The good ones, the bad ones and the ugly ducklings," *Nephrol. Dial. Transplant.*, vol. 21, no. 2, pp. 257–260, 2006.
[359] D. Brancaccio, M. Gallieni, and M. Cozzolino, "Treatment of hyperparathyroidism - Why is it crucial to control serum phosphate?," *Nephrol. Dial. Transplant.*, vol. 11, no. 3, pp. 420–423, 1996.
[360] G. Zhang and A. M. El Nahas, "Colchicine and the progression of experimental renal fibrosis," *Nephrol. Dial. Transplant.*, vol. 11, no. 3, pp. 559–560, Mar. 1996.
[361] "ICMJE | Recommendations | Clinical Trials." [Online]. Available: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. [Accessed: 13-Nov-2019].
[362] "ICMJE | About ICMJE | Clinical Trials Registration." [Online]. Available: http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/. [Accessed: 13-Nov-2019].
[363] "ICMJE | News & Editorials." [Online]. Available: http://www.icmje.org/news-and-editorials/update_2005.html. [Accessed: 13-Nov-2019].
[364] T. O. Carpenter *et al.*, "Burosumab therapy in children with X-linked hypophosphatemia," *N. Engl. J. Med.*, vol. 378, no. 21, pp. 1987–1998, 2018.
[365] G. Normand *et al.*, "AGE content of a protein load is responsible for renal performances: A pilot study," *Diabetes Care*, vol. 41, no. 6, pp. 1292–1294, 2018.
[366] J. C. Schefold *et al.*, "The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): A prospective randomized controlled trial," *Crit. Care*, vol. 18, no. 1, pp. 1–11, 2014.
[367] H. T. Silva *et al.*, "Planned randomized conversion from tacrolimus to sirolimus-based immunosuppressive regimen in de novo kidney transplant recipients," *Am. J. Transplant.*, vol. 13, no. 12, pp. 3155–3163, 2013.
[368] K. Y. Zhang *et al.*, "Cross-over study of influence of oral vitamin C supplementation on inflammatory status in maintenance hemodialysis patients," *BMC Nephrol.*, vol. 14, no. 1, 2013.
[369] Y. Matsumoto *et al.*, "Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients," *J. Am. Coll. Cardiol.*, vol. 63, no. 6, pp. 528–536, 2014.
[370] R. B. De Oliveira *et al.*, "Disturbances of Wnt/β-catenin pathway and energy metabolism in early CKD: Effect of phosphate binders," *Nephrol. Dial. Transplant.*, vol. 28, no. 10, pp. 2510–2517, 2013.
[371] M. Gaggl *et al.*, "Effect of oral sodium bicarbonate supplementation on progression of chronic

kidney disease in patients with chronic metabolic acidosis: Study protocol for a randomized controlled trial (SoBic-Study)," *Trials*, vol. 14, no. 1, 2013.
[372] P. A. McCullough *et al.*, "Cardiovascular toxicity of epoetin-alfa in patients with chronic kidney disease," *Am. J. Nephrol.*, vol. 37, no. 6, pp. 549–558, 2013.
[373] T. Ueda *et al.*, "Efficacy and safety of axitinib versus sorafenib in metastatic renal cell carcinoma: Subgroup analysis of Japanese patients from the global randomized phase 3 AXIS trial," *Jpn. J. Clin. Oncol.*, vol. 43, no. 6, pp. 616–628, 2013.
[374] O. Berwanger *et al.*, "Acetylcysteine for the prevention of renal outcomes in patients with diabetes mellitus undergoing coronary and peripheral vascular angiography: A substudy of the acetylcysteine for contrast-induced nephropathy trial," *Circ. Cardiovasc. Interv.*, vol. 6, no. 2, pp. 139–145, 2013.
[375] M. Pakfetrat, J. R. Shahroodi, A. A. Zolgadr, H. A. Larie, M. H. Nikoo, and L. Malekmakan, "Effects of zinc supplement on plasma homocysteine level in end-stage renal disease patients: A double-blind randomized clinical trial," *Biol. Trace Elem. Res.*, vol. 153, no. 1–3, pp. 11–15, 2013.
[376] Y. Chen, G. Wu, and M. Xu, "The effect of l-thyroxine substitution on oxidative stress in early-stage diabetic nephropathy patients with subclinical hypothyroidism: a randomized double-blind and placebo-controlled study," *Int. Urol. Nephrol.*, vol. 50, no. 1, pp. 97–103, 2018.
[377] A. Tasanarong, A. Vohakiat, P. Hutayanon, and D. Piyayotai, "New strategy of α-and γ-tocopherol to prevent contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures," *Nephrol. Dial. Transplant.*, vol. 28, no. 2, pp. 337–344, 2013.
[378] M. L. Carrió *et al.*, "Does post-cardiac surgery magnesium supplementation improve outcome?," *Magnes. Res.*, vol. 25, no. 4, pp. 159–167, 2012.
[379] M. M. Vickers *et al.*, "Association of hypomagnesemia with inferior survival in a phase III, randomized study of cetuximab plus best supportive care versus best supportive care alone: NCIC CTG/AGITG CO.17," *Ann. Oncol.*, vol. 24, no. 4, pp. 953–960, 2013.
[380] L. Samad and Z. Zaidi, "Tubed vs tubeless PCNL in children," *J. Pak. Med. Assoc.*, vol. 62, no. 9, pp. 892–896, 2012.
[381] J. J. Bissler *et al.*, "The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant cell astrocytoma," *Pediatr. Nephrol.*, vol. 33, no. 1, pp. 101–109, 2018.
[382] B. Pitt *et al.*, "Rationale and design of ARTS: A randomized, double-blind study of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease," *Eur. J. Heart Fail.*, vol. 14, no. 6, pp. 668–675, 2012.
[383] D. W. Johnson *et al.*, "Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes," *J. Am. Soc. Nephrol.*, vol. 23, no. 6, pp. 1097–1107, 2012.
[384] G. Wong *et al.*, "The risk of cancer in people with diabetes and chronic kidney disease," *Nephrol. Dial. Transplant.*, vol. 27, no. 8, pp. 3337–3344, 2012.
[385] J. R. Dillman *et al.*, "Comparative investigation of IV iohexol and iopamidol: Effect on renal function in low-risk outpatients undergoing CT," *Am. J. Roentgenol.*, vol. 198, no. 2, pp. 392–397, 2012.
[386] G. Choukroun *et al.*, "Correction of postkidney transplant anemia reduces progression of allograft nephropathy," *J. Am. Soc. Nephrol.*, vol. 23, no. 2, pp. 360–368, 2012.
[387] M. Maldonado-Avila *et al.*, "Comparison of three analgesic drug regimens with twelfth subcostal nerve block for pain control during extracorporeal shock wave lithotripsy," *Int. Urol. Nephrol.*, vol. 50, no. 1, pp. 49–53, 2018.
[388] M. Jalalzadeh, F. Mirzamohamadi, and P. Zargham, "Prevalence of helicobacter pylori in long-term dialysis patients," *Nephrourol. Mon.*, vol. 3, no. 1, pp. 8–14, 2011.
[389] D. K. Packham *et al.*, "Sulodexide fails to demonstrate renoprotection in overt type 2 diabetic nephropathy," *J. Am. Soc. Nephrol.*, vol. 23, no. 1, pp. 123–130, 2012.
[390] K. Kotani *et al.*, "Correlation between ischaemia-modified albumin and intermediate-density lipoprotein in haemodialysis patients with end-stage renal disease," *J. Int. Med. Res.*, vol. 39,

no. 4, pp. 1541–1545, 2011.
[391] K. Abdel-Kader, G. S. Fischer, J. Li, C. G. Moore, R. Hess, and M. L. Unruh, “Automated clinical reminders for primary care providers in the care of CKD: A small cluster-randomized controlled trial,” *Am. J. Kidney Dis.*, vol. 58, no. 6, pp. 894–902, 2011.
[392] S. H. Baek *et al.*, “Higher serum levels of osteoglycin are associated with all-cause mortality and cardiovascular and cerebrovascular events in patients with advanced chronic kidney disease,” *Tohoku J. Exp. Med.*, vol. 242, no. 4, pp. 281–290, 2017.
[393] N. Tangri *et al.*, “β-blockers for prevention of sudden cardiac death in patients on hemodialysis: A propensity score analysis of the HEMO study,” *Am. J. Kidney Dis.*, vol. 58, no. 6, pp. 939–945, 2011.
[394] A. J. Hoitsma, E. S. Woodle, D. Abramowicz, P. Proot, and Y. Vanrenterghem, “FTY720 combined with tacrolimus in de novo renal transplantation: 1-year, multicenter, open-label randomized study,” *Nephrol. Dial. Transplant.*, vol. 26, no. 11, pp. 3802–3805, 2011.
[395] M. E. Emans *et al.*, “Determinants of Red Cell Distribution Width (RDW) in cardiorenal patients: RDW is not related to erythropoietin resistance,” *J. Card. Fail.*, vol. 17, no. 8, pp. 626–633, 2011.
[396] M. C. J. Slagman *et al.*, “Vascular endothelial growth factor C levels are modulated by dietary salt intake in proteinuric chronic kidney disease patients and in healthy subjects,” *Nephrol. Dial. Transplant.*, vol. 27, no. 3, pp. 978–982, 2012.
[397] Y. Takatori *et al.*, “Icodextrin increases technique survival rate in peritoneal dialysis patients with diabetic nephropathy by improving body fluid management: A Randomized controlled trial,” *Clin. J. Am. Soc. Nephrol.*, vol. 6, no. 6, pp. 1337–1344, 2011.
[398] R. Smith-Bindman *et al.*, “Ultrasonography versus computed tomography for suspected nephrolithiasis,” *N. Engl. J. Med.*, vol. 371, no. 12, pp. 1100–1110, 2014.
[399] D. Nitsch, A. G. Mann, C. Bulpitt, P. J. Roderick, and A. Fletcher, “Impairment of kidney function and reduced quality-of-life in older people: A cross-sectional study,” *Age Ageing*, vol. 40, no. 3, pp. 381–387, 2011.
[400] J. Lee *et al.*, “B1-Adrenergic receptor polymorphisms and response to B-blockade in the African-American Study of Kidney Disease and Hypertension (AASK),” *Am. J. Hypertens.*, vol. 24, no. 6, pp. 694–700, 2011.
[401] F. T. Billings IV, S. K. Ball, L. J. Roberts, and M. Pretorius, “Postoperative acute kidney injury is associated with hemoglobinemia and an enhanced oxidative stress response,” *Free Radic. Biol. Med.*, vol. 50, no. 11, pp. 1480–1487, 2011.
[402] A. E. Barden *et al.*, “N-3 fatty acids reduce plasma 20-hydroxyeicosatetraenoic acid and blood pressure in patients with chronic kidney disease,” *J. Hypertens.*, vol. 33, no. 9, pp. 1947–1953, 2015.
[403] R. A. Posma *et al.*, “Effect of Metformin on Renal Function After Primary Percutaneous Coronary Intervention in Patients Without Diabetes Presenting with ST-elevation Myocardial Infarction: Data from the GIPS-III Trial,” *Cardiovasc. Drugs Ther.*, vol. 29, no. 5, pp. 451–459, 2015.
[404] D. Cooney *et al.*, “A pharmacist based intervention to improve the care of patients with CKD: A pragmatic, randomized, controlled trial,” *BMC Nephrol.*, vol. 16, no. 1, pp. 1–9, 2015.
[405] T. Higuchi *et al.*, “Effects of levocarnitine on brachial-ankle pulse wave velocity in hemodialysis patients: A randomized controlled trial,” *Nutrients*, vol. 6, no. 12, pp. 5992–6004, 2014.
[406] D. Vavrincova-Yaghi *et al.*, “Early posttransplant tryptophan metabolism predicts long-term outcome of human kidney transplantation,” *Transplantation*, vol. 99, no. 8, pp. e97–e104, 2015.
[407] K. Soji *et al.*, “Efficacy of add-on therapy of aliskiren to an angiotensin II receptor blocker on renal outcomes in advanced-stage chronic kidney disease: a prospective, randomized, open-label study,” *Clin. Exp. Nephrol.*, vol. 19, no. 4, pp. 631–638, 2015.
[408] Y. Luo *et al.*, “Remedial hydration reduces the incidence of contrast-induced nephropathy and short-term adverse events in patients with ST-segment elevation myocardial infarction: A

single-center, randomized trial," *Intern. Med.*, vol. 53, no. 20, pp. 2265–2272, 2014.
[409] D. W. Johnson *et al.*, "A randomized, placebo-controlled trial of pentoxifylline on erythropoiesis-stimulating agent hyporesponsiveness in anemic patients with CKD: The handling erythropoietin resistance with oxpentifylline (HERO) trial," *Am. J. Kidney Dis.*, vol. 65, no. 1, pp. 49–57, 2015.
[410] S. Turedi *et al.*, "The High Risk of Contrast-induced Nephropathy in Patients with Suspected Pulmonary Embolism Despite Three Different Prophylaxis: A Randomized Controlled Trial," *Acad. Emerg. Med.*, vol. 23, no. 10, pp. 1136–1145, 2016.
[411] K. J. Manley, "Will mouth wash solutions of water, salt, sodiumbicarbonate or citric acid improve upper gastrointestinal symptoms in chronic kidney disease," *Nephrology*, vol. 22, no. 3, pp. 213–219, 2017.
[412] A. Srivastava, S. Singh, I. R. Dhayal, and P. Rai, "A prospective randomized study comparing the four tract dilation methods of percutaneous nephrolithotomy," *World J. Urol.*, vol. 35, no. 5, pp. 803–807, 2017.
[413] P. H. Groop *et al.*, "Dipeptidyl peptidase-4 inhibition with linagliptin and effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: Rationale and design of the MARLINA-T2D™ trial," *Diabetes Vasc. Dis. Res.*, vol. 12, no. 6, pp. 455–462, 2015.
[414] M. Cavallin *et al.*, "Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: A randomized trial," *Hepatology*, vol. 62, no. 2, pp. 567–574, 2015.
[415] T. Takayama *et al.*, "Improvements in augmentation index and urinary albumin excretion with benidipine in hypertensive patients with chronic kidney disease," *Int. Heart J.*, vol. 57, no. 1, pp. 53–60, 2016.
[416] M. Rossi *et al.*, "Dietary protein-fiber ratio associates with circulating levels of indoxyl sulfate and p-cresyl sulfate in chronic kidney disease patients," *Nutr. Metab. Cardiovasc. Dis.*, vol. 25, no. 9, pp. 860–865, 2015.
[417] I. C. Macdougall, N. V. Dahl, K. Bernard, Z. Li, A. Batyky, and W. E. Strauss, "The Ferumoxytol for Anemia of CKD Trial (FACT) - a randomized controlled trial of repeated doses of ferumoxytol or iron sucrose in patients on hemodialysis: background and rationale," *BMC Nephrol.*, vol. 18, no. 1, pp. 1–10, 2017.
[418] R. L. Lins *et al.*, "Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: Results of a randomized clinical trial," *Nephrol. Dial. Transplant.*, vol. 24, no. 2, pp. 512–518, 2009.
[419] T. K. Choueiri *et al.*, "Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: The alliance A031203 CABOSUN trial," *J. Clin. Oncol.*, vol. 35, no. 6, pp. 591–597, 2017.
[420] A. Y. Wang *et al.*, "Angiotensin-converting enzyme inhibitor usage and acute kidney injury: A secondary analysis of RENAL study outcomes," *Nephrology*, vol. 19, no. 10, pp. 617–622, 2014.
[421] S. Williams *et al.*, "Physical Activity and Sleep Patterns in Hemodialysis Patients in a Suburban Environment," *Blood Purif.*, vol. 43, no. 1–3, pp. 235–243, 2017.
[422] I. C. Macdougall *et al.*, "Renal function in patients with non-dialysis chronic kidney disease receiving intravenous ferric carboxymaltose: An analysis of the randomized FIND-CKD trial," *BMC Nephrol.*, vol. 18, no. 1, pp. 1–18, 2017.
[423] R. Kullar, F. M. Wagenlehner, M. W. Popejoy, J. Long, B. Yu, and E. J. C. Goldstein, "Does moderate renal impairment affect clinical outcomes in complicated intra-abdominal and complicated urinary tract infections? Analysis of two randomized controlled trials with ceftolozane/tazobactam," *J. Antimicrob. Chemother.*, vol. 72, no. 3, pp. 900–905, 2017.
[424] C. Torino *et al.*, "The agreement between auscultation and lung ultrasound in hemodialysis patients: The LUST study," *Clin. J. Am. Soc. Nephrol.*, vol. 11, no. 11, pp. 2005–2011, 2016.
[425] M. M. Zedan *et al.*, "Montelukast as an add-on treatment in steroid dependant nephrotic syndrome, randomised-controlled trial," *J. Nephrol.*, vol. 29, no. 4, pp. 585–592, 2016.

[426] J. Gummer *et al.*, “Association between serum hepcidin-25 and primary resistance to erythropoiesis-stimulating agents in chronic kidney disease: a secondary analysis of the HERO trial,” *Nephrology*, vol. 22, no. 7, pp. 548–554, 2017.
[427] C. Baigent *et al.*, “Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease,” *Am. Heart J.*, vol. 160, no. 5, pp. 785–794, 2010.
[428] B. Escudier *et al.*, “Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): Final analysis of overall survival,” *J. Clin. Oncol.*, vol. 28, no. 13, pp. 2144–2150, 2010.
[429] R. Quinn and P. Ravani, “ACCESS HD pilot: A randomised feasibility trial Comparing Catheters with fistulas in Elderly patientS Starting haemodialysis,” *BMJ Open*, vol. 6, no. 11, 2016.
[430] G. R. Hetzel *et al.*, “Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: A prospective randomized multicentre trial,” *Nephrol. Dial. Transplant.*, vol. 26, no. 1, pp. 232–239, 2011.
[431] I. W. Wu, K. H. Hsu, C. Y. Sun, C. J. Tsai, M. S. Wu, and C. C. Lee, “Oral adsorbent AST-120 potentiates the effect of erythropoietin-stimulating agents on Stage 5 chronic kidney disease patients: A randomized crossover study,” *Nephrol. Dial. Transplant.*, vol. 29, no. 9, pp. 1719–1727, 2014.
[432] D. L. Zhang, J. Liu, S. Liu, Y. Zhang, and W. H. Liu, “The differences of asymmetric dimethylarginine removal by different dialysis treatments,” *Ren. Fail.*, vol. 32, no. 8, pp. 935–940, 2010.
[433] B. A. Zachara *et al.*, “The effect of selenium supplementation in the prevention of DNA damage in white blood cells of hemodialyzed patients: A pilot study,” *Biol. Trace Elem. Res.*, vol. 142, no. 3, pp. 274–283, 2011.
[434] M. Verduijn *et al.*, “Is fetuin-A a mortality risk factor in dialysis patients or a mere risk marker? A Mendelian randomization approach,” *Nephrol. Dial. Transplant.*, vol. 26, no. 1, pp. 239–245, 2011.
[435] K. Koyama *et al.*, “Randomized Controlled Trial of the Effect of Short-term Coadministration of Methylcobalamin and Folate on Serum ADMA Concentration in Patients Receiving Long-term Hemodialysis,” *Am. J. Kidney Dis.*, vol. 55, no. 6, pp. 1069–1078, 2010.
[436] T. Nakamura, N. Fujiwara, Y. Kawagoe, T. Sugaya, Y. Ueda, and H. Koide, “Effects of telmisartan and enalapril on renoprotection in patients with mild to moderate chronic kidney disease,” *Eur. J. Clin. Invest.*, vol. 40, no. 9, pp. 790–796, 2010.
[437] S. M. Ordaz-Medina *et al.*, “Is systemic inflammation of hemodialysis patients improved with the use of enalapril? results of a randomized, double-blinded, placebo-controlled clinical trial,” *ASAIO J.*, vol. 56, no. 1, pp. 37–41, 2010.
[438] A. Gulati, V. Sridhar, T. Bose, P. Hari, and A. Bagga, “Short-term efficacy of sevelamer versus calcium acetate in patients with chronic kidney disease stage 3-4,” *Int. Urol. Nephrol.*, vol. 42, no. 4, pp. 1055–1062, 2010.
[439] M. Kessler *et al.*, “C.E.R.A. once every 4 weeks in patients with chronic kidney disease not on dialysis: The ARCTOS extension study,” *Hemodial. Int.*, vol. 14, no. 2, pp. 233–239, 2010.
[440] T. A. Mori *et al.*, “The effects of ω3 fatty acids and coenzyme Q10 on blood pressure and heart rate in chronic kidney disease: A randomized controlled trial,” *J. Hypertens.*, vol. 27, no. 9, pp. 1863–1872, 2009.
[441] Y. Matsue *et al.*, “Early treatment with tolvaptan improves diuretic response in acute heart failure with renal dysfunction,” *Clin. Res. Cardiol.*, vol. 106, no. 10, pp. 802–812, 2017.
[442] M. Dessì *et al.*, “Influence of dialysis techniques and alternate vitamin supplementation on homocysteine levels in patients with known MTHFR genotypes,” *Clin. Exp. Nephrol.*, vol. 19, no. 1, pp. 140–145, 2015.
[443] J. M. Hofstra, A. J. W. Branten, J. J. J. M. Wirtz, T. C. Noordzij, P. W. G. Du Buf-Vereijken, and J. F. M. Wetzels, “Early versus late start of immunosuppressive therapy in idiopathic membranous nephropathy: A randomized controlled trial,” *Nephrol. Dial. Transplant.*, vol. 25, no. 1, pp. 129–136, 2010.

[444] A. Vasheghani-Farahani *et al.*, “Sodium Bicarbonate Plus Isotonic Saline Versus Saline for Prevention of Contrast-Induced Nephropathy in Patients Undergoing Coronary Angiography: A Randomized Controlled Trial,” *Am. J. Kidney Dis.*, vol. 54, no. 4, pp. 610–618, 2009.

[445] G. Simone *et al.*, “Laparoscopic versus Open Nephroureterectomy: Perioperative and Oncologic Outcomes from a Randomised Prospective Study,” *Eur. Urol.*, vol. 56, no. 3, pp. 520–526, 2009.

[446] V. Belozeroff, W. G. Goodman, L. Ren, and K. Kalantar-Zadeh, “Cinacalcet lowers serum alkaline phosphatase in maintenance hemodialysis patients,” *Clin. J. Am. Soc. Nephrol.*, vol. 4, no. 3, pp. 673–679, 2009.

[447] Y. Kaneshiro, A. Ichihara, M. Sakoda, A. Kurauchi-Mito, K. Kinouchi, and H. Itoh, “Add-on benefits of amlodipine and thiazide in nondiabetic chronic kidney disease stage 1/2 patients treated with valsartan,” *Kidney Blood Press. Res.*, vol. 32, no. 1, pp. 51–58, 2009.

[448] J. A. González-Fajardo, L. Mengibar, J. A. Brizuela, J. Castrodeza, and C. Vaquero-Puerta, “Effect of Postoperative Restrictive Fluid Therapy in the Recovery of Patients with Abdominal Vascular Surgery,” *Eur. J. Vasc. Endovasc. Surg.*, vol. 37, no. 5, pp. 538–543, 2009.

[449] S. Ouzouni, E. Kouidi, A. Sioulis, D. Grekas, and A. Deligiannis, “Effects of intradialytic exercise training on health-related quality of life indices in haemodialysis patients,” *Clin. Rehabil.*, vol. 23, no. 1, pp. 53–63, 2009.

[450] M. Renke *et al.*, “The effect of N-acetylcysteine on proteinuria and markers of tubular injury in non-diabetic patients with chronic kidney disease: A placebo-controlled, randomized, open, cross-over study,” *Kidney Blood Press. Res.*, vol. 31, no. 6, pp. 404–410, 2009.

[451] F. Fedele, N. Bruno, B. Brasolin, C. Caira, A. D’Ambrosi, and M. Mancone, “Levosimendan improves renal function in acute decompensated heart failure: Possible underlying mechanisms,” *Eur. J. Heart Fail.*, vol. 16, no. 3, pp. 281–288, 2014.

[452] N. S. Sung, “Central Challenges Facing the National Clinical Research Enterprise,” *JAMA*, vol. 289, no. 10, p. 1278, Mar. 2003.

[453] S. L. Zheng, F. T. Chan, E. Maclean, S. Jayakumar, and A. A. Nabeebaccus, “Reporting trends of randomised controlled trials in heart failure with preserved ejection fraction: a systematic review,” *Open Hear.*, vol. 3, no. 2, p. e000449, Jul. 2016.

[454] M. T. Sims, A. M. Bowers, J. M. Fernan, K. D. Dormire, J. M. Herrington, and M. Vassar, “Trial registration and adherence to reporting guidelines in cardiovascular journals,” *Heart*, vol. 104, no. 9, pp. 753–759, May 2018.

[455] L. Q. Liu, P. J. Morris, and L. H. M. Pengel, “Compliance to the CONSORT statement of randomized controlled trials in solid organ transplantation: A 3-year overview,” *Transpl. Int.*, vol. 26, no. 3, pp. 300–306, 2013.

[456] Y. Q. Huang, K. Traore, B. Ibrahim, M. J. Sewitch, and L. H. P. Nguyen, “Reporting quality of randomized controlled trials in otolaryngology: Review of adherence to the CONSORT statement,” *J. Otolaryngol. - Head Neck Surg.*, vol. 47, no. 1, pp. 1–7, 2018.

[457] M. Ethgen, L. Boutron, P. G. Steg, C. Roy, and P. Ravaud, “Quality of reporting internal and external validity data from randomized controlled trials evaluating stents for percutaneous coronary intervention,” *BMC Med. Res. Methodol.*, vol. 9, no. 1, p. 24, Dec. 2009.

[458] S. Adie, I. A. Harris, J. M. Naylor, and R. Mittal, “CONSORT Compliance in Surgical Randomized Trials,” *Ann. Surg.*, vol. 258, no. 6, pp. 872–878, Dec. 2013.

[459] D. Rikos, E. Dardiotis, A.-M. Aloizou, V. Siokas, E. Zintzaras, and G. M. Hadjigeorgiou, “Reporting Quality of Randomized Controlled Trials in Restless Legs Syndrome Based on the CONSORT Statement.,” *Tremor Other Hyperkinet. Mov. (N. Y).*, vol. 9, pp. 1–6, 2019.

[460] A. C. Plint *et al.*, “Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review,” *Med. J. Aust.*, vol. 185, no. 5, pp. 263–267, Sep. 2006.

[461] L. Turner *et al.*, “Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals,” *Cochrane Database Syst. Rev.*, no. 11, Nov. 2012.

[462] F. S. Collins and L. A. Tabak, “Policy: NIH plans to enhance reproducibility.,” *Nature*, vol. 505, no. 7485, pp. 612–3, Jan. 2014.

[463] H. V. Vesterinen, K. Egan, A. Deister, P. Schlattmann, M. R. MacLeod, and U. Dirnagl, “Systematic survey of the design, statistical analysis, and reporting of studies published in the 2008 volume of the Journal of Cerebral Blood Flow and Metabolism,” *J. Cereb. Blood Flow Metab.*, vol. 31, no. 4, pp. 1064–1072, 2011.

[464] K. H. J. Ting, C. L. Hill, and S. L. Whittle, “Quality of reporting of interventional animal studies in rheumatology: a systematic review using the ARRIVE guidelines.,” *Int. J. Rheum. Dis.*, vol. 18, no. 5, pp. 488–94, Jun. 2015.

[465] D. Baker, K. Lidster, A. Sottomayor, and S. Amor, “Two Years Later: Journals Are Not Yet Enforcing the ARRIVE Guidelines on Reporting Standards for Pre-Clinical Animal Studies,” *PLoS Biol.*, vol. 12, no. 1, 2014.

[466] J. E. N. Gulin, D. M. Rocco, and F. García-Bournissen, “Quality of Reporting and Adherence to ARRIVE Guidelines in Animal Studies for Chagas Disease Preclinical Drug Research: A Systematic Review,” *PLoS Negl. Trop. Dis.*, vol. 9, no. 11, p. e0004194, Nov. 2015.

[467] J. C. McGrath and E. Lilley, “Implementing guidelines on reporting research using animals (ARRIVE etc.): New requirements for publication in BJP,” *Br. J. Pharmacol.*, vol. 172, no. 13, pp. 3189–3193, 2015.

[468] V. Leung, F. Rousseau-Blass, G. Beauchamp, and D. S. J. Pang, “Arrive has not arrived: Support for the arrive (animal research: Reporting of in vivo experiments) guidelines does not improve the reporting quality of papers in animal welfare, analgesia or anesthesia,” *PLoS One*, vol. 13, no. 5, pp. 1–13, 2018.

[469] J. P. Briggs, “The Quality of Reporting of Kidney Research: A Challenge to JASN.,” *J. Am. Soc. Nephrol.*, vol. 30, no. 1, pp. 1–2, 2019.

[470] K. Hair, M. R. Macleod, and E. S. Sena, “A randomised controlled trial of an Intervention to Improve Compliance with the ARRIVE guidelines (IICARus),” *Res. Integr. Peer Rev.*, vol. 4, no. 1, pp. 1–17, 2019.

[471] J. S. Ross, G. K. Mulvey, E. M. Hines, S. E. Nissen, and H. M. Krumholz, “Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis,” *PLoS Med.*, vol. 6, no. 9, p. e1000144, Sep. 2009.

[472] N. Rasmussen, K. Lee, and L. Bero, “Association of trial registration with the results and conclusions of published trials of new oncology drugs,” *Trials*, vol. 10, no. 1, p. 116, Dec. 2009.

[473] “Animal Study Registry - Wikipedia.” [Online]. Available: https://en.wikipedia.org/wiki/Animal_Study_Registry. [Accessed: 21-Nov-2019].

[474] “Animal Study Registry.” [Online]. Available: https://www.animalstudyregistry.org/asr_web/index.action. [Accessed: 21-Nov-2019].

List of abbreviations

RCT	Randomized Controlled Trials
AKI	Acute Kidney Injury
GN	Glomerulonephritis
UTI	Urinary Tract Infections
RRT	Renal Replacement Therapies
PD	Peritoneal Dialysis
CKD	Chronic Kidney Injury
ESKD	End Stage KIdney Disease
IF	Impact Factor
JASN	Journal of the American Society of Nephrology
NDT	Nephrology Dialysis Transplantation
NEJM	The New England Journal of Medicine
AJKD	American Journal of Kidney Diseases
Lancet	The Lancet
Kidney Int.	Kidney International
ICMJE	International Committee of Medical Journal Editors
NC3R	The National Centre for the Replacement, Refinement and Reduction of Animals in Research

Acknowledgement

Mein herzlicher Dank gilt Herrn Prof. Dr. Hans-Joachim Anders für die Überlassung des interessanten Themas, für die ausdauernde und motivierende Unterstützung und Förderung auch über die Promotion hinaus. Ebenso geht mein Dank an Louise Wilkens für ihre Hilfe.

Mein besonderer Dank gilt meinen Eltern, die immer für mich da sind, und nie an mir gezweifelt haben.

Des Weiteren möchte ich mich bei Elena, Giorgos und Isidoros für ihre Unterstützung und Hilfe bei der Anfertigung dieser Doktorarbeit bedanken.

Eidesstattliche Versicherung

Tomidis Chatzimanouil, Markos Kyriakos

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