International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 5 | Issue: 6 | Nov – Dec 2024 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v5i6.62

The Role of Candesartan in Heart Failure Management: A Literature Review

Nabila Nidaul Fitria Robbani[1], Sri Purwaningsih[2*], Nia Dyah Rahmianti[3,4], Meity Ardiana[3,5]

[1]Medical Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Cardiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[4]Department of Cardiology, Universitas Airlangga General Academic Hospital, Surabaya, Indonesia
[5]Department of Cardiology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

E-mail: Nabila.nidaul.fitria-2021@fk.unair.ac.id; sri-p@fk.unair.ac.id; Niadyah.r@fk.unair.ac.id; meityardiana@fk.unair.ac.id

*Corresponding author details: Sri Purwaningsih; sri-p@fk.unair.ac.id

ABSTRACT

Background: Heart failure (HF) is a prevalent cardiovascular condition with increasing prevalence due to an aging population and higher rates of comorbidities. Candesartan, an angiotensin II receptor blocker (ARB), has gained recognition as an effective treatment option for heart failure, particularly for patients with reduced ejection fraction (HFrEF). It works by inhibiting the angiotensin II type 1 receptor, which reduces vasoconstriction, fluid retention, and cardiac remodeling, all key contributors to heart failure progression. Despite its clinical significance, the full scope of its efficacy and optimal usage remains under investigation. ***Objective:*** This review aims to evaluate the effectiveness of candesartan in the treatment of heart failure, focusing on its impact on morbidity, mortality, and clinical outcomes, based on clinical studies and trials. ***Method:*** A thorough literature review was conducted using databases such as PubMed, Google Scholar, ScienceDirect, and NEJM. Relevant studies were identified using keywords like "candesartan," "heart failure," and "mechanism of action of candesartan," focusing on clinical trials and studies assessing its role in heart failure management. ***Result:*** Clinical trials, particularly the CHARM study, show that candesartan significantly reduces mortality and hospitalization in heart failure patients, especially those with HFrEF. However, its use requires monitoring for potential side effects, including hypotension and renal dysfunction. Further studies are needed to refine dosing and assess long-term safety.

Keywords: heart failure; ARB; candesartan.

INTRODUCTION

Heart failure is a clinical syndrome defined by symptoms such as shortness of breath, edema on extremities, and fatigue, along with indicators such as high jugular venous pressure and pulmonary crackles caused by structural and/or functional heart abnormalities [1]. According to WHO (2021), cardiovascular diseases are the leading cause of death. Mortality due to cardiovascular diseases is estimated to have reached 17.9 million in 2019, accounting for 32% of all deaths worldwide [2]. Heart failure, as one of the forms of cardiovascular disease, remains a significant public health issue with an increasing burden of risk factors and comorbidities, especially among individuals aged 65 and older. [3,4]. The incidence of heart failure itself remains steady, however, the prevalence is expected to increase as the population ages and therapy advances [5]. The benefits of lowering risk factors and enhancing primary prevention and treatment compliance are likely to outweigh the impact of any innovative treatment strategy. Individuals will live with heart failure for longer, so healthcare initiatives should focus on controlling multi-morbidity and chronicity [3].

Excessive activation of the renin-angiotensin system (RAS) is associated with heart failure. Activation of RAS results in an increased synthesis of angiotensin I (AI), which is then converted to angiotensin II (AII) by the angiotensin-converting enzyme (ACE). AII is a strong vasoconstrictor that also stimulates aldosterone secretion, causing salt and water retention. AII and aldosterone are also related to other potentially harmful effects on the cardiovascular system, such as endothelial, sympathetic activation, collagen formation, and reduced nitric oxide production. Together, these consequences impose strain on the heart, potentially leading to heart failure [6]. Numerous clinical trials have shown that effective medical therapy can lower morbidity and mortality in congestive heart failure (CHF) patients.

ACE inhibitors are a key component of medical treatment for CHF. A significant number of patients have participated in clinical studies using ACE inhibitors in the diagnosis of CHF. Due to the major similarities between ACE inhibitors and ARBs, it has been proposed that ARBs may play a role in the treatment of CHF [7]. Angiotensin Receptor Blocker (ARB) is one of the recommended heart failure medications by ACC/AHA [8]. Losartan, valsartan, candesartan, irbesartan, olmesartan, eprosartan, and telmisartan are the current seven ARBs available on the market. Although originating from the same pharmacological class, these ARBs differ in some elements of their chemical component [9]. Among ARB drugs, candesartan and valsartan are the only ones found to improve outcomes in heart failure patients. Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program provides the majority of evidence supporting its usage in heart failure cases [10]. Candesartan has been recognized as a therapeutic alternative for heart failure patients and it significantly reduces vasoconstriction, aldosterone secretion, and cardiac remodelling by inhibiting angiotensin II type 1 (AT1) receptors. The CHARM experiment has shown that Candesartan improves clinical symptoms while also lowering hospitalization rates and mortality in heart failure patients, especially those with reduced ejection fraction [11].

Although treatment for heart failure has improved, the prevalence rate is still predicted to rise. Several previous studies have highlighted candesartan as a potential treatment for heart failure. However, understanding its effectiveness, particularly regarding its use, is still limited. Therefore, this literature review aims to provide a deeper analysis of candesartan usage in heart failure cases based on previous research.

METHODS

To conduct a literature review, we gathered journals from several sources such as Google Scholar, PubMed, ScienceDirect, and NEJM. The research was conducted through a comprehensive literature search using relevant keywords, including "heart failure," "ARB," and "candesartan." The thematic search terms applied were: "usage of candesartan in heart failure," "ARB in heart failure," and "mechanism of action of candesartan in heart failure." To expand the literature review, we also explored clinical studies related to the use of candesartan as a treatment for heart failure, such as the "CHARM" study, the role of candesartan in patients with heart failure with preserved ejection fraction (HFpEF), and the treatment protocol and dosing of candesartan in heart failure.

RESULT AND DISCUSSION

Candesartan Mechanism of Action

Candesartan is a derivative of tetrazole, which is a heterocyclic ring having four nitrogen atoms and five members. Candesartan cilexetil is an ester prodrug that is used in clinical settings [12]. A nonpeptide selective blocker of the angiotensin II receptor subtype 1 is candesartan cilexetil. It is a prodrug whose varied absorption transforms it into its active metabolite. It has a nine-hour half-life, a narrow volume of distribution, and is heavily protein-bound. One of the two angiotensin receptor blockers authorised for the treatment of heart failure is candesartan [10]. Like direct renin inhibitors like aliskiren and ACE inhibitors like enalapril, candesartan also has an effect on the renin-angiotensin-aldosterone system (RAAS). When renal perfusion is decreased, the sympathetic tone rises, and sodium chloride transport to the macula densa cells in the nephron's distal convoluted tubule decreases, the renal juxtaglomerular cells usually produce renin. Renin transforms the angiotensinogen produced by the liver into angiotensin I. In the lungs, the angiotensin-converting enzyme (ACE) further transforms angiotensin I into angiotensin II. By inhibiting the effects of angiotensin II and antagonistically binding to the type 1 angiotensin II receptor, candesartan reduces blood pressure and fluid retention [13]. The way that candesartan works is comparable to that of other drugs in its class, such as irbesartan and losartan. In the presence of angiotensin II, candesartan functions as an overwhelming antagonist and attaches to its binding sites, dissociating gradually, as shown in animal models. Three distinct subtypes of the angiotensin II receptor have been identified: AT1, AT2, and AT4. The AT1 receptor is more than 1000 times more sensitive to candesartan than the other AT receptors. The AT1 receptor seems to be responsible for almost all of angiotensin II's cardiovascular actions. Candesartan has been demonstrated to be more potent than eprosartan, irbesartan, valsartan, or the active metabolite of losartan in an in vitro examination that compared the inhibition of the AT1 receptor by several AT1 receptor antagonists utilising an AT1 receptor expression system [14].

Study Review of Candesartan Usage in Heart Failure Cases

A previous study utilizing the CHARM trial reported that candesartan, when used as therapy in combination with standard treatments such as ACE inhibitors, beta-blockers, and an aldosterone antagonist significantly lowers all-cause mortality, death due to cardiovascular, and heart failure hospitalizations in patients with congestive heart failure and LVEF ≤ 40% [15]. Another study by Lund et al. (2018) discovered that candesartan displayed a better effect than placebo in heart failure reduced ejection fraction (HFrEF) and heart failure midrange ejection fraction (HFmrEF), but not in heart failure preserved ejection fraction (HFpEF). Candesartan significantly lowered the primary composite outcome in both HFrEF and HFmrEF, on first and recurring heart failure hospitalization. Meanwhile, HRrEF, also substantially reduced the number of deaths due to cardiovascular and all-cause deaths [16]. Candesartan-based combination therapy was demonstrated as an effective therapy both for hypertension and CHF with reduced ejection fraction. It has been shown to be well tolerated among significant subgroups of patients with diabetes mellitus and heart failure [17].

Another review study stated that candesartan is used as a supplement to ACE inhibitor and beta-blocker medication in patients with heart failure and impaired LV function as well as in patients who are unable to tolerate ACE inhibitors [11]. In contrast, Damman et al. (2016) in their study showed that decreased glomerular filtration rate (GFR) and worsening renal function (WRF) were more prevalent with the use of candesartan compared to placebo [18]. A comparison study between the use of losartan and candesartan in heart failure patients showed that candesartan is associated with less all-cause mortality than losartan [19].

Safety and Adverse Effects of Candesartan

Complete blocking of the RAAS does not result from ACE suppression of angiotensin II production. In actuality, despite long-term ACE-I drugs, angiotensin II returns to pre-treatment levels. This is partially caused by the production of angiotensin II through non-ACE-dependent mechanisms including the enzymes chymase, cathepsin G, elastase, and tissue plasminogen activator.

The two main receptor subtypes that Angiotensin II targets are AT1 and AT2. There is a good characterisation of the AT1 receptor. Vasoconstriction, norepinephrine release, blood vessel sensitisation to norepinephrine, sympathetic activity, aldosterone production, and vascular hypertrophy are all consequences of AT1 receptor activation. It has been suggested that AT2 activation reverses the effects of AT1 by having antigrowth and vasodilatory actions, though this is less certain. Furthermore, blocking AT1 receptors raises the amount of angiotensin II in the blood, which can then be used to counteract AT2 receptors and carry out these suggested positive effects. However, this AT2-counter-regulatory function has been contested by accumulating data. While some research indicates that AT2 receptors have neutral effects on cardiac impact and function, animal models have shown that AT2 receptors may have cardiac hypertrophic and proliferative functions. Although the impact of unopposed AT2 stimulation is still unknown, these findings imply that AT1 blockage may be helpful in HF patients.

Candesartan, a non-peptide angiotensin II receptor antagonist, selectively inhibits the binding of angiotensin II to the AT1 receptor. It demonstrates insurmountable receptor antagonism with a high affinity for AT1 receptors and slow dissociation. The affinity of candesartan for AT1 receptors is approximately 80 to 100 times greater than that of losartan and its active metabolite E3174, respectively. Although AT1 activation leads to vasoconstriction, sympathetic activation, and other adverse effects, the role of AT2 remains uncertain, with some studies suggesting both beneficial and detrimental effects on cardiac function. Thus, candesartan offers therapeutic benefits by selectively blocking AT1, minimizing the potential unopposed effects of AT2 stimulation[20]. Heart failure and hypertension are frequently treated with candesartan, an angiotensin II receptor blocker (ARB). But like all drugs, it has the potential to have side effects. Headache, lightheadedness, and weakness or extreme fatigue are the most frequent adverse effects. Additionally, candesartan may cause hypotension, or a drop in blood pressure, especially in people who are taking diuretics or have low salt or fluid levels. Peripheral oedema, or swelling in the legs, ankles, or feet, and kidney-related problems, including a decreased need to urinate, have also been seen. Furthermore, some people may have nausea, vomiting, disorientation, chest pain, or trouble breathing.

Seizures, hyperkalaemia (high potassium), and symptoms including muscle weakness or extreme fatigue are other possible adverse effects. A slow heartbeat, irregular heart rhythm, or the feeling of missing heartbeats are examples of adverse effects linked to the heart. Rarely, there may be severe allergic responses that include asthma or trouble breathing, a racing heart, fever, enlarged lymph nodes, and swelling of the cheeks, lips, mouth, tongue, or throat, which can make swallowing difficult or cause tightness in the throat. Additionally, skin responses like hives, redness, or itching may be seen. Dizziness, lightheadedness, fainting, stomach cramps, and joint discomfort are some of the less frequent adverse effects[21].

Treatment and Dosage Protocol of Candesartan in Heart Failure Cases

Oral administration of candesartan cilexetil results in its rapid and complete conversion to its active form, candesartan, through ester hydrolysis during gastrointestinal absorption. Candesartan cilexetil's oral bioavailability varies, ranging from roughly 15% to 42%. Food has no apparent effect on its absorption. The medication has a relatively limited volume of distribution (0.13 L/kg) and is strongly protein-bound (>99%), reaching peak plasma concentrations in 3–5 hours (tmax). Almost all of the candesartan's excretion (99%) occurs through the urine and faeces, where 70% to 80% of the medication is removed unaltered, and 20% to 30% is converted into an inactive metabolite. In HFrEF patients who are intolerant to ACE-I, candesartan may be used as a first line of treatment or as a substitute medication, depending on the findings of the renal function test and serum electrolyte levels[20].

Dose titration and optimization to the optimal dose or tolerated dose of ARB drugs can be performed periodically during hospitalization and outpatient care. Titration during hospitalization can be done more quickly by considering the patient's clinical, blood pressure, renal function evaluation, and serum potassium levels. Renal function and serum electrolytes can be evaluated at 1 - 2 weeks after initiation of ARB therapy and then can be monitored every 3 to 6 months after optimal ARB dosing. Initial dose: 4 mg orally once a day; double dose every 2 weeks, as tolerated, to target dose of 32 mg orally once a day[22].

The recommended initial dose for treating heart failure is 4 mg once daily. By doubling the dosage at around two-week intervals, as tolerated by the patient, the

target dose of 32 mg once daily is reached. Candesartan cilexetil's adverse event profile in adult heart failure patients was in line with the medication's pharmacology and the patients' health. In the CHARM program, comparing candesartan cilexetil in total daily doses up to 32 mg once daily (n=3803) with placebo (n=3796), 21.0% of patients discontinued candesartan cilexetil for adverse events vs. 16.1% of placebo patients [23].

Researchers demonstrated using a Pop-PK modeling technique that the primary causes of candesartan clearance variations were weight, eGFR, and the occurrence of diabetes as a comorbidity. Additionally, a reduction of more than 25% in CL/F may result from a combination of these factors. According to these findings, individuals with HF who exhibit these combinations of characteristics may benefit from a dosage modification in clinical practice, or at the very least, their condition (particularly potassium) should be more often evaluated both during dose titration and after starting candesartan[24].

CONCLUSION

In conclusion, candesartan has emerged as an effective treatment option for heart failure, particularly for patients with reduced ejection fraction (HFrEF), where it has shown to significantly reduce mortality, hospitalizations, and improve clinical outcomes. Its mechanism of action, which involves the selective inhibition of the AT1 receptor, leads to reduced vasoconstriction, aldosterone secretion, and cardiac remodeling, all of which are beneficial for heart failure patients. While candesartan is generally well tolerated, it is not without potential side effects, including hypotension, hyperkalemia, and renal impairment, which necessitate careful monitoring, especially during dose titration. Although the medication has proven effective in numerous clinical trials, particularly the CHARM study, further research is needed to a better understanding on its long-term efficacy, safety, and the optimal dosing strategies for diverse patient populations, including those with comorbid conditions like diabetes. Given the increasing prevalence of heart failure, continued exploration into the role of candesartan, especially in combination therapy with other heart failure medications, is essential for improving patient outcomes and addressing the growing burden of this condition.

ACKNOWLEDGEMENT

The author would like to sincerely thank the supervisors for their expert guidance and unwavering support, which were instrumental in the completion of this review study. We also extend our heartfelt appreciation to all the literature sources that provided valuable insights, enriching our understanding of the concepts discussed in this research.

REFERENCES

[1] Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., Falk, V., González-Juanatey, J. R., Harjola, V. P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G. M. C., Ruilope, L. M., Ruschitzka, F., Rutten, F. H., … ESC Scientific Document Group (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal, 37(27), 2129–2200. https://doi.org/10.1093/eurheartj/ehw128

[2] World Health Organization. Cardiovascular diseases. World Health Organization. Retrieved December 8, 2024, from https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1

[3] Groenewegen, A., Rutten, F. H., Mosterd, A., & Hoes, A. W. (2020). Epidemiology of heart failure. European journal of heart failure, 22(8), 1342-1356. https://doi.org/10.1002/ejhf.1858

[4] Roger, V. L. (2021). Epidemiology of heart failure: a contemporary perspective. Circulation research, 128(10), 1421-1434. https://doi.org/10.1161/CIRCRESAHA.121.318172

[5] Savarese, G., & Lund, L. H. (2017). Global Public Health Burden of Heart Failure. Cardiac failure review, 3(1), 7–11. https://doi.org/10.15420/cfr.2016:25:2

[6] Heran, B. S., Musini, V. M., Bassett, K., Taylor, R. S., & Wright, J. M. (2012). Angiotensin receptor blockers for heart failure. The Cochrane database of systematic reviews, 2012(4), CD003040. https://doi.org/10.1002/14651858.CD003040.pub 2

[7] Eisenberg, M. J., & Gioia, L. C. (2006). Angiotensin II receptor blockers in congestive heart failure. Cardiology in Review, 14(1), 26-34. DOI: 10.1097/01.crd.0000182409.91935.85

[8] van der Meer, P., Gaggin, H. K., & Dec, G. W. (2019). ACC/AHA versus ESC guidelines on heart failure: JACC guideline comparison. Journal of the American College of Cardiology, 73(21), 2756-2768. https://doi.org/10.1016/j.jacc.2019.03.478

[9] Meredith, P. (2010). Comparative ARB pharmacology. Br J Cardiol, 17(2), s3-s5. https://bjcardio.co.uk/2010/05/comparative-arb-pharmacology/

[10] Ripley, T. L., Chonlahan, J. S., & Germany, R. E. (2006). Candesartan in heart failure. Clinical interventions in aging, 1(4), 357–366. https://doi.org/10.2147/ciia.2006.1.4.357

[11] Östergren, J. (2004). Candesartan for the treatment of hypertension and heart failure. Expert Opinion on Pharmacotherapy, 5(7), 1589-1597. https://doi.org/10.1517/14656566.5.7.1589

[12] Husain, A., Azim, M. S., Mitra, M., & Bhasin, P. S. (2011). A review on candesartan: pharmacological and pharmaceutical profile. Journal of Applied Pharmaceutical Science, (Issue), 12-17. Available at: https://japsonline.com/admin/php/uploads/290_p df.pdf

[13] Bulsara KG, Patel P, Makaryus AN. Candesartan. [Updated 2024 Feb 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519501/

[14] Smith, K. V., Dunning, J. R., Fischer, C. M., MacLean, T. E., Bosque-Hamilton, J. W., Fera, L. E., ... & Desai, A. S. (2022). Evaluation of the usage and dosing of guideline- directed medical therapy for heart failure with reduced ejection fraction patients in clinical practice. Journal of Pharmacy Practice, 35(5), 747-751. https://doi.org/10.1177/08971900211004840

[15] Young, J. B., Dunlap, M. E., Pfeffer, M. A., Probstfield, J. L., Cohen-Solal, A., Dietz, R., ... & Swedberg, K. (2004). Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation, 110(17), 2618-2626. https://doi.org/10.1161/01.CIR.0000146819.43235.A9

[16] Lund, L. H., Claggett, B., Liu, J., Lam, C. S., Jhund, P. S., Rosano, G. M., ... & Solomon, S. D. (2018). Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. European journal of heart failure, 20(8), 1230-1239. https://doi.org/10.1002/ejhf.1149

[17] Khawaja, Z., & Wilcox, C. S. (2011). An overview of candesartan in clinical practice. Expert Review of Cardiovascular Therapy, 9(8), 975–982. https://doi.org/10.1586/erc.11.90

[18] Damman, K., Solomon, S. D., Pfeffer, M. A., Swedberg, K., Yusuf, S., Young, J. B., ... & McMurray, J. J. (2016). Worsening renal function and outcome in heart failure patients with reduced and preserved ejection fraction and the impact of angiotensin receptor blocker treatment: data from the CHARM-study programme. European journal of heart failure, 18(12), 1508-1517. https://doi.org/10.1002/ejhf.609

[19] Eklind-Cervenka, M., Benson, L., Dahlström, U., Edner, M., Rosenqvist, M., & Lund, L. H. (2011). Association of candesartan vs losartan with all-cause mortality in patients with heart failure. Jama, 305(2), 175-182. doi:10.1001/jama.2010.1949

[20] Ripley, T. L., Chonlahan, J. S., & Germany, R. E. (2006). Candesartan in heart failure. Clinical Interventions in Aging, 1(4), 357–366. https://doi.org/10.2147/ciia.2006.1.4.357

[21] Poppen, A. (2024, August). Candesartan (atacand): Uses, side effects, interactions, pictures, warnings & dosing. WebMD. https://www.webmd.com/drugs/2/drug-8183/candesartan-oral/details

[22] Hasanah, D., Zulkarnain, E., Arifianto, H., Sasmaya, H., Suciadi, L., Dewi, P., Soerarso, R., Nauli, S., Putri, V., Aditya, W., & Sarastri, Y. (2023). Heart Failure Management Guidelines. PERKI IndonesianHeartAssociation.https://www.inaheart.org/storage/guideline/d4c92daca60a4c18c6d846209646c2 4e

[23] DailyMed (2024). DailyMed - Candesartan Cilexetil Tablet. U.S. National Library of Medicine. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=8d9a7eb7-fe06-4fd4-b6f2-1dd88d91838d

[24] Kassem, I., Sanche, S., Li, J., Bonnefois, G., Dubé, M. P., Rouleau, J. L., ... & de Denus, S. (2021). Population pharmacokinetics of candesartan in patients with chronic heart failure. Clinical and Translational Science, 14(1), 194-203. https://doi.org/10.1111/cts.12842