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Adverse Drug Reaction of Angiotensin Receptor Blockers (Valsartan, Candesartan, Losartan): a Systematic Review

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Abstract

Hypertension is a significant global health problem, with a growing prevalence worldwide. The most commonly documented ADRs of hypertension medication in primary care records include those associated with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). The purpose of this paper is to review and evaluate the potential adverse drug reactions (ADRs) associated with the use of Angiotensin Receptor Blockers (ARBs), specifically valsartan, candesartan, and losartan in the management of hypertension and related diseases. We conducted a systematic review of randomized controlled trial articles that involved valsartan, candesartan, and losartan monotherapy compared with placebo or other standard antihypertensive drugs. PubMed and Google Scholar databases were used in the search for articles in May 2024 and 21 articles were included in this review. This study comprised 21 randomized controlled trials. The study participants' ages ranged from 34.4 years to 76 years. Sample sizes ranged from 16 to 1381 patients with a total 4606 patients. A total of 44 ADRs were observed and the most likely ADRs were headache, dizziness, hypotension, hyperkalemia, nausea, upper respiratory tract infection, and fatigue. Generally, the ADRs that occurred were not fatal and did not lead to discontinuation of therapy. The safety and tolerability profiles of ARBs are among the best for antihypertensive drugs. Overall, the comparison of ARB agents between valsartan, candesartan, and losartan in this class is similar. The most frequent adverse events in the group receiving therapy include headache, dizziness, hypotension, hyperkalemia, nausea, nasopharyngitis, and fatigue.

Keywords: angiotensin receptor blockers; adverse drug reaction; adverse events; hypertension; safety

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Introduction

Hypertension (HTN) is a condition where the systolic blood pressure (SBP) value is 130 mmHg or more and/or the diastolic blood pressure (DBP) is more than 80 mmHg[1]. Systemic arterial hypertension is the most significant modifiable risk factor for morbidity and mortality globally. It is associated with an increased risk of cardiovascular disease (CVD), which includes coronary heart disease, peripheral arterial disease, heart failure, myocardial infarction (MI), and atrial fibrillation[2].

The prevalence of hypertension varies between regions and countries[3]. The prevalence of hypertension in Indonesia remains high[4]. In 2023, the Ministry of Health in the 2023 Survei Kesehatan Indonesia (SKI) recorded the prevalence of hypertension in the population aged ≥ 18 years in Indonesia at 30.8% based on blood pressure measurements[5]. This value shows the high prevalence of hypertension, although it has decreased from 34.11% when compared to the Riset Kesehatan Dasar (Riskesdas) in 2018[6]. There are an estimated 63.309.620 cases of hypertension in Indonesia, and the country has a 427.218 fatality rate from the disease[7]. The percentage of hypertension in the age group 31-44 years (31.6%), age 45-54 years (45.3%), age 55-64 years (55.2%).6 Globally, an estimated 1.28 billion persons aged 30-79 years have hypertension, with the majority (two-thirds) living in low- and middle-income nations. Only 54% of them have been diagnosed with the condition, 42% are being treated for hypertension, and 21% are considered to have their hypertension under control[8].

In an effort to manage this condition, pharmacological and non-pharmacological management have been the main approaches applied in clinical practice. Blood pressure (BP) must be reduced to desired values using antihypertensive medications[9]. Thiazide diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) are commonly used as initial antihypertensive treatment[10]. Patients with hypertension and cardiovascular disease (CVD) are frequently treated with renin-angiotensin aldosterone system (RAAS) inhibitors, such as angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs)[11].

ARBs are among the most often used treatments for hypertension patients since they are effective and well tolerated[12]. The second class of medications to be licensed as principal antihypertensive agents is the class of angiotensin-converting enzyme inhibitors (ARBs)[13]. Losartan, candesartan, irbesartan, valsartan, telmisartan, olmesartan, and eprosartan have been approved for the treatment of hypertension[14]. Based on research at the Hypertension Kidney Polyclinic of DR. M. Djamil Hospital 2011, valsartan (20.6%) is the fourth antihypertensive drug after hydrochlorothiazide (35.5%), captopril (26.2%), amlodipine (15.2%)[15]. In line with other studies that the use of Antihypertensive Drugs in Hospitalized Patients at Panembahan Senopati Hospital Overall, the most widely used ARB class is Valsartan as many as 26 cases[16]. In the Outpatient Department of Dr. Mohammad Hoesin Hospital Palembang for the period October - November 2021, the frequency of ARB administration in hypertensive patients was quite high (59.0%) with the most commonly used ARB being candesartan (94.0%)[17]. Candesartan (34.78%) was most widely used in the internal medicine department of Dr. Achmad Darwis Hospital in the study of Widyastuti et al. (2022) followed by the CCB group, namely amlodipine (17.39%)[18]. ARBs are becoming a popular choice for treating hypertension, but using

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them comes with a number of drawbacks, including potential adverse effects.19 Adverse drug reactions (ADRs) are important to be considered in treatment using this drug. The most commonly documented ADRs in primary care records include those associated ACEI and ARB. According to earlier research, 3.9% of ACEI/ARB users may experience adverse drug reactions (ADRs), which can include angioedema, palpitations, hyperkalemia, dizziness, hypotension, gastrointestinal problems, excessive urine, and chronic dry cough[19,20].

According to the WHO's definition, an ADRs is "a response to a drug that is noxious and unintended and which occurs at doses which are normally used in man for the prophylaxis, diagnosis or the therapy of a disease, or for the modification of the physiological functions"[21]. Factors related with higher frequency of adverse reactions include the quantity of medications taken, the patient's genetic disposition, age, pregnancy, and external factors such as food and drug interactions[22]. While ARBs have been shown to be effective in decreasing blood pressure, ADRs associated with their use can may negatively impact patients' treatment outcomes,[23] impair patient adherence to the medication[24], worsen quality of life, and even require discontinuation of treatment which precluded treatment options to achieve their blood pressure target[20]. Previous studies have revealed that up to one-third of individuals with hypertension have had their medication reduced and/or halted due to ADRs, which limited therapeutic alternatives to attain their blood pressure target[20].

The rising incidence of hypertension in Indonesia emphasizes a deeper insight into the adverse effects of ARBs being the preferred therapeutic choices for treating hypertension. Although ARBs have demonstrated efficacy in the management of hypertension, attention to the potential ADRs associated with their use is important, as they may itself influence the clinical course of treatment for patients. As such, the study is anticipated to offer more comprehensive information on the safety of ARBs in the form of a description of ADRs that arise during treatment for health professionals who may be involved in evidence-based clinical practice. This paper aimed to review and assess the possible ADRs arising from the use of ARBs, with specific reference to valsartan, candesartan, and losartan, in management of hypertension and other risk factors related diseases.

Methods

Article selections

The recommended reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guideline is followed in this review[25]. This systematic review was produced according to a literature search conducted in May 2024 on the PubMed and Google Scholar database by listing nine keywords for searching the eligible articles, namely, "adverse effects", "adverse drug reaction", "ADRs", "angiotensin receptor blockers", "ARB", "safety", "valsartan monotherapy", "candesartan monotherapy", "losartan monotherapy" with other synonyms. Boolean operators "AND" and "OR" are used in the search to improve search efficiency and facilitate the discovery of relevant original articles based on the title/abstract. The search included a verified RCT filter for PubMed, which was subsequently customized to other databases. This review focused on the ADRs of valsartan, candesartan, and losartan. Inclusion and exclusion criteria were used in the selection of articles that could potentially be analyzed. After sorting appropriate titles and literature abstracts, the full text article was reviewed in accordance with the inclusion criteria. Randomized clinical trials (RCTs),

original research with full text publications published in English during the previous ten years, and human subjects were the inclusion criteria. Exclusion criteria were case reports, case series, cohort studies, review articles and other types of abstracts (non-clinical trial studies), publications more than 10 years prior, non-human studies, studies that did not conduct safety or ADRs monitoring of ARB drugs.

Subject Characteristics

Subjects involved in the studies were patients diagnosed as hypertension according to JNC 8 criteria, with systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg[26]. Inclusion criteria included patients aged >18 years, no gender restrictions, and patients receiving valsartan or candesartan or losartan monotherapy.

Data Selection, Data Extraction, and Risk of bias

References were independently reviewed by two authors to ensure objectivity and documented the reason for exclusion. Data were extracted independently by one author. Extracted data then created a matrix using Microsoft Excel included first author name, journal and year of publication, study design, demographic characteristics of subjects (population, mean age range, sample size), study duration, intervention, comparator, ADRs monitoring method, and ADRs.

The Jadad Scale is a measure for assessing the methodological quality of clinical trials, specifically randomized controlled trials was used to evaluate the possibility of bias. The Jadad Scale is made up of three components, each of which is rated on a scale resulting in a total score ranging from 0 to 5.27 The three items used to assess the quality of RCTs consist of randomization, blinding, dropouts and withdrawals. Five questions had to be answered: Was there a description of the study that included the terms "random," "randomization," and "randomly"? Was the process used to create the randomization sequence explained and suitable? Was double blind research described in the study? Was the double blinding procedure explained and suitable? Was a description of dropouts and withdrawals provided?

Results and Discussion

Literature Search Results

Several keywords and their synonyms were used in conducting article searches through PubMed and Google Scholar. The article search focused on 3 types of ARB drugs, namely valsartan, candesartan, and losartan which are more widely prescribed in Indonesia. Boolean operators are the words "AND", "OR" and "NOT" were used for searching through PubMed. The Google Scholar search used the "Advanced search" feature and was set to English articles only. A total of 412 articles were identified in the PubMed database, 93 articles were identified on Google scholar. All identified results were then transferred into the citation manager and checked for duplication. A total of 415 articles were screened based on title, type of article, and abstract directly from the database webpage. We excluded 375 articles due to non-compliance with the criteria. 40 full articles based on relevant techniques including randomization and treatment groups, and whether the assessment parameters met the review objectives, were assessed for eligibility. A total of 19 articles were excluded due to incomplete descriptions of the overall safety or tolerability profile, in combination therapy, and inappropriate subject characteristics. After reading the methodologies and results of these papers, this systematic review included 21 papers in the end. The article selection process can be seen in Figure 1.

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Study characteristics and interventions

This study comprised 21 randomized controlled trials, with major characteristics indicated in Table 1. The participants' ages ranged from 34,4 years to 76 years. Sample sizes ranged from 16 to 1381 patients. The articles acquired are RCT studies carried out across several nations, including Taiwan, Italy, Slovenia, Korea, Germany, Spain, France, Netherlands, South Africa, South Korea, Spain, Ukraine, UK, USA, Georgia, Malaysia, China, India, Brazil, Belgium, Canada, Russia, South Africa, South Korea, and, Lithuania. This study focused on looking at ADRs in 3 types of ARBs namely valsartan (n=9), candesartan (n=5), and losartan (n=7). This article was published between 2014 and 2023. A total of 4604 patients were reported receiving valsartan (n=1963), candesartan (n=1993), and losartan (n=648) monotherapy. The least time of observation was 6 weeks. The longest observation is 4,5 years. The minimum dose of valsartan was 80 mg/day, and the highest dose from all included studies was 320 mg/day. For candesartan, it is 4 mg/day and 32 mg/day, while losartan is only 1 dose of 50 mg/day. Only 12 studies mentioned the method of assessing adverse drug reactions and among them, one study used the Naranjo scale assessment and one study used the WHO probability scale. Then, 12 articles were multicenter studies. Of the 21 articles, 5 of them did not clearly describe the clinical setting. A total of 3 RCT compared ARB with placebo, 6 RCT with ACEI, 3 RCT with other ARB, 2 RCT with CCB, and other RCT with standard antihypertensive agent. The study characteristics included are summarized in Table 1.

Quality assessment of the included studies

For over ten years, it has been proposed that the validity or quality of primary trials or clinical reports should be examined under blind settings for the purpose of decreasing or preventing the inclusion of selection bias in systematic reviews and meta-analyses[28]. Six studies had a complete score of 5 points[29–34]. All included studies used randomization, but six studies did not describe in detail the randomization method used. The most unmet parameter was the description of the blinding method. Only 11 out of 21 articles used the double-blind method and 10 of them explained the description of the method. There were five studies that had the lowest score in the Jadad assessment[35–39]. Blinding methods and randomization are necessary to ensure data quality and produce robust results. Three studies that included were single blind, the other seven were open label studies. A higher Jadad total score signifies study quality[28].The summary of the risk of study bias based on Jadad's assessment is provided in Table 2.

Study outcomes

Several studies did not specify the method of assessing undesirable drug effects. Adverse effects were investigated through open-ended questions and the use of self-reported semi-structured questionnaires, which asked about the suspected adverse effects of the drug under study[40]. One study by Aftab et al., 2017 used the Naranjo scale assessment and one study by Maharshi et al., 2016 used the WHO probability scale. This scale was developed to help standardize assessment of causality for entire adverse drug reactions[41].

Four studies by Ruggenenti et al., 2019, Park et al., 2018, Ruggenenti et al., 2021, Ito et al., 2023 mentioned the incidence of hypotension[37,42,43]. Four studies also mentioned the effects of hyperkalemia, Ruggenenti et al., 2021, Ito et al., 2023., Aftab et al., 2017., Lai et al., 2022. Studies by Zappe et al., 2015 and Mujeeb et al., 2015 reported the occurrence of back pain. Hajjar et al., 2020 and Shin et al., 2019 experienced urinary frequency. Headache and dizziness were reported as the

most frequent ADRs by 12 and 10 studies, respectively. Insomnia was reported in 2 studies by Shin et al., 2019 and Lai et al., 2022. Upper respiratory tract infection, reported by 2 studies Lai et al., 2022, and Wang et al., 2020. Rash/skin disorder was reported in 3 studies Hajjar et al., 2020, Lai et al., 2022, and Ito et al., 2023. Nasopharyngitis occurred in 3 studies by Zappe et al., 205, Lee et al., 2016, and Ito et al., 2023. Mujeeb & Jalikar reported the occurrence of pharyngitis. Nausea was also reported in 3 studies by Chen et al., 2015., Park et al., 2016., Zappe et al., 2015.

In randomized controlled trials comparing angiotensin receptor blockers to placebo, headache, dizziness, hypotension, hyperkalemia, nausea, rash/skin disorder, and nasopharyngitis (respiratory infection) are the most frequently reported side effects (table 3). Reported discontinuation or withdrawal rates in major ARB trials are low. ARBs are better tolerated than ACE inhibitors, with decreased rates of coughing and angioedema[44]. ARBs have a similar tolerability profile to placebo and are superior than ACE inhibitors including in terms of cough induction[45]. Over the last 20 years, ARBs have showed remarkable safety when taken alone or in conjunction with other antihypertensive medications[45]. Caldeira et al. (2012) did a systematic review and meta-analysis to evaluate the tolerability of ARBs in individuals who had intolerance to ACE inhibitors. ARBs were found to have less cough events than ACE inhibitors in 11 RCTs comparing them with ACE inhibitors, diuretics, or placebo, and in one RCT comparing high-dose and low-dose ARBs (RR 0.37; 95% CI 0.28, 0.48). ARB-associated angioedema risk was thus comparable to placebo risk (RR 1.62; 95% CI 0.17, 15.79). ARBs were associated with increased rates of hypotension, hyperkalaemia, and renal impairment when compared to placebo. But stopping ARBs had a similar effect as a placebo[46]. Studies by Ruggenenti et al., Shin et al., Chen et al., White et al., mentioned treatment-related side effects were not serious and were all transient. The reported side effects consisted of hyperkalemia, worsening of renal function, symptomatic hypotension[42]. Common causes of non-serious events were gastrointestinal problems, insomnia, constipation, headache, and dizziness[30]. GI problems, insomnia, constipation, headache, and dizziness were non-serious ADRs[30]. The Valsartan group showed a generally mild side effect profile with no serious treatment-related AEs, all 18 reported TEAEs were of mild or moderate severity with no deaths during the study[38].

During the trial period conducted by Wang et al., common AEs (≥5%), in the valsartan monotherapy 160 mg group were Dizziness (2), Headache (1), cough (2) from a total of 21 patients[29]. Ruggenenti et al., 2021 compared the effects of valsartan with the ACEi benazepril and their combination, overall, the distribution of serious and non-serious adverse events was similar in the 3 treatment groups. One or more bouts of treatment-related hyperkalemia were experienced by two (1.0%) patients on benazepril, four (2.0%) patients on valsartan, and thirteen patients on combination therapy (P=0.044 versus valsartan; 6.4%, P=0.003 versus benazepril). It can be concluded that valsartan monotherapy was related with a decrease in the frequency of cough reports, but it also showed an increase in the number of episodes of symptomatic hypotension. 47 Based on a study by Park et al., 2016, hypotension and related symptoms were the most frequent adverse drug reaction. None of the low-dose group's side effects (dizziness, hypotension, and syncope) that are linked to low blood pressure were found. In the low-dose group, worsening azotemia was also not observed[39]. This results are in line with research by Ruggenenti et al., 2021.

Park et al., 2018 found that the most typical ADRs in the special population with acute STEMI and subnormal left ventricular ejection fraction (<50%), were hypotension and symptoms related to hypotension. Adverse events specifically related to low blood pressure (dizziness, hypotension, and syncope) occurred at high doses. Among adverse events, drug-related ADRs were more frequent in the maximally tolerated dose group (7.96%) than in the low-dose group (0.69%) ($P < 0.001$)[37]. The fundamental reason for selecting the ARB medicine valsartan is that it is the only ARB agent that has been found to have clinical efficacy comparable to ACE inhibitors in patients with MI[48]. Nine (4,3%) patients on benazepril, fifteen (7,5%) patients on valsartan, and twenty patients on combination therapy (9.9%, $P = 0.033$ versus benazepril) all reported treatment-related hypotension at least once. While none of these events were life-threatening, the valsartan group's two patients required medication withdrawals. Deaths were not linked to cardiovascular events: four were associated with benazepril, five with valsartan, and one with combination medication but these occurrences were judged unrelated to the study's interventions[47]. In a meta-analysis published in 2023, Escobar et al., 2023 compared MACE (Major adverse cardiovascular events) between patients receiving ARBs and ACEi by pooling data from nine studies. They found that while MACE was slightly higher in patients receiving ACEi (13.12%) than in patients receiving ARBs (13.07%), the difference was not statistically significant[49].

When ACEI or ARBs are combined with first-generation DHP CCB nifedipine, the risk of peripheral edema development is not decreased in comparison to nifedipine alone. The combination of ACEI, ARBs, and diuretics reduces the development of peripheral edema in upper generation DHP CCB patients. Combination therapy with ACEI, ARBs, and diuretics reduced the incidence of peripheral edema in top-generation DHPCCB. However, combination with ARBs did not show the best results[50]. Combination of a second-generation or higher DHP CCB with an ACEI or ARB or diuretic decreases the likelihood of peripheral edema development compared with single DHP CCB treatment[50]. The capacity of RAAS inhibitors to reduce postcapillary resistance (venous dilatation) and normalize hydrostatic pressure inside the capillary bed explains this elegant pathophysiologic observation and reduces fluid extravasation[51]. At the moment, the most popular combination in Indonesia is diuretics along with CCBs and ARBs[52]. According to Park et al., low-dose nifedipine had a higher rate of side effects than low-dose valsartan.

The RCT study of Zappe et al., reported ADRs that occurred in the valsartan monotherapy group with different consumption times, including headache, nasopharyngitis, bronchitis, cough, nausea, vertigo, upper abdominal pain, diarrhea, and back pain. In line with Ruggenenti et al. study, findings by of Zappe et al., showed that cough was the most common side effect, with a greater incidence rate in the lisinopril group (8.1%) compared to the morning and evening valsartan groups (2.2 and 3.2%)[39]. In the valsartan a.m. group, nausea was more common (2.2%), whereas in the valsartan p.m. group, bronchitis was more common (4.1%). Headache, nasopharyngitis, upper abdominal pain were slightly more common with valsartan a.m. than valsartan p.m. The incidence of vertigo and diarrhea occurred in equal numbers for both. Back pain was reported more frequently with valsartan p.m. than valsartan a.m[53].

Mancia et al., 2015 discovered that when nifedipine-candesartan cilexetil combination therapy was used instead of

nifedipine monotherapy, the incidence of treatment-related adverse events was lower. Participants with renal impairment and hypercholesterolemia, combination therapy also had a reduced incidence of edema than nifedipine GITS monotherapy had an estimated amount of adverse events, and the subgroups with diabetes, hypercholesterolemia, and CV risk factors had a reduction of approximately 25%[54].

In comparison to the candesartan group, the lisinopril group had more participants who reported coughing (24 [27.0%] vs. 7 [8.0%]; P =0.005). Candesartan group reported greater skin rashes (9.1% vs. 1.1%; P =0.008). Moreover, treatment with candesartan was found to have a superior effect on episodic memory as measured by the delayed recall and retention indices of the HVLT-R (Hopkins Verbal Learning Test-Revised) when compared to lisinopril after controlling for systolic blood pressure and stratification variables[31]. Headache (21%), dizziness or lightheadedness (17%), edema/swelling (15%), excessive tiredness, asthenia, fatigue, weakness (10%), general pain (8%), rash (9%), palpitation & urinary frequency (5%) occurred in the valsartan monotherapy group from the study of Hajjar et al., with candesartan 8 mg and lisinopril 10 mg treatment groups[31]. Edema (8.7%), headaches (3.5%), and vasodilatory TEAEs (11.8%) among ADRs seen by valsartan users, which showed a 50% reduction in headache when candesartan was combined with nifedipine GITS, that may improve patient adherence[33]. According to research by Kjeldsen et al. (2014), CCB-ARB combinations have been associated with a significantly reduced incidence of headache and edema than CCB alone. This discovery may enhance adherence and help patients reach their blood pressure goals[33].

According to Lee et al. (2016) and Ito et al. (2023), there was no discernible statistical difference for any of the adverse events. The rates of adverse medication responses were 12.8% and 16.8% in the azilsartan and candesartan groups, respectively (P=0.559). The rates of hypotension and hyperkalemia were 0% and 2.1% in the azilsartan group, and 1.1% and 1.1% in the candesartan group, respectively[43]. The azilsartan group had a greater incidence of overall adverse events than the candesartan group, although there were no differences in the occurrences of each adverse event, including hypotension and hyperkalemia associated with the study medicines[43]. A study by Takahara et al. (2014) showed that both treatment with azilsartan 10 mg and candesartan cilexetil 8 mg were similar in terms of rare side effects[55]. In a retrospective research of single center analysis, Fukushima et al., 2023, evaluated the increase in serum potassium in patients receiving CCB medication. The study found that patients getting ARB therapy had greater serum potassium levels (0.05 mEq/L, p=0.02) than those receiving CCB therapy. However, no significant relationship was found between ARB use and hyperkalemia (adjusted HR 0.91, 95% CI 0.42-1.99, p=0.82). As a result of the increase in serum potassium levels upon ARB beginning, serum potassium levels must be constantly monitored throughout ARB medication. However, the risk of hyperkalemia appears to be similar between ARB and CCB treatment[56].

In study by Lee et al. 2016, treatment-emergent adverse events (TEAEs) are often reported adverse effects that worsened after or before the medicine was administered. Patients with high blood triglyceride (TG) levels (≥ 150 mg/dL) had a 1.62-fold increased risk of ALT elevation compared to those with normal TG levels[57]. Frequently reported treatment-emergent adverse events, such as dizziness, headache, and elevated liver enzymes, are expected events, which have been reported

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from previous studies of other ARBs on the market[32]. In adults with primary hypertension, Li et al. (2015) assess the effects of ARBs and ACE inhibitors on overall mortality, cardiovascular events, and the rates of withdrawals due to adverse effects (WDAEs). a high level of evidence indicated a slightly lower incidence of WDAE for ARBs as compared with ACE inhibitors (RR 0.83; 95% CI 0.74 to 0.93; absolute risk reduction (ARR) 1.8)[58]. Symptomatic hypotension, decreased renal function (elevated creatinine), and hyperkalemia were observed in the CHARM program at rates of 18.8%, 12.5%, and 6.3%, respectively[59].

The study by Aftab et al., 2016 stated that headache was the most commonly reported ADRs in both standard and treatment groups during HD sessions and no cases of post-dialysis hyperkalemia and hypotension were reported in their study[60]. Aftab et al., (2017) documented ADRs throughout therapy, including two patients in the losartan group and experienced mild hyperkalemia, as validated by the Naranjo scale. Similarly, the Naranjo scale revealed four coughs, three cases of dizziness, and one case of dyspepsia[61]. The study by Gismondi et al., 2015 also compared ARBs (losartan group) with ACEi (benazepril group). According to Gismondi et al. (2015), two patients (12.5%) in the losartan group and one (7.1%) in the benazepril group experienced edema, but none of the patients stopped their medication[35]. According to Lai et al. (2022), elevated triglycerides, elevated total cholesterol, and UTI, and URTI were the most frequent adverse events[62]. A retrospective cohort analysis found that ARB was linked to a higher incidence of UTI (HR: 1.20, 95% CI 1.03–1.39) among women exclusively, however this association was not deemed statistically significant[63]. Maharshi et al., 2016 reported, patients treated with losartan demonstrated a substantial drop in serum albumin after treatment, which may be attributed to the hepatotoxic characteristics of ARBs[36,64]. The cohort study by Bolotova et al., 2020 showed the most common adverse effects of losartan monotherapy were hypotension, increased transaminase levels (SGOT and SGPT) known as transaminitis, hyperkalemia, renal insufficiency, angioedema[65–67]. In the prospective and retrospective cohorts of this trial, hypotension resulted in withdrawal in 19% and 14% of the patients, respectively and hyperkalemia was observed in 6% and 0% individuals, respectively[65].

Fuchs et al., 2021 stated that there were no significant differences in reports or ADRs by treatment group (losartan compared to Chlorthalidone/Amiloride). The most frequent complaints were dizziness, headaches, exhaustion, back pain, and URTI[40]. Headache, fatigue, URTI, dizziness, and back pain were the most common complaints[13]. Four patients (two losartan and two valsartan) in the study by Mujeeb & Jalikar (2015) had ALT or AST elevations >3x the upper limit of normal.13 Details of adverse drug events observed in the valsartan monotherapy group can be seen in Table 2.

A total of 44 ADRs (Table 3) were observed and the most likely ADRs were headache, dizziness, hypotension, hyperkalemia, nausea, URTI (nasopharyngitis), and fatigue. Generally, the ADRs that occurred were not fatal and did not lead to discontinuation of therapy. Therefore, it can be concluded that by considering risk factors, prevention and management of ADRs can drastically improve adherence as well as patient outcomes. As a result, ARBs are better tolerated, with improved compliance in the management of hypertension or other comorbidities, and are an appropriate choice for individuals who are intolerant to ACE inhibitors. Valsartan, candesartan, losartan are the first ARB

therapies considered in clinical heart failure in patients intolerant to ACEi. Valsartan is a good first choice among other ARBs in MI, DM, and metabolic syndrome. Losartan in clinical stroke, diabetic nephropathy, and hyperuricemia. Candesartan with potentially beneficial effects on cognitive decline[68].

Conclusion

ARBs have one of the best safety and tolerability profiles among antihypertensive medications, therefore the comparison of ARB agents in this class between valsartan, candesartan, and losartan is similar. The main finding of this review is that the most frequent adverse events in the group receiving therapy are headache, dizziness, hypotension, hyperkalemia, nausea, upper respiratory tract infection (nasopharyngitis), and fatigue. Most of the AEs were of mild or moderate severity. Other reported adverse effects include bradycardia, urinary frequency, UTI, Back pain, Arthralgia, palpitation, GI problem and others. Generally, the ADRs that occurred were not fatal and did not lead to discontinuation of therapy. Therefore, by considering risk factors, prevention and management of ADRs can significantly improve adherence and patient outcomes. This study has some limitations. First, we included only 2 databases in English Language. Secondly, no meta-analysis was conducted considering the clinical heterogenity and heterogeneous data complexity of the randomized controlled trials (RCT) evaluated.

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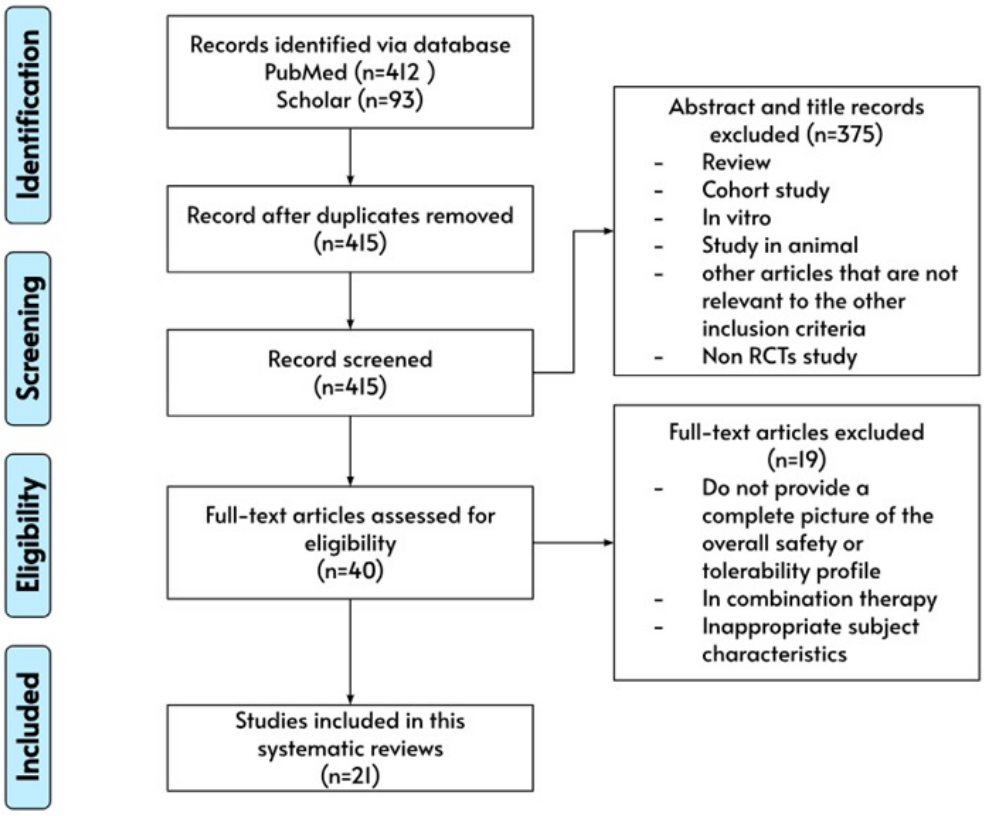

Figure 1. PRISMA 2020 flowchart of article selection

Table 1. Quality assessment by Jadad scale

No.	Authors, year	Randomization	Description of randomization	Double-blind method	Description of the blinding method	Description of withdrawal/ drop-out	Total score
1.	Wang et al., 2020[29]	1	1	1	1	1	5
2.	Ruggenenti et al., 2019[42]	1	1	0	0	1	3
3.	Shin et al., 2019[30]	1	1	1	1	1	5
4.	Chen et al., 2015[38]	1	0	0	0	1	2
5.	White et al., 2016[69]	1	0	1	1	1	4
6.	Park et al., 2018[37]	1	0	0	0	1	2
7.	Ruggenenti et al., 2021[47]	1	1	0	0	1	3
8.	Park et al., 2016[39]	1	0	0	0	1	2
9.	Zappe et al., 2015[53]	1	0	1	1	1	4
10.	Mancia et al., 2017[70]	1	1	1	1	0	4
11.	Hajjar et al., 2020[31]	1	1	1	1	1	5
12.	Kjeldsen et al., 2014[33]	1	1	1	1	1	5
13.	Lee et al., 2016[32]	1	1	1	1	1	5
14.	Ito et al., 2023[43]	1	1	0	0	1	3
15.	Aftab et al., 2016[60]	1	1	0	0	1	3
16.	Aftab et al., 2017[71]	1	1	0	0	1	3
17.	Gismondi et al., 2015[35]	1	1	0	0	0	2
18.	Maharshi et al., 2016[36]	1	1	0	0	0	2
19.	Lai et al., 2022[34]	1	1	1	1	1	5
20	Fuchs et al., 2021[40]	1	1	1	1	0	4
21.	Mujeeb & Jalikar, 2015[13]	1	0	1	0	1	3

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Table 2. Basic characteristics of the research that are included

No	Authors, year	Journal	Study design	Demographic characteristics of subjects	Study duration	Intervention	Comparator	Drug safety monitoring methods	Advers Effects in valsartan monotherapy group
1.	Wang et al., 2020 [29]	J Chin Med Assoc	Randomized, double blind	Population: mild-moderate HTN Mean age range (yr): 57.3 Patients: (G1 = 21, G2 = 21) Setting: Taipei Veterans General Hospital.	8 weeks	G2: valsartan 160 mg/day	G1: amlodipine/ valsartan 5/80 mg FDC	Laboratory analyses, including electrocardiography, vital signs, coded with the Medical Dictionary for Regulatory Activities.	URTI (3), dizziness (2), headache (1), cough (2)
2.	Ruggenenti et al., 2019 [42]	Diabetes Obes Metab	Randomized, PROBE (open label, multicentre, blinded endpoint)	Population: T2DM with HTN Mean age range (yr): 63-66 Patients: (G1 = 34, G2 = 36, G3=33) Setting: 10 centers in Italy and one in Slovenia.	4,5 year	G2: valsartan 320 mg/day	G1: benazepril 20 mg/day G3 : combination	Collected and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.	Hyperkalaemia (3), hypotension (3), transient kidney function worsening (6), major CV events: acute MI (2), Coronary revascularization (3)
3.	Shin et al., 2019 [30]	Hindawi Cardiovascular therapeutics	Randomized, single center, double-blind study	Population: acute ischemic stroke with HTN Mean age range (yr): 57.5 and 59.1 Patients: (G1 = 31, G2 = 31) Setting: Gachon University Gil Medical Center	8-week	G1: valsartan 80 mg/day	G2: fimasartan 60 mg/day	Adjudicated by an independent adjudication committee, being classified as serious or nonserious	18 subjects (58.1%) in the valsartan group experienced Bradycardia, GI problem, Anxiety, Urinary frequency, Dizziness, Insomnia, tremor

4.	Chen et al., 2015 [38]	American Journal of Therapeutics	Randomized, single-center, open label, 3-way crossover trial	Population : healthy adults Mean age range (yr): 34.4 Patient: (G1=30) Setting: not specifically mentioned	36 days	G1: valsartan 320 mg	G2: nebivolol 20 mg G3: nebivolol 20 mg tablets plus valsartan 320 mg	Descriptive statistics based on the Safety population.	Constipation, Nausea, Cough, Rhinorrhea
5.	White et al., 2016 [69]	Journal of Hypertension	Randomized, double-blind	Population: HTN; Mean age range (yr): 54; Patients: 242; Setting: not specifically mentioned	6 week	valsartan 320 mg	baseline	Not specifically mentioned	Headache (7.4%), dizziness (5%), UTI (3.7%)
6.	Park et al., 2018 [37]	ESC Heart Failure	Randomized, multicentre, single-blind	Population: Korean patients with acute STEMI and subnormal left ventricular (LV) ejection fraction (<50%); Mean age range (yr): 58.4-59.5; Patients: (G1=333; G2= 162); Setting: multicentre trial conducted in 17 regional hospitals in Korea.	1 year	G1: valsartan 320 mg; G2: valsartan 80 mg	baseline	Not specifically mentioned	G1: (25/314, 7.96%); G2: (1/145, 0.69%) Dizziness, dizziness postural, hypotension, Orthostatic hypotension, and hypotension related symptoms

7.	Ruggenen et al., 2021 [47]	PLoS Med	Randomized, PROBE study (open label, multicenter, blinded endpoint)	Population: patients HTN > 40 years with T2DM; Mean age range (yr): 64.3-65.0; Patients: (G1=201; G2= 201; G3=202); Setting: Istitution di Ricerche Farmacologiche Mario Negri IRCCS and 8 diabetology or nephrology units in Italy.	66 month	G2: valsartan to 160 mg/day	G1: benazepril 10 mg/day; G3: benazepril/ valsartan combination therapy to 5/180 mg/day	Not specifically mentioned	2 (1.0%) patients on benazepril, 4 (2.0%) on valsartan, and 13 on combination therapy (6.4%) had at least one incidence of hyperkalemia associated to therapy. Nine (4.3%) patients on benazepril, 15 (7.5%) patients on valsartan, and twenty patients on combination therapy reported treatment related hypotension at least once.
8.	Park et al., 2016 [39]	Clinical Therapeutics	Randomized, active controlled, open-label, multicenter study	Population: Patient with stage II or higher HTN ; Mean age range: 48.2-49.4; Patients: (G1=181; G2=181); Setting : 17 study centers in South Korea	8 weeks	G1: valsartan 80 mg/day up-titration to 160 mg/day	G2 : nifedipine GITS dose 30 mg up-titration to 60 mg	Not specifically mentioned	Valsartan 80 mg (32/181): Headache (8), Palpitations (2), Nausea (2), Nasopharyngitis (2), Dizziness(2), Hypoesthesia (2) Valsartan 160 mg (11/68) : Upper abdominal pain (2), Nasopharyngitis (2), Headache (1)
9.	Zappe et al., 2015 [53]	Journal of Hypertension	Randomized, double blind, double dummy, active controlled, multicentre study	Population: grade 1 or 2 HTN; Mean age range: 61.2-61.7; Patients: (G1= 359; G2= 367; G3= 356); Setting : 94 centres in five countries	26-week,	G1 : valsartan 320 mg a.m; G2: valsartan 320 mg p.m	G3: lisinopril 40 mg	regular monitoring and recording of all adverse events.	Headache 13 (3,6%); 12 (3,2%), Nasopharyngitis 9 (2.5); 8 (2.2) Bronchitis 8 (2.2); 15 (4.1) Cough 8 (2.2); 12 (3.2) Diarrhea 4(1.1); 4(1.1) Back pain 3(0.8); 9(2.4) Nausea 8 (2.2); 1(0.3) Vertigo 6 (1.6); 6(1.6) Upper abdominal pain 5 (1.4); 3(0.8)

10.	Mancia et al., 2017 [70]	Journal of Human Hypertension	Randomized, double blind, placebo controlled, parallel group, multicentre multifactorial study	Population: grade 1 or 2 HTN; Mean age range: 53.7- 61.6; Patients: 1381; Setting : 131 study centres in 12 countries	8 weeks	Candesartan cilexetil 4, 8, 16 or 32 mg	Placebo	Not specifically mentioned	Headache, Oedema
11.	Hajjar et al., 2020 [31]	JAMA Network Open Neurology	Randomized, double blind, single centre	Population: individuals with MCI and HTN; Mean age range: 65.8-66.; Patients: (G1=87); Setting : single-centre in the metropolitan Atlanta, Georgia.	1 year	G1: candesartan (8 mg)	G2: lisinopril (10 mg)	Periodic assessment of medical history data and clinical measures, BP, heart rate, routine laboratory measurements, and surveillance of adverse events.	Headache (21%), dizziness or lightheadedness (17%), edema/swelling (15%), excessive tiredness, asthenia, fatigue, weakness (10%), general pain (8%), rash (9%). palpitation & urinary frequency (5%).
12.	Kjeldsen et al., 2014[33]	Journal of Hypertension	Randomized, placebo controlled double blind, multicentre study	Population: Grade I and II HTN; Mean age range: 54.0; Patients: 346; Setting : 131 study centres in 12 countries	8-week	Candesartan cilexetil (4, 8, 16, 32 mg)	Placebo	Coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 vital sign assessments; and routine laboratory evaluations, self-reporting of symptoms.	Oedema (8.7%), headache (3.5%), Vasodilatory TEAEs (11.8%)
13.	Lee et al., 2016[32]	Clinical Therapeutics	Multicenter, randomized, double blind, active comparator, and parallel group study	Population: mild to moderate essential HTN.; Mean age range: 54.5; Patients: (G1=84); Setting : 12 centers, including Kyungpook National University Hospital in South Korea.	12 weeks	G1: candesartan 8 mg	G2: fimasartan 60 mg, fimasartan 120 mg	AE assessments, laboratory tests, physical examinations, 12-lead ECG, and chest radiography	Headache in 22 patients (7.6%), including 7 (7.2%), 9 (9.3%), and 6 (6.4%) in the fimasartan 60 mg, fimasartan 120 mg, and candesartan 8 mg groups, respectively. Dizziness and nasopharyngitis occurred in candesartan 8 mg (3,2%).

14.	Ito et al., 2023[43]	Scientific reports	Multicenter, randomized, open labeled, active controlled , parallel group	Population: HFmrEF or HFpEF patients with HTN; Mean age range: 76.0; Patients: (G1=95); Setting : not specifically mentioned	48 weeks	G1: candesartan 8 mg	G2: azilsartan 20 mg	Not specifically mentioned	Hypotension and hyperkalemia was similar among the groups. Skin and subcutaneous tissue disorders (8.4%) Renal and urinary disorders (8.4%) dizziness (5%) Nervous system disorders (8.4%) Nasopharyngitis (9.4%)
15.	Aftab et al., 2016 [60]	Scientific Reports	Multicentre prospective, randomized parallel design, single-blind trial.	Population: Post dialysis hypertensive patients (>140/90mmHg); Mean age range: (standard 54.0 years, treatment 53.7 years); Patients: (standard: 44) and (treatment = 44); Setting : three private dialysis centres, The Hospital Universiti Sains Malaysia (HUSM)	8 weeks.	Losartan 50mg	Standard antihypertensive therapy (except RAAS inhibitors)	Not specifically mentioned	Headache (most common). Ten (22.7%) patients in the Losartan group reported ≤2 and Two (4.5%) reported 3–5 instances of headaches during HD sessions. Shortness of breath (5 patients), headache (10 patients), leg cramps (13 patients)
16.	Aftab et al., 2017 [61]	Scientific Reports	Multicentre prospective, randomized parallel design, single-blind trial.	Population: Post dialysis euvolemic patients with systolic blood pressure >140 mmHg; Mean age range: (standard 54.0 years, treatment 53.7 years); Patients: (standard 44) and (treatment arm = 44); Setting : Hospital Universiti Sains Malaysia (HUSM) in Kelantan and its associated dialysiscentres	12 months	Losartan 50 mg	Antihypertensive therapy (except RAAS inhibitors) including calcium channel blockers, diuretics, alpha and beta blockers,	classified according to K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Confirmed by the Naranjo scale assessment.	2 patients in the intervention arm, so receiving losartan, suffered from mild hyperkalemia, 4 coughing, 3 dizziness and 1 dyspepsia

17.	Gismondi et al., 2015[35]	Journal of the Renin Angiotensin Aldosterone System	Randomized, open label	Population: T2DM and HTN; Mean age range: 57; Patients: (G1= 16; G2=14) Setting : not specifically mentioned	12 weeks	G1: losartan 50 mg	G2: benazepril 10 mg	Not specifically mentioned	Two (12.5%) patients had edema
18.	Maharshi et al., 2016 [36]	Indian J Physiol Pharmacol	Open label, randomized, prospective clinical study	Population: stage 1 HTN; Mean age range: 50,17; Patients: (G1=30); Setting : outpatient department of Internal Medicine Lady Hardinge Medical College & Associated Hospitals.	3 months	G1: losartan 50 mg	G2: enalapril 5 mg	WHO probability scale	No serious ADR was reported. Losartan treated patients showed post treatment significant reduction in mean serum albumin
19.	Lai et al., 2022 [34]	Circulation: Cardiovascular Quality and Outcomes	Multicenter, randomized, double blind, double dummy, active controlled, non inferiority trial,	Population: mild (grade 1) essential HTN; Mean age range: 52.5; Patients: (G1=314) Setting : 17 centers throughout China	8 weeks	G1: losartan 50 mg	G2: Songling Xuemaikang capsule (SXC) 500 mg	Vital signs and clinical laboratory data, unified enzymatic methods.	Most common were UTI, URTI, elevated total cholesterol, elevated triglyceride, and hyperuricemia. AEs related to study medication are hyperuricemia, hyperkalemia, proteinuria, headache, rash, abdominal pain, elevated LDL-cholesterol, insomnia, sinus bradycardia
20.	Fuchs et al., 2021 [40]	Acta Diabetologica	Multicenter, Randomized, double blind controlled trial	Population: patients stage I HTN with T2DM.; Mean age range: 56,2; Patients: (G1=50); Setting : 21 academic medical centers in Brazil	18 months	G1: losartan 50 mg	G2: chlorthalidone/ amiloride combination pill 12,5/2,5 mg	Open questions and use of a semi structured self reported questionnaire, which queried presumed adverse effects of the study drugs.	Musculoskeletal & upper respiratory complaints, dizziness, headache
21.	Mujeeb & Jalikar, 2015 [13]	J of Evolution of Med and Dent Sci	Multicenter, randomized double-blind trial	Population: HTN; Mean age range: 52 years.; Patients:150 Setting : not specifically mentioned	8-week	Losartan 50 mg	placebo	were examined by Fisher's exact test for differences among treatment groups.	Two patients had elevations of AST or aspartate ALT of >3x ULN or >3x the baseline value. UTI, headache, fatigue, back pain, arthralgia, pharyngitis

Abbreviations: CV, cardiovascular; BP, blood pressure; GI, Gastrointestinal; RCT, randomized control trial; HTN, hypertension; T2DM, type 2 diabetes mellitus; HFmrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; MCI, mild cognitive impairment; UTI, urinary tract infection; range; URTI, upper respiratory tract infection; MACE, major cardiovascular event; PROBE, prospective, randomized, open-label, blinded endpoint; RAS, renin–angiotensin system; RAAS, renin-angiotensin-aldosterone system; AEs, adverse events; TEAE, treatment-emergent adverse events; HD, hemodialysis

Table 3. Summary of ADRs of the three ARB drugs

Dizziness	URTI	Palpitation
Headache	Orthostatic hypotension	Vasodilatory
Hiperkalemia	Palpitation	Nervous system disorder
Hypotension	Nasopharyngitis	Shortness of breath
Cough	Hypoesthesia	Reduction in mean serum albumin
Transient kidney function worsening	Upper abdominal pain	Elevated lipid profile (triglyceride, cholesterol)
Bradikardia	Bronchitis	Hyperuricemia
GI problem	Vertigo	Proteinuria
Anxiety	Diarrhea	Musculoskeletal complaints
Urinary frequency	Edema	Elevated liver enzymes (increase AST/ALT > 3x the normal upper limit of normal (ULN)
Insomnia	Lightheadedness	Back pain
Tremor	Asthenia	Arthralgia
Constipation	Fatigue/weakness	Pharyngitis
Nausea	General pain	
Rhinorrhea	Rash/skin and subcutaneous tissue	
UTI		