Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2021 Nov 24; 9(F):608-612.
https://doi.org/10.3889/oamjms.2021.7596
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Systematic Review Article*

Efficacy and Safety of Candesartan 16 mg versus 64 mg Candesartan in Renal Disease Patients with Proteinuria: A Systematic Review and Meta-analysis

Andry Gonius[1]*, Arnaz Adisaputra[2], Farahdina Farahdina[3], Salsabila Nabilah Rifdah[6], Astried Indrasari[4], Artaria Tjempakasari[5]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [2]Department of General Medicine, Faculty of Medicine, Brawijaya University, Malang, Indonesia; [3]Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; [4]Department of Internal Medicine, Abdoel Wahab Syahranie General Hospital, Samarinda, Indonesia; [5]Department of Internal Medicine, Division of Nephrology, Dr Soetomo Hospital, Surabaya, Indonesia; [6]Department of General Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Edited by: Ksenija Bogoeva-Kostovska
Citation: Gonius A, Adisaputra A, Farahdina F, Rifdah SN, Indrasari A, Tjempakasari A. Efficacy and Safety of Candesartan 16 mg versus 64 mg Candesartan in Renal Disease Patients with Proteinuria: A Systematic Review and Meta-analysis. Open Access Maced J Med Sci. 2021 Nov 24; 9(F):608-612. https://doi.org/10.3889/oamjms.2021.7596
Keywords: Candesartan; Proteinuria; Blood pressure; Efficacy; Safety
***Correspondence:** Andry Gonius, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia. E-mail: andrygonius93@gmail.com
Received: 13-Oct-2021
Revised: 09-Nov-2021
Accepted: 22-Nov-2021

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Chronic kidney disease (CKD) is a global health burden in the world. One of the complications of CKD is proteinuria. Candesartan is a drug that is often used in CKD patients to improve proteinuria. There are several studies that suggest that using a higher dose of candesartan can further improve its effectiveness in reducing proteinuria in CKD patient

AIM: This paper is aimed to review the effectiveness and safety at a supramaximal dose of 64 mg to a dose of 16 mg of candesartan.

METHODS: We performed a literature search using PubMed, SCOPUS, EuropePMC, ProQuest, and Cochrane Central Databases using these keywords: "candesartan" and "16 mg" and "64 mg" or "proteinuria renal disease" or "albuminuria" and "blood pressure" that were published within the year of 1980–2021. Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) protocol were used to conduct this meta-analysis. We included randomized controlled trials, prospective cohort, retrospective or clinical observational evaluating the effect of candesartan in 16 mg or 64 mg in proteinuria renal disease patients regardless of clinical status. Non-randomized, controlled trials reporting efficacy were included if these trials were in the scope of our topic. Duplicate studies were excluded. Dichotomous variables were analyzed with the Mantel-Haenszel statistical method using risk ratio as the summary statistic and reported with 95% confidence intervals (CIs).

RESULTS: Forty-six studies were initially generated using our search keyword. After applying inclusion and exclusion criteria, we included two studies in our analysis. Our pooled analysis found that candesartan 16mg dosage administration, compared to 64mg, was not associated with proteinuria reduction (std mean diff: −10.92 [95% CI: −40.09–18.26], p = 0.46).

CONCLUSION: Candesartan supramaximal dosage 64 mg did not differ significantly in proteinuria reduction and blood pressure reduction against candesartan 16 mg. More studies are needed to determine this efficacy and safety.

Introduction

Chronic kidney disease (CKD) is a global health burden in the world. About 13.4% world population suffered from CKD and approximately 4902–7083 million needing hemodialysis because of CKD[1]. Reduction in renal function has been associated with proteinuria, elevated blood pressure, and deterioration of quality of life. Candesartan is one of angiotensin receptor blocker (ARB) which can decrease blood pressure and improve proteinuria, which are beneficial in patient with CKD[2].

Anti-fibrotic and antihypertensive effect of candesartan seems related with dosage of candesartan. Study from Schmieder *et al.* found that candesartan at supramaximal dose (64 mg) significantly reduced proteinuria compared to standard dose (16 mg). Beneficial effect of high dosage of ARB (Angiotensin Receptor Blocker) was investigated in several studies such as IRMA2 trial and Supra Maximal Atacand Renal Trial (SMART) trial [3], [4]. Candesartan cilexetil is a prodrug that is distributed globally and metabolized to candesartan during absorption in gastrointestinal tract. Maximal dosage approved by FDA is 32 mg and supramaximal dosage of 64 mg has not been approved [5]. Despite that, some studies have explored the possibilities of using higher ARB dosage to improve proteinuria in CKD patients. ROAD trial reported that by titrating losartan upward to its maximum dosage (200 mg), there was a greater proteinuria reduction compared to conventional dose. This study also reported that this high dose treatment was generally well-tolerated [6]. A study from Aranda, *et al.* found that long-term administration of high dose telmisartan (80 mg twice daily) could decrease proteinuria better than standard dose (80 mg once daily) in nondiabetic hypertensive nephropathy [7]. Therefore, we postulated that supramaximal dose of candesartan (64 mg) can induced greater proteinuria reduction compared to standard dose, as seen in other ARBs.

This systematic review and meta-analysis will compare candesartan 16 mg with 64 mg dosage in correlation with proteinuric renal disease. The primary outcome of this study is to compare candesartan 16 mg with 64 mg related proteinuria/albuminuria excretion. The secondary outcome is blood pressure improvement.

Methods

We systematically searched PubMed, SCOPUS, EuropePMC, ProQuest, and Cochrane Central Databases with the search terms "candesartan" and "16 mg" and "64 mg" or "proteinuria renal disease" or "albuminuria" and "blood pressure" that were published within the year of 1980–2021. Preferred Reporting Items for Systematic reviews and Meta-Analysis protocol was used to conduct this meta-analysis. Duplicate results were excluded from the study. The remaining articles were independently screened for relevance by its abstracts with all authors. The full-text of the selected abstract then was thoroughly read, and those that fulfilled our criteria were included in the study. The final inclusion of studies was based on the agreements of all investigators. Any disagreement was resolved by consensus of all authors.

The retrieved articles' titles and abstracts were scanned for potential relevance and review inclusion eligibility. To be included, the article had to meet strict criteria, as listed in Table 1, with the search and inclusion criteria primarily targeting published studies presenting clinical efficacy and/or safety types of evaluations of candesartan in proteinuria renal disease. Pre-printed and grey literature journal in this search is also included in the article searched (until June 20th 2020).

The results of the four independent searches were matched to find the common results; the three physicians reviewed the unmatched findings once more, to check if they met the inclusion eligibility criteria. No cases of further disagreement between the physicians occurred. Should any disagreement occurred, the relative articles would have been omitted from the analysis. Only articles written or translated into English were included in this systematic review.

Data extracted from the identified publication included: Study design and outcome, number of patients, follow-up during intervention, intervention information, efficacy, and safety of the procedures. Table 2 summarized all studies that we included in our analysis.

The quality of the studies was appraised independently by two authors using the Modified Newcastle-Ottawa Scale (NOS). A score of 0–9 was allocated to each study, with studies having a total score of >7 defined as high quality. Any disagreement in the quality assessment was resolved by discussion with a third author.

Table 1: Article inclusion and exclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
Types of studies	Randomized controlled trials, prospective cohort, retrospective or clinical observational evaluating the effect of candesartan in 16 mg or 64 mg in proteinuria renal disease patients regardless of clinical status Non-randomized, controlled trials reporting efficacy were allowed if these trials is in the scope of our topic	Combination anti-hypertension, dosage not related
	All evidence levels, including safety data were acceptable for safety analysis inclusion.	a. Reviews, editorials, opinions, case reports, case series, comments, and letters without original data b. Non-clinical (i.e., experimental, animal, or *in vitro*) studies c. Clinical trials with major quality issues and a high risk of bias were excluded from efficacy analysis, but could be included in safety analyses
Types of participants	Patients (more than 17 years old, sex or race) with proteinuria renal disease who had received candesartan monotherapy	Patients without proteinuria renal disease
Types of intervention	candesartan monotherapy consumption	a. Co-administration of other type anti-hypertension b. Non adherence of treatment plan
Types of comparators	Different dosage of candesartan	
Types of efficacy outcome measures	Could include (but not limited to): a. Proteinuria or albuminuria b. Renal clearance c. Systolic or diastolic blood pressure	
Safety outcome measures	Could include (but not limited to): a. Mortality b. Overall incidence of serious adverse event (quantitative) c. Overall incidence of adverse events related to candesartan such as hyperkalemia (quantitative) d. Qualitative assessment of specific adverse events/serious adverse events related to use candesartan	

To perform a meta-analysis, Review Manager 5.4 (Computer program, The Cochrane Collaboration, London, UK) and Comprehensive Meta-Analysis 3.3 (Computer program, New Jersey, USA) were used to perform all statistical analysis. The heterogeneity was considered significant for $p < 0.05$, and its magnitude was substantial when I^2 was greater than 50%. A random-effects model was used to report the results of heterogeneous data otherwise a fixed-effects model was used. Dichotomous variables were analyzed with the Mantel-Haenszel statistical method using risk ratio (RR) as the summary statistic and reported with 95% confidence intervals (CI). Funnel Plot was used to screen for publication bias.

Results

Characteristics of included studies

An initial search generated 46 potentially relevant studies, of which 22 were immediately excluded

Table 2: Characteristic of the included study

Author	Year	Study design	Quality score	Duration of follow-up	Intervention	Total and age of participant	Outcome			
							Proteinuria	Renal clearance	Potassium serum	Blood pressure
Burgess *et al*. [5]	2009	Randomized controlled trial	9	30 weeks	Candesartan 16 mg/day versus 64 mg/day in	56.5 ± 12.2 yo (16 mg) 54.8 ± 12.4 yo (64 mg)	2.80 ± 0.07 reduction in 16 mg versus 2.83 ± 0.06 reduction in 64 mg	47.00 (8.50% reduction in 16 mg) 50.00 (9.50% reduction in 64 mg)	4.43 (0% increase of potassium in 16 mg) 0.05% increase in 64 mg)	−0.6 ± 11.6 mmHg reduction in 16 mg versus−3.3 ± 18.6 mmHg reduction in 64 mg (systolic) −0.6 ± 8.6 mmHg reduction in 16 mg versus−0.8 ± 9.3 mmHg reduction in 64 mg (diastolic)
Schmieder *et al*. [3]	2005	Randomized controlled trial	9	20 weeks	candesartan 16 mg versus 32 mg versus 64 mg	32 patients (53 ± 12 years)	2.38 ± 0.01 g/d in 16 mg 2.14 ± 0.01 g/d in 32 mg versus 2,54 ± 0.01 g/d in 64 mg	16 mg no data. 94 ± 52 ml/min in 32 mg versus 102 ± 66 ml/min in 64 mg	N/A	137 ± 12 mmHg in 16 mg versus 129 ± 12 mmHg in 32 mg versus 131 ± 13 mmHg in 64 mg (systolic) 82 ± 12 mmHg versus 83 ± 10 mmHg in 32 mg versus 83 ± 8 mmHg in 64 mg

*N/A: Not available

due to duplication. After the first screening of title and abstracts, ten studies were excluded. An additional ten studies were excluded after full-text review, which resulted in two studies included in this systematic review and meta-analysis (Figure 1).

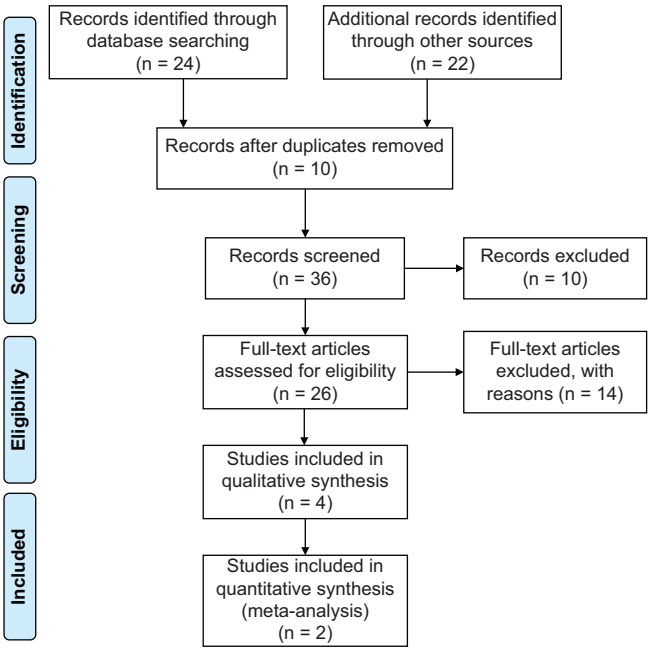

Figure 1: Flow diagram following the preferred reporting items for systematic reviews and meta-analyses guidelines [8]

In data synthesis, we included two papers assessing the association between candesartan dosage administration and proteinuria reduction. Our pooled analysis found that candesartan 16 mg dosage administration, compared to 64 mg, was not associated with proteinuria reduction (std mean diff: -10.92 [95%CI: -40.09 – 18.26], p = 0.46) (Figure 2). The summary of the correlation and effect estimates between candesartan administration and proteinuria reduction in our present study is outlined in Table 3.

The baseline characteristics of the included studies are presented in Table 2.

For quality evaluation through NOS, studies were considered high quality if they scored 7 stars or more. In this analysis, three studies considered high quality, with the remaining one receive fewer than 7 stars.

Candesartan dosage 16 mg versus 64 mg analysis

To test the impact of candesartan use on proteinuria outcome, we included two studies [3], [5]. These data, including candesartan dosage of 16 mg and 64 mg, demonstrate non-significant proteinuria reduction between 16 mg and 64 mg dosage (RR −10.92 [−40.09, 18.26], p = 0.46).

The secondary outcome cannot be measured by statistic measure because there were no available data on mean difference in the study from Schmeider [3].

Discussion

The objective of this study is to review the effect of higher dose ARBs in improving proteinuria. The optimal dose of candesartan as one of the most commonly used ARBs is 16–32 mg and the supramaximal dose used to pursue decreased albuminuria, decreased GFR, and decreased blood pressure has not been studied extensively by the studies mentioned in this systematic review.

Table 3: Summary of the association between candesartan and proteinuria reduction in our study

Outcome parameter	Number of study	Model	Outcome measure		Std mean difference	95% CI	pE	pHet	p
			Candesartan 16 mg	Candesartan 64 mg					
Proteinuria reduction	2	Random	0.58±0.01	0.77±0.01	−10.92	−40.09–18.26	21.158	0.000	0.46

Data were presented in mean±SD. CI: Confidence interval, pE: *P* Egger, pHet: pHeterogeneity

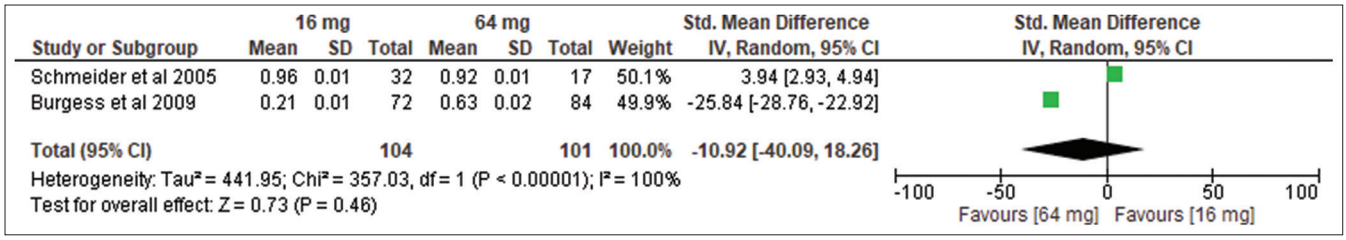

Figure 2: Forest plot between two studies mentioned

A recent study from Burgess *et al.* through the SMART showed that the administration of candesartan at a dose of 64 mg and 128 mg was able to significantly reduce proteinuria up to −22.23 ± 6.17 and −36.95 ± 7.05 compared to candesartan at a dose of 16 mg (−7.59 ± 5.69). There was also a decrease in systolic blood pressure of −3.3 ± 18.6 mmHg and −4.0 ± 12.4 mmHg at 64 mg and 128 mg, respectively, compared to candesartan 16 mg −0.6 ± 11.6 mmHg. In all three groups, there was an increase in serum creatinine level and three patients had their treatment discontinued because of this. No eGFR changes reported by the authors [5].

This study also compared the safety of supramaximal doses of candesartan 16 mg versus candesartan 64 mg in serum potassium (4.43 ± 0.47, 4.57 ± 0.64) in patients with CKD, respectively [5]. Another study did not provide data regarding the safety effect of hyperkalemia on supramaximal use of candesartan in patients with CKD [4], [8], [9], [10], [11]. The study of this meta-analysis showed no significant effect of 64 mg candesartan against 16 mg candesartan (p = 0.46) with only two studies included.

Suppression of proteinuria and blood pressure is an important part in the management of CKD patients associated with improved clinical outcomes and decreased progression of CKD itself. Many studies show that ACE inhibitors and ARBs are the best regimen in patients with CKD compared to other antihypertensive groups. In some clinical trials, ARBs have had a superior effect with increasing dosage [4], [9], [12], [13], [14].

A study from Weinberg, *et al.* try to implement supramaximal dose of candesartan to improve its anti-proteinuria effect. In this study, patients were initially treated with 16 or 32 mg dose of candesartan. After 1–2 months, candesartan was titrated upward to 96 mg, with 16–32 mg of increment. They found that proteinuria was progressively reduced in dose-dependent fashion. No hyperkalemia event was reported in this study, all patients had similar serum potassium across all dosing range (4.3–4.5 mmol/l). There was slight increase of serum creatinine found in some patients, but generally this treatment was well-tolerated [10]. Another study using 8, 16, and 32 mg dosing regimen found that the two highest dose markedly reduced proteinuria compared with the lowest dose, but 16 mg group performed better compared to the 32 mg group. There was slight increase in serum potassium level in all three regimens compared to placebo (4.2 ± 0.1, 4.2 ± 0.1, 4.4 ± 0.1, in 8, 16, and 32 mg group, respectively) but no hyperkalemia event was found. Serum creatinine level was not reported in this study, but the authors found a slight decrease of eGFR in all candesartan group. The authors argued that this decrease was caused by blood pressure reduction and it could be reversed. Finally, the authors conclude that 16 mg is the optimum dose for improving proteinuria [4], somewhat in line with our findings.

This study has several limitations. There were only two randomized controlled studies that met the systematic review and meta-analysis criteria. We were also unable to generate secondary outcomes for this review due to the absence of data on secondary outcomes such as blood pressure as a percentage of the mean. In the future, further research is needed on the supramaximal dose of candesartan on the effects of proteinuria, blood pressure, potassium levels, and eGFR.

Conclusion

Candesartan supramaximal dosage 64 mg did not differ significantly in proteinuria reduction and blood pressure reduction compared with candesartan in 16 mg standard dosage.

References

1. Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. Adv Exp Med Biol. 2019;1165:3-15. https://doi.org/10.1007/978-981-13-8871-2_1
   PMid:31399958
2. Eijkelkamp WB, Zhang Z, Remuzzi G, Parving HH, Cooper ME, Keane WF, *et al.* Albuminuria is a target for renoprotective therapy independent from blood pressure in patients with type 2 diabetic nephropathy: Post hoc analysis from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. J Am Soc Nephrol. 2007;18(5):1540-6. https://doi.org/10.1681/ASN.2006050445
   PMid:17409317
3. Schmieder RE, Klingbeil AU, Fleischmann EH, Veelken R, Delles C. Additional antiproteinuric effect of ultrahigh dose

candesartan: A double-blind, randomised, prospective study. J Am Soc Nephrol. 2005;16:3038-45. https://doi.org/10.1681/ASN.2005020138

PMid:16120821

4. Rossing K, Schjoedt KJ, Jensen BR, Boomsma F, Parving HH. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. Kidney Int. 2005;68:1190-8. https://doi.org/10.1111/j.1523-1755.2005.00511.x

PMid:16105050

5. Burgess E, Muirhead N, de Cotret PR, Chiu A, Pichette V, Tobe S. Supramaximal dose of candesartan in proteinuric renal disease. J Am Soc Nephrol. 2009;20(4):893-900. https://doi.org/10.1681/ASN.2008040416

PMid:19211712

6. Hou FF, Xie D, Zhang X, Chen PY, Zhang WR, Liang M, *et al*. 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(6):1889-98. https://doi.org/10.1681/ASN.2006121372

PMid:17494885

7. Aranda P, Segura J, Ruilope LM, Aranda FJ, Frutos MA, López V, *et al*. Long-term renoprotective effects of standard versus high doses of telmisartan in hypertensive nondiabetic nephropathies. Am J Kidney Dis. 2005;46(6):1074-9. https://doi.org/10.1053/j.ajkd.2005.08.034

PMid:16310573

8. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097

PMid:19621072

9. Rossing K, Christensen PK, Hansen BJ, Carstensen B, Parving HH. Optimal dose of candesartan for renoprotection in Type 2 diabetic patients with nephropathy: A double-blind randomized cross-over study. Diabetes Care 2003;26(1):150-5. https://doi.org/10.2337/diacare.26.1.150

PMid:12502672

10. Weinberg MS, Weinberg AJ, Cord R, Zappe DH. The effect of high-dose angiotensin II receptor blockade beyond maximal recommended doses in reducing urinary protein excretion. J Renin Angiotensin Aldosterone Syst. 2001;2(1):S196-8. https://doi.org/10.1177/14703203010020013401

PMid:28095227

11. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, *et al*, AIPRD Study Group. Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. Ann Intern Med. 2003;139(4):244-52. https://doi.org/10.7326/0003-4819-139-4-200308190-00006

PMid:12965979

12. Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I, Collaborative Study Group. Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to Type 2 diabetes. N Engl J Med. 2001;345:851-60. https://doi.org/10.1056/NEJMoa011303

PMid:11565517

13. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, *et al*, RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-9. https://doi.org/10.1056/NEJMoa011161

PMid:11565518

14. 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. 2009;43(1):S1-290.

PMid:15114537