Systematic Review

Randomized Controlled Trials on Renin Angiotensin Aldosterone System Inhibitors in Chronic Kidney Disease Stages 3–5: Are They Robust? A Fragility Index Analysis

Ivana Capuano [1,*,†], Pasquale Buonanno [2,†], Eleonora Riccio [3], Antonio Bianco [4] and Antonio Pisani [1]

1   Department of Public Health, University of Naples "Federico II", 80131 Naples, Italy
2   Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", 80131 Naples, Italy
3   Institute for Biomedical Research and Innovation, National Research Council of Italy, 80125 Palermo, Italy
4   Interdepartmental Research Center for Arterial Hypertension and Associated Pathologies (CIRIAPA)-Hypertension Research Center, University of Naples "Federico II", 80131 Naples, Italy
*   Correspondence: ivanacapuano@libero.it; Tel.: +39-081-746-4521
†   These authors have contributed equally to this work and share first authorship.

Abstract: Inhibition of the renin-angiotensin-aldosterone system (RAAS) is broadly recommended in many nephrological guidelines to prevent chronic kidney disease (CKD) progression. This work aimed to analyze the robustness of randomized controlled trials (RCTs) investigating the renal and cardiovascular outcomes in CKD stages 3–5 patients treated with RAAS inhibitors (RAASi). We searched for RCTs in MEDLINE (PubMed), EMBASE databases, and the Cochrane register. Fragility indexes (FIs) for every primary and secondary outcome were calculated according to Walsh et al., who first described this novel metric, suggesting 8 as the cut-off to consider a study robust. Spearman coefficient was calculated to correlate FI to p value and sample size of statistically significant primary and secondary outcomes. Twenty-two studies met the inclusion criteria, including 80,455 patients. Sample size considerably varied among the studies (median: 1693.5, range: 73–17,276). The median follow-up was 38 months (range 24–58). The overall median of both primary and secondary outcomes was 0 (range 0–117 and range 0–55, respectively). The median of FI for primary and secondary outcomes with a p value lower than 0.05 was 6 (range: 1–117) and 7.5 (range: 1–55), respectively. The medians of the FI for primary outcomes with a p value lower than 0.05 in CKD and no CKD patients were 5.5 (range 1–117) and 22 (range 1–80), respectively. Only a few RCTs have been shown to be robust. Our analysis underlined the need for further research with appropriate sample sizes and study design to explore the real potentialities of RAASi in the progression of CKD.

Keywords: chronic kidney disease 1; renin-angiotensin-aldosterone system inhibitors; fragility index; randomized controlled trials; robustness

1. Introduction

Inhibition of the renin-angiotensin-aldosterone system (RAAS) is a key strategy in the treatment of hypertension, cardiovascular and renal diseases. In particular, current guidelines recommend the use of RAAS inhibitors (RAASi) as first-line antihypertensive therapy for patients with proteinuric chronic kidney disease (CKD) and diabetic nephropathy on the basis of randomized controlled trials (RCTs) [1]. These studies demonstrated that RAASi are superior to other antihypertensive drugs in delaying the nephropathy progression to end stage renal disease (ESRD), providing a significant renal and cardiovascular protection for CKD patients in the earlier stages [2,3]. Unfortunately, only a few RCTs are available on patients with advanced CKD 3–5 to define whether angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) can effectively delay ESRD and reduce mortality in this population [4]. Fragility index (FI) is a novel parameter proposed

by Walsh et al. to challenge the robustness of clinical studies. It can be used to test RCTs with dichotomous outcomes and 1:1 randomization of patients in control and experimental groups. FI is defined as the minimum number of patients of the experimental group that should pass from event to nonevent class in order to make a statistically significant difference between groups nonsignificant (i.e., to produce a *p* value lower than 0.05). A small FI indicates a more fragile study because its statistical significance is based on a small number of patients who experienced the treatment effect [5]. FI has been used so far to explore robustness in many clinical fields such as cardiology, urology, critical care, orthopedics, neurosurgery, and nephrology [6–12]. We performed the present study to explore this novel metric and assess the fragility of RCTs published on renal and cardiovascular outcomes of RAASi.

2. Materials and Methods

2.1. Participants

We included studies investigating patients aged ≥ 18 years with CKD 3–5 (defined as glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 or elevated serum creatinine level > 1.2 mg/dL) not under dialysis treatment.

2.2. Interventions and Comparators

Patients in the intervention group were treated with ACEIs and/or ARBs and they were compared to patients treated with placebo and/or control therapy, defined as therapy with drugs other than RAASi.

2.3. Systematic Review Protocol

We performed a systematic literature search to identify studies addressing our topic according to the recommendations of the Cochrane Collaboration, as well as the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for Reporting Systematic Reviews (PRISMA).

2.4. Data Sources and Search Strategy

We searched for RCTs in MEDLINE (PubMed), EMBASE databases, and the Cochrane register. The terms "chronic kidney disease", "randomized controlled trial", and all spellings of ACEi and ARBs were used individually or in different combinations to screen the literature. We also reviewed the references lists of identified trials to detect other potential studies to be included in our analysis. Missing data or more detailed information were requested from authors when not available in their publications. We included only articles in English without sample size restrictions. Articles were evaluated by two independent reviewers (P.B. and I.C.) and disagreements were resolved by discussion or by a third investigator (E.R.). This study was registered on SRDR+ (https://srdrplus.ahrq.gov/ (accessed on 10 October 2020)).

2.5. Study Selection and Data Extraction

After screening titles and abstracts, 45 studies reporting renal and cardiovascular outcomes of RAASi in patients with non-dialysis chronic kidney disease stages 3–5 were considered (Figure 1). We considered both studies focusing on patients suffering from CKD and studies conducted on the general population; in the latter case, we extracted the data about CKD patients. The full text of each article was reviewed by two authors and 22 articles were included in the present paper [13–34]. COPE and IDNT studies included three arms in their design, so we considered each of them as two different studies comparing two groups. In particular, the COPE study included a group treated with ARB, one group with beta-blockers, and one group with thiazide diuretics, and we considered two comparisons: ARB vs. beta-blockers and ARB vs. thiazide diuretics [31]. The IDNT study included a group treated with ARB, an active control (amlodipine), and a placebo group, and we considered the comparison ARB vs. active control and ARB vs. placebo [32].

Consequently, we had 24 comparisons from 22 articles. Twenty one studies were excluded for the following reasons: one study compared dual block of RAAS versus monotherapy with ACEi or ARB [35]; one study compared ARBs versus ACEi [36]; two were not in English language [37,38]; one did not specify the number of events [39]; one was without 1:1 randomization [40]; fifteen had no dichotomous outcome [41–55]. The data about clinical outcomes of RAASi treatment derived mostly from non-nephrological journals. The total population consisted of 80,455 individuals. We extracted information using standard data extraction forms, which included baseline patient characteristics, intervention, dose of drug, follow-up duration, outcome events, and adverse events. These data were extracted from both studies which were conducted only for CKD 3–5 patients and studies which included subgroup populations with CKD 3–5 at baseline. We used standard criteria (Cochrane risk of bias tool) to assess the inherent risk of bias in the trials, as shown in Table S4. Two investigators (I.C. and P.B.) independently undertook data extraction and quality assessment using a standardized approach. Any disagreements between the two investigators were resolved by consultation with a third reviewer (E.R.).
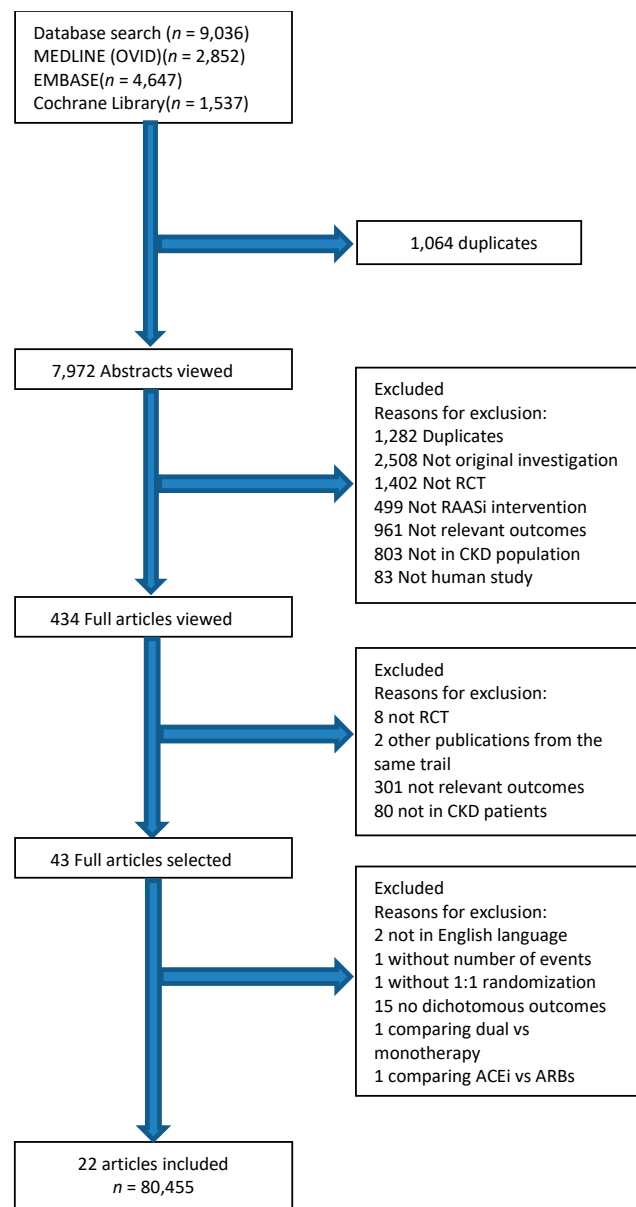

Figure 1. Flow diagram.

2.6. Risk of Bias

Sources of bias were divided into five domains (i.e., randomization, deviation from intended interventions, accounting for missing data, measurements, and selectively reporting results) and evaluated by the Cochrane Risk of Bias Tool 2.0. According to this tool, studies have been classified into three categories: low risk, some concerns, and high risk of bias. Studies with all the five domains at low risk were overall considered at low risk; one domain with some concerns led the study to be classified as affected by some concerns of bias. Trials with two domains with some concerns, or one domain with high risk of bias, were considered at high risk.

2.7. Data Analysis: Fragility Index Calculation

Fragility index was determined using the method of Walsh et al. for both primary and secondary outcomes: we first determined p value through Fisher's exact test and then we progressively moved patients in the experimental arm from the event to the nonevent group until p value became higher than 0.05. The minimum number of patients to make p value exceed 0.05 represents FI [5]. Correlations between FI and p value and sample size were investigated using the Spearman rank test. In order to normalize the FI on the basis of the sample size, we calculated the fragility quotient (FQ), which is the result of the ratio between the FI and the total sample size.

3. Results

3.1. Characteristics of Trials

Table 1 summarizes the RCTs' characteristics. Sample size considerably varied among the studies (median: 1693.5, range: 73–17,276). The median follow-up was 38 months (range 24–58). Fifty percent of the studies had a statistically significant p value and 14% of them presented a p value lower than 0.001. Fifty percent of the trials focused their attention only on CKD patients whereas the others investigated the effects of RAASi in the general population. The majority of studies were blinded, but only 12.5% of trials showed an adequate allocation concealment. Data were elaborated by intention-to-treat analysis in 54.5% of the included RCTs.

Table 1. Characteristics of included trials.

Trial Characteristics	Studies (*n*)
Sample size, median (min–max)	1693.5 (73–17,276)
Follow-up (months), median (min–max)	38 (24–58)
ACEi vs. placebo	8
ARB vs. placebo	4
ACEi vs. active control	5
ARB vs. active control	6
RAASi vs. active control or ACE-I vs. no treatment	1
Primary endpoint	
p-value	
>0.05	10
0.01–0.05	8
0.001–0.01	2
<0.001	4
Secondary endpoints	
All-cause mortality	
Reported *p*-value < 0.05	3
Total	8
Cardiovascular mortality	
Reported *p*-value < 0.05	2
Total	5

Table 1. *Cont.*

Trial Characteristics	Studies (*n*)
All-cause hospitalization	
Reported *p*-value < 0.05	2
Total	2
CV hospitalization	
Reported *p*-value < 0.05	2
Total	2
Major CV events	
Reported *p*-value < 0.05	4
Total	6
Major cerebrovascular events	
Reported *p*-value < 0.05	2
Total	5
New or worsening nephropathy	
Reported *p*-value < 0.05	1
Total	2
Allocation concealment	
None or unknown	21
Yes	1
Intention-to-treat analysis	
Yes	12
No or unclear	10
Blinding to treatment	
Yes	14
No or unclear	8
Journals	
Nephrological	5
General medical	17
Type of population	
CKD	10
CKD and no CKD	12

3.2. Fragility Index

Figure 2 shows the frequency of fragility index values for primary and secondary outcomes (panels A and B, respectively); for both primary (Figure 2A) and secondary (Figure 2B) outcomes, most of the studies showed a fragility index of 0. The overall median of primary outcomes fragility index was 0 (range 0–117) and for secondary outcomes it was also 0 (range 0–55). Medians of FI for primary and secondary outcomes with a *p* value lower than 0.05 were 6 (range: 1–117) and 7.5 (range: 1–55), respectively. Medians of FI for primary outcomes with a *p* value lower than 0.05 in CKD and no CKD patients were 5.5 (range 1–117) and 22 (range 1–80), respectively; this difference between medians of FI in CKD and no CKD populations was confirmed also for secondary outcomes with *p* value lower than 0.05: 5.5 (range 1–33) and 13.5 (range 1–55), respectively (Table 2) (see supplementary material for details about the fragility index for studies with a *p* value lower than 0.05; Table S2 and Table S3 report the fragility index for primary and secondary outcomes, respectively). The median (and range) of FQ for all the studies in CKD and no CKD patients with a statistically significant primary outcome (i.e., *p* < 0.05) were 7.9‰ (0.7–36‰) and 2.7‰ (0.3–11.1‰), respectively. A similar result was found for secondary outcomes: the median and range of FQ for studies with statistically significant results in CKD and no CKD patients were 8.3‰ (2.0–31.8‰) and 4.6 (1.2–19.1‰), respectively. Figure 3 reports the scatter plots of FI versus *p* value for both primary and secondary outcomes, which show a strong inverse correlation (rs = −0.7902 and −0.7196, respectively; *p* < 0.0001); a strong positive correlation was also found between FI and studies' sample size for primary and secondary outcomes (rs = 0.6315 and 0.6013, respectively; *p* < 0.01).
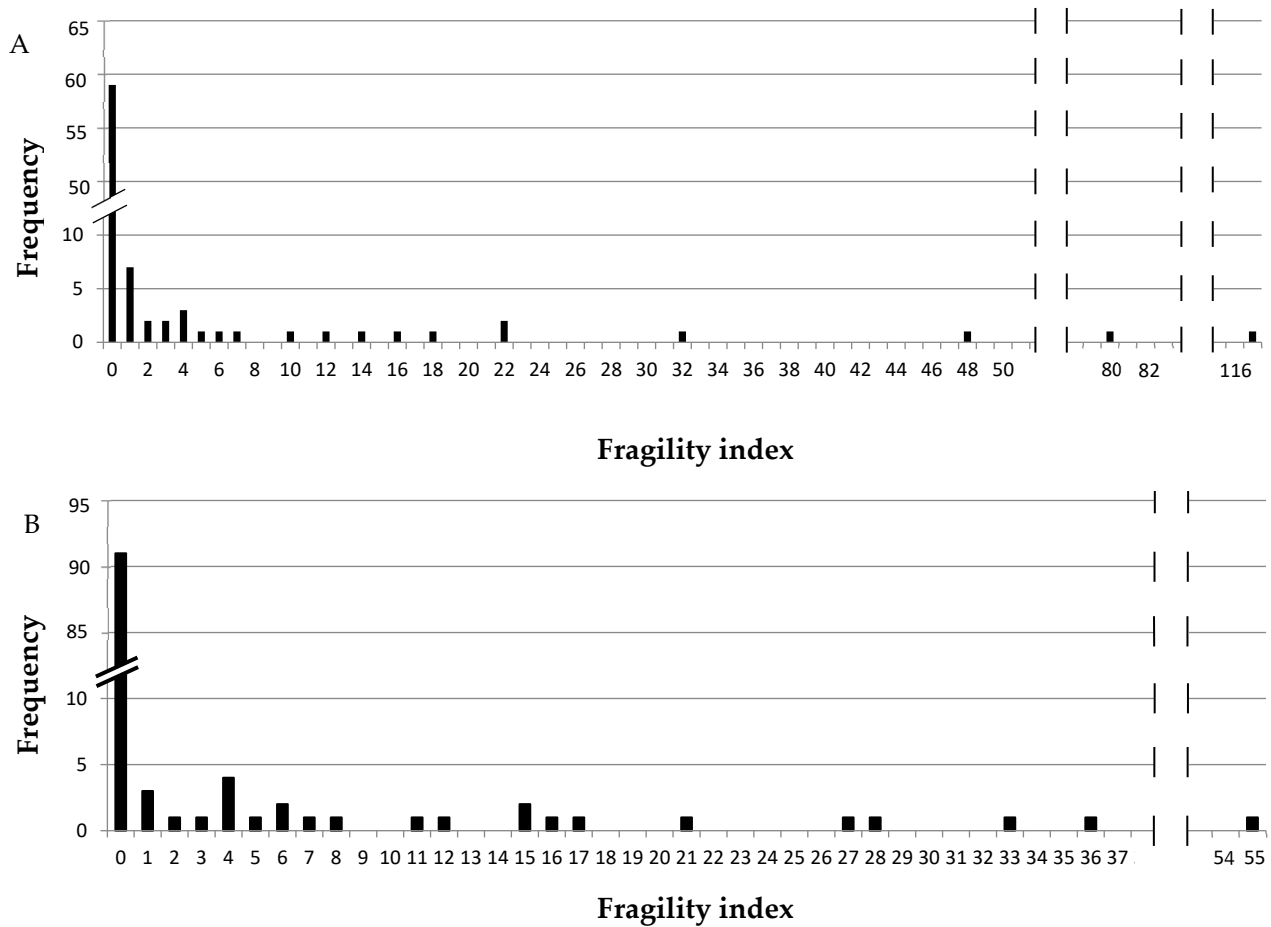
Figure 2. Frequency of fragility index values. Panels (**A,B**) show the absolute frequency of fragility index values for primary and secondary outcomes, respectively.

Table 2. Median of fragility index for primary and secondary outcomes with *p* value lower than 0.05 stratified by CKD and no CKD condition.

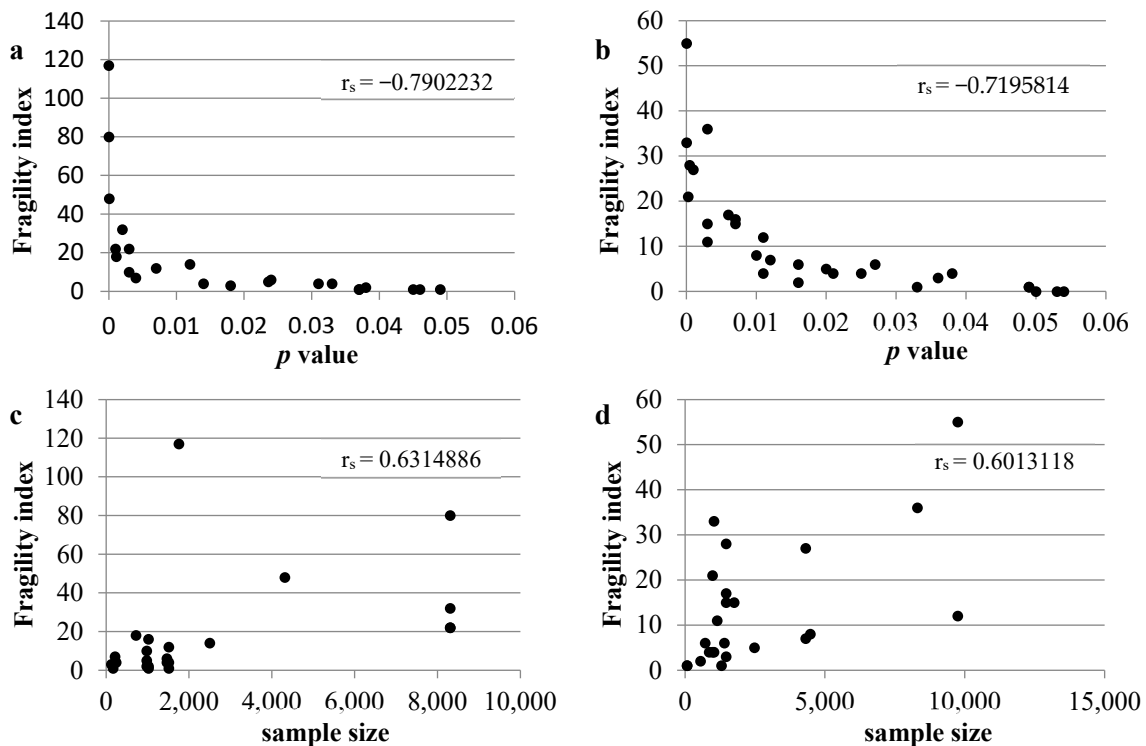| Outcome	FI Median (Range)
Primary	
CKD	5.5 (1–117)
no CKD	22 (1–80)
Secondary	
CKD	5.5 (1–33)
No CKD	13.5 (1–55)

Figure 3. Scatter plots of fragility index. Fragility index versus *p* value for primary (**a**) and secondary (**b**) outcomes; fragility index versus sample size for primary (**c**) and secondary (**d**) outcomes.

4. Discussion

The aim of this study was to explore the robustness of RCTs investigating clinical outcomes related to RAASi treatment in CKD stages 3–5. We found that sample size and follow up period showed great variability among the selected studies. Furthermore, only 50% of them reported significant primary and secondary outcomes. Fragility indexes of studies with significant *p* values were very low for both primary and secondary outcomes in CKD patients, whereas a higher FI was registered in the non-CKD population. In addition, FI was shown to strongly correlate with *p* value and sample size.

Our results agree with the previous observation of Strippoli GFM et al. which underlined the lack of adequate trial methods and study design in nephrological research and a poor number of RCTs compared to other internal medicine specialties; in particular, we found strikingly poor attention to allocation concealment and little use of intention-to-treat analysis [3]. Allocation concealment is often confused with blinding. Concealment is a practice to make the researcher unaware of the sequence of patient allocation so he cannot know the group to which the next patient will be assigned. Concealment avoids conscious or unconscious exclusion of patients who could not respond to researcher expectations if assigned to a particular experimental group. On the other hand, blinding refers to the unawareness of patients, care providers, and sometimes data analyzers, about the intervention administered to the participants; this practice reduces placebo effect in single blinded studies and also the misinterpretations of results by clinicians in double blinded trials [56].

Intention-to-treat analysis is another essential practice to avoid overestimations of treatment; this study design analyzes results, holding each participant and the corresponding outcome in his original group regardless of the treatment he is actually receiving, and regardless of withdrawal or deviation from the protocol. It allows researchers to preserve randomization, it avoids reduction of study power if a large number of patients withdraw from the protocol, and it prevents the exclusion of patients who are supposed not to respond to researcher expectations during the study [57].

One of the most important findings of our study is that the median FI for RCTs investigating RAASi treatment in CKD stages 3–5 population is very low, thus underlining the weakness of these trials. There is not a cut-off value for FI but 8 is generally deemed as the minimum value to consider a study robust. As with FI, there is no cutoff for FQ to distinguish robust vs. fragile studies, but it is intuitive that if only about 8 patients in a total sample size of 1000 patients (as in the case of primary outcome in studies investigating the role of RAASi in CKD patients) are sufficient to turn a significant outcome into a nonsignificant result, those studies cannot be considered very robust and, consequently, their findings should be considered with caution. On the contrary, RCTs including no CKD patients far exceed the FI cut off value of 8. This finding could be explained by the complexity of patients suffering from CKD, particularly in the advanced stages which are characterized by the presence of many comorbidities [58]. Our results did not differ from similar studies investigating FI in the RCTs of other specialties; Evaniew N. et al. and Ridgeon EE et al. reported a median FI of 2 in the field of spine surgery and critical care, respectively, while Narayan VM et al. calculated a median FI of 3 in urological RCTs [6,8,10]. Shochet LR analyzed nephrological RCTs published in five nephrology journals and five general journals for a period ranging from 2005 to 2014 and found that the 127 studies meeting the inclusion criteria had a median FI of 3 [12]. Our study mirrors the abovementioned results with a median FI of 5.5 both for primary and secondary outcomes. While the majority of studies indicate a lack of robustness for RCTs in many medical fields, fragility index values in cardiology and internal medicine are often higher than 8 [59]. It is noteworthy that we found robust FIs in studies with no CKD patients and that these findings come from studies conducted by cardiologists and specialists in internal medicine.

Our work underlined the need for studies enrolling an adequate number of patients; in fact, sample size was strongly correlated with FI, so larger studies were more robust. This finding is not obvious, as other works on fragility index did not find any relationship between FI and sample size [11]; however, the larger the sample size is, the smaller are the differences which can be significant in the statistical analysis, thus producing significant findings even with little difference in the number of events between the intervention and control groups. Our study showed that by increasing the sample size, the differences in events in the treatment group are augmented, thus producing a higher FI.

5. Conclusions

Our study demonstrated that the results of RCTs investigating the favorable renal and cardiovascular outcomes of RAASi in patients affected by CKD 3–5 need to be read with extreme caution. Further research with appropriate sample sizes and study design is needed to explore the real potentialities of RAASi in the progression of CKD.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am. J. Kidney Dis.* **2004**, *43* (Suppl. 1), S1–S290.
2. Taler, S.J.; Agarwal, R.; Bakris, G.L.; Flynn, J.T.; Nilsson, P.M.; Rahman, M.; Sanders, P.W.; Textor, S.C.; Weir, M.R.; Townsend, R.R.; et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for man-agement of blood pressure in CKD. *Am. J. Kidney Dis.* **2013**, *62*, 201–213. [CrossRef] [PubMed]
3. Xie, X.; Liu, Y.; Perkovic, V.; Li, X.; Ninomiya, T.; Hou, W.; Zhao, N.; Liu, L.; Lv, J.; Zhang, H.; et al. Renin-Angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: A Bayesian network meta-analysis of randomised clinical trials. *Am. J. Kidney Dis.* **2016**, *67*, 728–741. [CrossRef] [PubMed]
4. Strippoli, G.F.M.; Craig, J.; Schena, F.P. The Number, Quality, and Coverage of Randomized Controlled Trials in Nephrology. *J. Am. Soc. Nephrol.* **2004**, *15*, 411–419. [CrossRef] [PubMed]
5. Walsh, M.; Srinathan, S.K.; McAuley, D.F.; Mrkobrada, M.; Levine, O.; Ribic, C.; Molnar, A.O.; Dattani, N.D.; Burke, A.; Guyatt, G.; et al. The statistical significance of randomized controlled trial results is frequently fragile: A case for a Fragility Index. *J. Clin. Epidemiol.* **2014**, *67*, 622–628. [CrossRef]
6. Narayan, V.M.; Gandhi, S.; Chrouser, K.; Evaniew, N.; Dahm, P. The fragility of statistically significant findings from randomised controlled trials in the urological literature. *Br. J. Urol.* **2018**, *122*, 160–166. [CrossRef]
7. Ruzbarsky, J.J.; Khormaee, S.; Daluiski, A. The Fragility Index in Hand Surgery Randomized Controlled Trials. *J. Hand Surg.* **2019**, *44*, 698.e1–698.e7. [CrossRef]
8. Ridgeon, E.E.; Young, P.; Bellomo, R.; Mucchetti, M.; Lembo, R.; Landoni, G. The Fragility Index in Multicenter Randomized Controlled Critical Care Trials. *Crit. Care Med.* **2016**, *44*, 1278–1284. [CrossRef]
9. Vargas, M.; Buonano, P.; Marra, A.; Iacovazzo, C.; Servillo, G. Fragility Index in Multicenter Randomized Controlled Trials in Critical Care Medicine That Have Shown Reduced Mortality. *Crit. Care Med.* **2020**, *48*, e250–e251. [CrossRef]
10. Evaniew, N.; Files, C.; Smith, C.; Bhandari, M.; Ghert, M.; Walsh, M.; Devereaux, P.J.; Guyatt, G. The fragility of statistically significant findings from randomized trials in spine surgery: A systematic survey. *Spine J.* **2015**, *15*, 2188–2197. [CrossRef]
11. Docherty, K.F.; Campbell, R.T.; Jhund, P.S.; Petrie, M.C.; McMurray, J.J. How Robust Are Clinical Trials in Heart Failure? *Eur. Heart J.* **2017**, *38*, 338–345. [CrossRef] [PubMed]
12. Shochet, L.R.; Kerr, P.G.; Polkinghorne, K.R. The fragility of significant results underscores the need of larger randomized controlled trials in nephrology. *Kidney Int.* **2017**, *92*, 1469–1475. [CrossRef] [PubMed]
13. Cinotti, G.A.; Zucchelli, P.C. Effect of Lisinopril on the progression of renal insufficiency in mild proteinuric non-diabetic nephropathies. *Nephrol. Dial. Transplant.* **2001**, *16*, 961–966. [CrossRef] [PubMed]
14. MacGregor, M.S.; Deighan, C.J.; Rodger, R.C.; Boulton-Jones, J. A Prospective Open-Label Randomised Trial of Quinapril and/or Amlodipine in Progressive Non-Diabetic Renal Failure. *Nephron Exp. Nephrol.* **2005**, *101*, c139–c149. [CrossRef]
15. Zucchelli, P.; Zuccalà, A.; Borghi, M.; Fusaroli, M.; Sasdelli, M.; Stallone, C.; Sanna, G.; Gaggi, R. Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int.* **1992**, *42*, 452–458. [CrossRef]
16. Tobe, S.W.; Clase, C.M.; Gao, P.; McQueen, M.; Grosshennig, A.; Wang, X.; Teo, K.K.; Yusuf, S.; Mann, J.F. Cardiovascular and Renal Outcomes With Telmisartan, Ramipril, or Both in People at High Renal Risk. *Circulation* **2011**, *123*, 1098–1107. [CrossRef]
17. Marin, R.; Ruilope, L.M.; Aljama, P.; Aranda, P.; Segura, J.; Diez, J. A random comparison of fosinopril and nifedipine GITS in patients with primary renal disease. *J. Hypertens.* **2001**, *19*, 1871–1876. [CrossRef]
18. Tokmakova, M.P.; Skali, H.; Kenchaiah, S.; Braunwald, E.; Rouleau, J.L.; Packer, M.; Chertow, G.M.; Moyé, L.A.; Pfeffer, M.A.; Solomon, S.D. Chronic kidney disease, cardiovascular risk, and response to angioten-sin-converting enzyme inhibition after myocardial infarction: The Survival And Ventricular Enlargement (SAVE) study. *Circulation* **2004**, *110*, 3667–3673. [CrossRef]
19. Solomon, S.D.; Rice, M.M.; Jablonski, K.A.; Jose, P.; Domanski, M.; Sabatine, M.; Gersh, B.J.; Rouleau, J.; Pfeffer, M.A.; Braunwald, E. Renal Function and Effectiveness of Angiotensin-Converting Enzyme Inhibitor Therapy in Patients With Chronic Stable Coronary Disease in the Prevention of Events with ACE inhibition (PEACE) Trial. *Circulation* **2006**, *114*, 26–31. [CrossRef]
20. Perkovic, V.; Ninomiya, T.; Arima, H.; Gallagher, M.P.; Jardine, M.; Cass, A.; Neal, B.; MacMahon, S.; Chalmers, J. Chronic Kidney Disease, Cardiovascular Events, and the Effects of Perindopril-Based Blood Pressure Lowering: Data from the PROGRESS Study. *J. Am. Soc. Nephrol.* **2007**, *18*, 2766–2772. [CrossRef]
21. Bowling, C.B.; Sanders, P.W.; Allman, R.M.; Rogers, W.J.; Patel, K.; Aban, I.B.; Rich, M.W.; Pitt, B.; White, M.; Bakris, G.C.; et al. Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: Insights from the SOLVD Treatment trial. *Int. J. Cardiol.* **2012**, *167*, 151–156. [CrossRef]
22. Maschio, G.; Alberti, D.; Janin, G.; Locatelli, F.; Mann, J.F.E.; Motolese, M.; Ponticelli, C.; Ritz, E.; Zucchelli, P.; The Angiotensin-Converting–Enzyme Inhibition in Progressive Renal Insufficiency Study Group. Effect of the Angiotensin-Converting–Enzyme Inhibitor Benazepril on the Progression of Chronic Renal Insufficiency. *N. Engl. J. Med.* **1996**, *334*, 939–945. [CrossRef] [PubMed]
23. Mann, J.F.; Gerstein, H.; Pogue, J.; Bosch, J.; Yusuf, S.; for the HOPE Investigators. Renal Insufficiency as a Predictor of Cardiovascular Outcomes and the Impact of Ramipril: The HOPE Randomized Trial. *Ann. Intern. Med.* **2001**, *134*, 629–636. [CrossRef]

24. Heerspink, H.J.L.; Ninomiya, T.; Perkovic, V.; Woodward, M.; Zoungas, S.; Cass, A.; Cooper, M.; Grobbee, D.E.; Mancia, G.; Mogensen, C.E.; et al. Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease. *Eur. Heart J.* **2010**, *31*, 2888–2896. [CrossRef] [PubMed]

25. Hou, F.F.; Zhang, X.; Zhang, G.H.; Xie, D.; Chen, P.Y.; Zhang, W.R.; Jiang, J.P.; Liang, M.; Wang, G.B.; Liu, Z.R.; et al. Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency. *N. Engl. J. Med.* **2006**, *354*, 131–140. [CrossRef] [PubMed]

26. Kasanuki, H.; Hagiwara, N.; Hosoda, S.; Sumiyoshi, T.; Honda, T.; Haze, K.; Nagashima, M.; Yamaguchi, J.-I.; Origasa, H.; Urashima, M.; et al. Angiotensin II receptor blocker-based vs. non-angiotensin II receptor blocker-based therapy in patients with angiographically documented coronary artery disease and hypertension: The Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE). *Eur. Heart J.* **2009**, *30*, 1203–1212. [CrossRef]

27. Saruta, T.; Hayashi, K.; Ogihara, T.; Nakao, K.; Fukui, T.; Fukiyama, K.; for the CASE-J Study Group. Effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease: Subanalysis of the CASE-J Study. *Hypertens. Res.* **2009**, *32*, 505–512. [CrossRef]

28. Nakamura, T.; Kanno, Y.; Takenaka, T.; Suzuki, H. An Angiotensin Receptor Blocker Reduces the Risk of Congestive Heart Failure in Elderly Hypertensive Patients with Renal Insufficiency. *Hypertens. Res.* **2005**, *28*, 415–423. [CrossRef]

29. Imai, E.; Chan, J.C.N.; Ito, S.; Yamasaki, T.; Kobayashi, F.; Haneda, M.; Makino, H.; for the ORIENT study investigators. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: A multicentre, randomised, placebo-controlled study. *Diabetologia* **2011**, *54*, 2978–2986. [CrossRef]

30. Brenner, B.M.; Cooper, M.E.; De Zeeuw, D.; Keane, W.F.; Mitch, W.E.; Parving, H.-H.; Remuzzi, G.; Snapinn, S.M.; Zhang, Z.; Shahinfar, S. Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. *N. Engl. J. Med.* **2001**, *345*, 861–869. [CrossRef]

31. Rakugi, H.; Ogihara, T.; Umemoto, S.; Matsuzaki, M.; Matsuoka, H.; Shimada, K.; Higaki, J.; Ito, S.; Kamiya, A.; et al.; for the Combination Therapy of Hypertension to Prevent Cardiovascular Events Trial Group. Combination therapy for hypertension in patients with CKD: A subanalysis of the Combination Therapy of Hypertension to Prevent Cardiovascular Events trial. *Hypertens. Res.* **2013**, *36*, 947–958. [CrossRef] [PubMed]

32. Berl, T.; Hunsicker, L.G.; Lewis, J.B.; Pfeffer, M.A.; Porush, J.G.; Rouleau, J.-L.; Drury, P.L.; Esmatjes, E.; Hricik, D.; Parikh, C.; et al. Cardiovascular Outcomes in the Irbesartan Diabetic Nephropathy Trial of Patients with Type 2 Diabetes and Overt Nephropathy. *Ann. Intern. Med.* **2003**, *138*, 542–549. [CrossRef] [PubMed]

33. Rahman, M.; Pressel, S.; Davis, B.R.; Nwachuku, C.; Wright, J.T.; Whelton, P.K.; Barzilay, J.; Batuman, V.; Eckfeldt, J.H.; Farber, M.A.; et al. Cardiovascular Outcomes in High-Risk Hypertensive Patients Stratified by Baseline Glomerular Filtration Rate. *Ann. Intern. Med.* **2006**, *144*, 172–180. [CrossRef] [PubMed]

34. Mimura, T.; Takenaka, T.; Kanno, Y.; Moriwaki, K.; Okada, H.; Suzuki, H. Vascular compliance is secured under angiotensin inhibition in non-diabetic chronic kidney diseases. *J. Hum. Hypertens.* **2007**, *22*, 38–47. [CrossRef] [PubMed]

35. Juarez, G.F.; Luño, J.; Barrio, V.; de Vinuesa, S.G.; Praga, M.; Goicoechea, M.; Cachofeiro, V.; Nieto, J.; Vega, F.F.; Tato, A.; et al. Effect of Dual Blockade of the Renin-Angiotensin System on the Progression of Type 2 Diabetic Nephropathy: A Randomized Trial. *Am. J. Kidney Dis.* **2013**, *61*, 211–218. [CrossRef]

36. Hou, F.F.; Xie, D.; Zhang, X.; Chen, P.Y.; Zhang, W.R.; Liang, M.; Guo, Z.J.; Jiang, J.P. Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: A Randomized Controlled Study of Benazepril and Losartan in Chronic Renal Insufficiency. *J. Am. Soc. Nephrol.* **2007**, *18*, 1889–1898. [CrossRef]

37. Peng, T.; Hu, S.; Guo, L.; Yang, X.D.; Xia, Q.; Li, X.H.; Jiang, P.; Pei, F.; Song, J. Comparison of the renoprotective effects of benidipine and valsartan in patients with essential hypertension with proteinuria. *Chin. J. Cardiol.* **2010**, *38*, 20–22.

38. Zhang, G.H.; Hou, F.F.; Zhang, X.; Liu, Q.F. Can angiotensin-converting enzyme inhibitor be used in chronic kidney disease patients with serum creatinine level greater than 266 micromol/L? *Zhonghua Nei Ke Za Zhi* **2005**, *44*, 592–596. (In Chinese)

39. Fox, K.M. European trial on reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: Randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* **2003**, *362*, 782–788. [CrossRef]

40. Heagerty, A.; Yusuf, S.; Teo, K.K.; Pogue, J.; Dyal, L.; Copland, I.; Schumacher, H.; Dagenais, G.; Sleight, P.; Anderson, C. Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. *N. Engl. J. Med.* **2008**, *358*, 1547–1559. [CrossRef]

41. Tong, P.C.Y.; Ko, G.T.C.; Chan, W.-B.; Ma, R.C.W.; So, W.Y.; Lo, M.K.W.; Lee, K.-F.; Ozaki, R.; Chow, C.-C.; Cockram, C.-S. The efficacy and tolerability of fosinopril in Chinese type 2 diabetic patients with moderate renal insufficiency. *Diabetes Obes. Metab.* **2006**, *8*, 342–347. [CrossRef] [PubMed]

42. Ruggenenti, P.; Perna, A.; Gherardi, G.; Garini, G.; Zoccali, C.; Salvadori, M.; Scolari, F.; Schena, F.P.; Remuzzi, G. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* **1999**, *354*, 359–364. [CrossRef]

43. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* **1997**, *349*, 1857–1863. [CrossRef]

44. Ihle, B.U. Whitworth JA, Shahinfar S, Cnaan A, Kincaid-Smith PS, Becker GJ. Angiotensin-converting enzyme inhibition in nondiabetic progressive renal insufficiency: A controlled double-blind trial. *Am. J. Kidney Dis.* **1996**, *27*, 489–595. [CrossRef]

45. Kanno, Y.; Takenaka, T.; Nakamura, T.; Suzuki, H. Add-On Angiotensin Receptor Blocker in Patients Who Have Proteinuric Chronic Kidney Diseases and Are Treated with Angiotensin-Converting Enzyme Inhibitors. *Clin. J. Am. Soc. Nephrol.* **2006**, *1*, 730–737. [CrossRef]

46. Esnault, V.L.; Brown, E.A.; Apetrei, E.; Bagon, J.; Calvo, C.; Dechatel, R.; Holdaas, H.; Krcmery, S.; Kobalava, Z. The effects of amlodipine and enalapril on renal function in adults with hypertension and nondiabetic nephropathies: A 3-year, randomized, multicenter, double-blind, placebo-controlled study. *Clin. Ther.* **2008**, *30*, 482–498. [CrossRef] [PubMed]

47. Wright, J.J.T.; Bakris, G.; Greene, T.; Agodoa, L.Y.; Appel, L.J.; Charleston, J.; Cheek, D.; Douglas-Baltimore, J.G.; Gassman, J.; Glassock, R.; et al. Effect of Blood Pressure Lowering and Antihypertensive Drug Class on Progression of Hypertensive Kidney DiseaseResults From the AASK Trial. *JAMA* **2002**, *288*, 2421–2431. [CrossRef]

48. Herlitz, H.; Harris, K.; Risler, T.; Boner, G.; Bernheim, J.; Chanard, J.; Aurell, M. The effects of an ACE inhibitor and a calcium antagonist on the progression of renal disease: The Nephros Study. *Nephrol. Dial. Transplant.* **2001**, *16*, 2158–2165. [CrossRef]

49. Kumagai, H.; Hayashi, K.; Kumamaru, H.; Saruta, T. Amlodipine is comparable to angiotensin-converting enzyme inhibitor for long-term renoprotection in hypertensive patients with renal dysfunction: A one-year, prospective, randomized study. *Am. J. Hypertens.* **2000**, *13*, 980–985. [CrossRef]

50. Hannedouche, T.; Landais, P.; Goldfarb, B.; Esper, N.E.; Fournier, A.; Godin, M.; Durand, D.; Chanard, J.; Mignon, F.; Suc, J.-M.; et al. Randomised controlled trial of enalapril and blockers in non- diabetic chronic renal failure. *BMJ* **1994**, *309*, 833–837. [CrossRef]

51. Sawicki, P.T.; Berger, M. Renal protective effect of enalapril in diabetic nephropathy. *BMJ* **1992**, *304*, 841–842. [CrossRef] [PubMed]

52. Kamper, A.-L.; Strandgaard, S.; Leyssac, P.P. Effect of Enalapril on the Progression of Chronic Renal Failure. *Am. J. Hypertens.* **1992**, *5*, 423–430. [CrossRef] [PubMed]

53. Fogari, R.; Zoppi, A.; Corradi, L.; Mugellini, A.; Lazzari, P.; Preti, P.; Lusardi, P. Long-term effects of ramipril and nitrendipine on albuminuria in hypertensive patients with type II diabetes and impaired renal function. *J. Hum. Hypertens.* **1999**, *13*, 47–53. [CrossRef] [PubMed]

54. Shoda, J.; Kanno, Y.; Suzuki, H. A Fiveyear Comparison of the Renal Protective Effects of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Patients with NonDiabeticNephropathy. *Intern. Med.* **2006**, *45*, 193–198. [CrossRef] [PubMed]

55. Bakris, G.L.; Copley, J.B.; Vicknair, N.; Sadler, R.; Leurgans, S. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int.* **1996**, *50*, 1641–1650. [CrossRef]

56. Schulz, K.F.; Altman, D.G.; Moher, D.; CONSORT Group. WITHDRAWN: CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *Int. J. Surg.* **2010**, *152*, 726–732. [CrossRef]

57. Ranganathan, P.; Pramesh, C.; Aggarwal, R. Common pitfalls in statistical analysis: Intention-to-treat versus per-protocol analysis. *Perspect. Clin. Res.* **2016**, *7*, 144–146. [CrossRef]

58. Fraser, S.D.S.; Roderick, P.J.; May, C.R.; McIntyre, N.; McIntyre, C.W.; Fluck, R.J.; Shardlow, A.; Taal, M.W. The burden of comorbidity in people with chronic kidney disease stage 3: A cohort study. *BMC Nephrol.* **2015**, *16*, 193. [CrossRef]

59. Khan, M.S.; Ochani, R.K.; Shaikh, A.; Usman, M.S.; Yamani, N.; Khan, S.U.; Murad, M.H.; Mandrola, J.; Doukky, R.; Krasuski, R.A. Fragility Index in Cardiovascular Randomized Controlled Trials. *Circ. Cardiovasc. Qual. Outcomes* **2019**, *12*, e005755. [CrossRef]