Cost efficacy of S-Amlodipine *vs*. Racemic Amlodipine in Hypertension Management

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Abstract

Background: An equivalent efficacy compared with racemic amlodipine with reduced or insignificant peripheral edema makes S-amlodipine a cost-effective treatment alternative in hypertension. S-amlodipine has also been proven to be effective, safe, and well-tolerated even when used as combination therapy with other antihypertensive agents. S-amlodipine has added benefits in optimizing atherogenic lipids and reduces cardiovascular outcomes. The present review was performed to assess the health economics of the use of S-amlodipine in hypertension.

Methods: Authors conducted a systematic review of published literature to evaluate the health economics and outcomes research of the use of S-amlodipine in hypertension treatment. The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used to report this review.

Results and discussion: The authors finalized a total of 34 articles, including randomized clinical trials, systematic review, and meta-analysis. The authors discuss the health care cost benefits associated with managing hypertension, use of amlodipine and its cost efficacy in managing hypertension, the significance of S-amlodipine in terms of equivalence of antihypertensive efficacy reduced side effects, and better cost implications.

Conclusion: The authors concluded that S-amlodipine in hypertension treatment is not only cost-effective, but it also reduces the risk of peripheral edema when compared with racemic amlodipine.

Key points for clinicians

• It is economically viable to treat patients with diastolic blood pressure more than or equal to 90 mm Hg, except those below 45 years of age.

• Amlodipine is a cost-saving therapy compared with angiotensin receptor II blockers in preventing stroke, myocardial infarction in hypertension patients.

• S-amlodipine has equivalent antihypertensive activity, with a significantly reduced risk of peripheral oedema compared with racemic amlodipine.

• Use of S-amlodipine is cost effective and can save health care expenditure compared with standard care.

Keywords: Amlodipine • S-Amlodipine • Cost-effectiveness • Hypertension • Untreated Hypertension • Peripheral edema

Introduction

Hypertension prevalence has been gradually rising around the world, with India being a significant contributor [1]. A recent Indian blood pressure survey has reported that one in three individuals among Indian adults have hypertension, reaching up to 234 million adults with hypertension currently. An increased incidence of hypertension is also seen among individuals between the age of 22-44 years. In India, almost 52% of all deaths in those aged over 70 are attributed to cardiovascular events [1].

A major challenge in hypertension is that it remains undiagnosed in many individuals with hypertensive condition. Unmanaged hypertension is linked with an increased risk of myocardial infarction, heart failure, stroke, chronic kidney disease, cognitive decline, and increased risk of death from cardiovascular diseases [2].

Hypertension is an important critical factor leading towards cardiovascular complications with substantial economic costs associated with it [3]. Early detection and management of high blood pressure in primary health care can avert the higher costs of complications and serve a significant role in saving healthcare resources [4]. Calcium channel blockers (CCBs) are the first line of therapy in managing hypertension [5]. Even though CCBs have similar effectiveness for preventing vascular outcomes than other drug classes, they seem to be better than other drug classes to prevent stroke and all-cause mortality [5, 6]. However, the CCBs are linked with a significant risk of peripheral edema, which reduces patient compliance. According to the ASCOT-BPLA trial, peripheral edema occurred in almost 23% of the patients treated with amlodipine. Sometimes, a need to change over to another drug also arises due to an adverse event of pedal edema [5]. This review offers an inclusive review of the health care cost benefits associated with managing hypertension, use of amlodipine and its cost efficacy in managing hypertension, the significance of S-amlodipine in terms of equivalence of antihypertensive efficacy, reduced side effects, and better cost implications *vs.* racemic amlodipine.

Methods

The authors conducted a systematic review of published literature to evaluate the cost-effectiveness of racemic amlodipine and S-amlodipine in managing hypertension. The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used to report this review.

Criteria for including studies for the review

The inclusion criteria for inclusion of reviews in the study were clinical trials, randomized clinical trials, systematic reviews, and meta-analyses published during 2007 to 2020 that investigated the economic and clinical benefits of amlodipine or S-amlodipine, articles discussing the combination therapy with amlodipine or S-amlodipine, and articles in English language only. The articles were excluded if they were based on any other antihypertensive agents, narrative reviews, opinion editorials, other grey literature, and articles in languages other than English.

Literature Search

The search was primarily conducted on Medline, PubMed, and Google Scholar.

The aim of the authors was to evaluate all the published literature including randomized clinical trials, clinical trials, retrospective and prospective research, systematic reviews, and meta-analysis for amlodipine and S-amlodipine. A search was conducted on the digital bibliographic database, Medline, PubMed, Google Scholar. The MeSH terms and search phrase used were (((cost-effectiveness) AND (health economics)) AND (outcomes research)) AND (S -amlodipine). In a backward chronological search, all the relevant articles were searched for citations that were not identified in the initial search. Titles and abstracts following the electronic search were examined, and full-text articles fulfilling the selection criteria were obtained. Full text of the selected articles was thoroughly screened to extract the study data.

Screening

Titles and abstracts from the electronic search were checked, and articles meeting the selection criteria were obtained. Relevant information from all the selected articles was extracted. Two investigators independently extracted data from selected literature, and any difference of opinion was resolved through deliberations and consensus between the authors. Where an agreement was not reached, a third author acted as the referee.

Qualitative analysis of the selected articles was then conducted by the investigators. Figure 1 depicts the entire process of screening, inclusion & exclusion criteria, and the inclusion of the eligible articles (Figure 1).

Data Items, Extraction, and Synthesis

The study data were extracted by reading the complete article. Selected articles were reported in a table comprising of the following fields: record number, the name of the author(s), publication year, article title, and journal. Relevant data for eligible articles were extracted by two authors using pre-structured data extraction grids. These grids were used to extract author name, year of reporting, geographic area, use of s-amlodipine, benefits, and adverse events associated with using S-amlodipine. The disagreements were resolved as detailed above.

Data synthesis and Analysis

Due to the fewer number of studies and heterogeneity among those reporting about S-amlodipine's health economics and outcomes in hypertension, the results are presented using narrative summaries.

Results and Discussion

A total of 34 articles were carefully chosen in the present review. Based on an assessment of the selected articles, the themes that emerged included cost-benefit of controlling hypertension and preventing associated complications, the cost-effectiveness of amlodipine in managing hypertension, clinical outcome trials, the cost-effectiveness of amlodipine *vs.* ARB, antihypertensive efficacy and safety of S-amlodipine, the pleiotropic effect of S-amlodipine, and financial benefits of S-amlodipine. The themes are discussed in detail below.

Cost-benefit of controlling hypertension and preventing associated complications

A plethora of therapeutic approaches are involved in the management of hypertension. Besides efficacy, adverse effects (AEs) play an essential role in managing hypertension and improving adherence with therapy [3].

A study reported that the total per-person annual expenditure related with hypertension increased significantly from $58.7 billion to $109.1 billion from 2003 to 2017 in the US. This increase in expenditure is attributed to an increase in the number of individuals treated for hypertension [7].

It is an indisputable fact that hypertension may increase an individual's risk for cardiovascular diseases by almost two to three times with huge economic implications. The cost of treating hypertension has a massive share in healthcare economics and utilizes substantial healthcare resources. A study conducted in India revealed that assessing the yearly expense of hypertension care for a standard Primary Healthcare Centre (PHC) amounts to almost INR 1.07 crores [4].

Existing evidence has stressed that managing hypertension is a cost-effective approach in lowering cardiovascular conditions and mortality. In a study, the cost-effective analysis of expenditure on hypertension demonstrated that the care of patients with current cardiovascular disease or stage 2 hypertension saved lives and the costs for males aged 35 to 74 years and females between the ages of 45 and 74 years. The results specified that the management of stage 1 hypertension was cost-effective (defined as <$50 000 per QALY) for all males and females among the ages of 45 and 74 years, although the treatment of females aged 35 to 44 years with stage 1 hypertension but without cardiovascular disease showed moderate or low cost-effectiveness [8]. Given the resource limitations in India, there is a need to effectively utilize the available health resources; the preventive approach and early management of

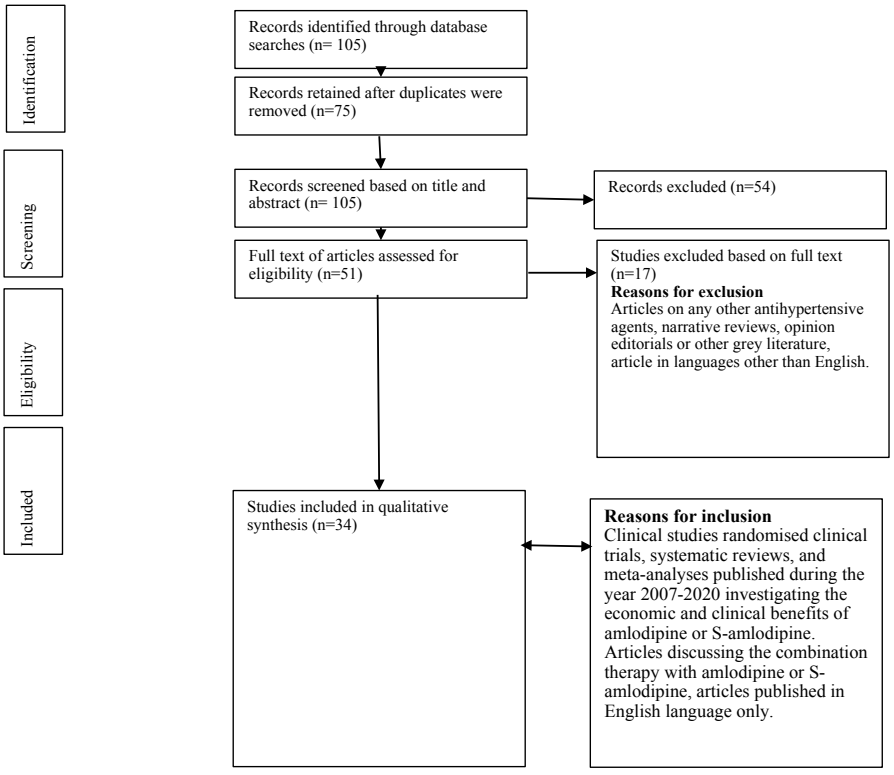

Figure 1: Flow diagram for study screening, selection, and inclusion.

hypertension assume immense significance [9].

An economic evaluation of antihypertensive treatment has indicated that it is economical to treat patients with diastolic blood pressure more than or equal to 90 mm Hg, except those under 45 years of age. The cost-effectiveness of this treatment further improves when other risk factors co-exist [10].

Cost-effectiveness of Amlodipine in Managing Hypertension

Among the medications, CCBs are the first-line antihypertensive agents advised for monotherapy or combination therapy as per the latest guidelines [3, 11-14]. Several analyses have assessed the cost-efficacy of amlodipine to prevent mortality and morbidity due to cardiovascular diseases [11].

Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) trial

In the within-trial evaluation of the ASCOT-BPLA trial, it was reported that despite the cost of the drugs being higher in the amlodipine group compared with the atenolol group, the costs were lower for all other resource groups, thereby counterbalancing 38-50% of the drug costs during the five-and-a-half-year trial period. These findings suggested that an amlodipine-based treatment was more reasonable in terms of health care costs than an atenolol-based treatment in patients with mild hypertension and further risk factors [12].

Prevention of Recurrent Venous Thromboembolism (Prevent) trial

The cost-effectiveness analysis of the PREVENT trial reported that when amlodipine besylate is added to standard care, the total cost reached up to € 139 050 per 1,000 patients treated for 36 months. This cost was reflected in €1,780 per patient who did not experience any vascular event [11]. Another analysis to study the cost-efficacy of amlodipine in the treatment of coronary atherosclerosis in the Swiss health system also corroborated the fact that the use of the calcium antagonist amlodipine in Coronary Heart Disease (CHD) patients is cost-effective [13]. In another analysis using a Markov cohort simulation model, amlodipine led to anticipated cost savings of US$ 2 566 per patient over three years, specifically by reducing the hospitalization due to cardiovascular-associated events and procedures [11].

Another analysis estimated the cost-efficacy of amlodipine in treatment of Swedish patients with CAD. The study results indicated that the use of amlodipine led to an improvement in clinical outcome and some financial savings in healthcare costs incurred over three years [14].

Coronary Angioplasty Restonosis Study (Capares) study

In a within-trial analysis comparing amlodipine besylate added to standard care with standard care alone, it was seen that amlodipine resulted in economical and more effective treatment than standard care. The use of amlodipine effectively decreased mortality, morbidity due to coronary diseases, and the requirement for revascularisation measures. The findings showed that the cost per 1,000 patients valued at €1 166,000 in the placebo and €950 000 in the amlodipine group led to a cost saving of €216 000, 18.5% of the total cost of routine care [15].

The findings in the evaluation of the health economic benefits of amlodipine in patients undergoing angioplasty in Canada and Norway showed that the potential cost savings over the treatment period of 4 months resulted from an improvement in the clinical outcomes for patients using amlodipine [16].

The analysis conducted in the UK patients using amlodipine compared with those on placebo after an angioplasty reported that the adjunctive use of amlodipine with Percutaneous Transluminal Coronary Angioplasty (PTCA) reduced the occurrence of all adverse clinical outcomes by 9.4% leading to a reduction in overall 4-month costs per patient using amlodipine of £204. When the cost of using amlodipine was compared with those not using amlodipine on an individual basis, the total projected cost was £3,833 and £4,037 respectively [17].

Amlodipine *vs* ARB: Cost-effectiveness

Amlodipine also provides blood-pressure independent benefit on stroke. CAD management is a high-cost revascularisation procedure and requires repeated admission to the hospital [18]. In a cost-efficient assessment between amlodipine and angiotensin II receptor blockers in Chinese patients, the findings reported total direct medical and drug expenditure on amlodipine and valsartan users to be 111, 731, 716 Yuan and 132, 058, 611 Yuan, respectively; total quality-adjusted life years for those on amlodipine and valsartan were 30, 648.5 and 30, 520.8, respectively. The study clearly showed that amlodipine was superior in terms of reduced costs and elevated QALYs. It was indicated that it is a cost-saving therapy compared with angiotensin II receptor blockers in preventing stroke myocardial infarction for Chinese hypertension patients [19].

Racemic Modifications of Amlodipine and Implications on Efficacy and Cost

Antihypertensive efficacy and safety of S-Amlodipine

S-amlodipine was developed from its racemic form to overcome the limitation of racemic amlodipine, such as a higher incidence of pedal edema (23%). S-amlodipine was approved in India in 2002 and is available in 47 countries, including China, Korea, Ukraine, the Philippines, and Nepal [3].

The LEADER study evaluated the comparative effectiveness of levoamlodipine using an ECHO (economic, clinical, humanistic, outcomes) model. The study reported a similar rate of composite major cardiovascular and cerebrovascular events (MACCE) (4.4% *vs.* 5.2%) occurred and reduced occurrence of adverse reactions (6.0% *vs.* 8.4%, P<0.001) with levoamlodipine maleate when compared with amlodipine besylate. The results showed that the rate of composite MACCE did not show statistical difference between the two groups after two years of treatment. However, a significant interaction between groups and diabetes with reference to the MACCE was observed. The patients without diabetes had lesser MACCE in the levoamlodipine maleate group. While the use of amlodipine is linked with adverse reactions including lower extremity edema, gingival pain and swelling, and headache; the LEADER study demonstrated that the rate of adverse reactions, especially edema, was considerably reduced in the levoamlodipine maleate group compared with the amlodipine besylate group [20].

It has been recognized in an Indian study by Pathak, Kelkar, and Manade that the S-amlodipine tablet at 2.5 mg produced a similar antihypertensive effect compared with amlodipine at 5 mg in hypertensive patients, thereby proving that S-amlodipine shows a similar effect at half the dose of amlodipine. Additionally, it was also shown that S-amlodipine led to a considerable lowering of blood pressure following 28 days of treatment. The baseline values for average systolic blood pressure in standing, supine, and sitting positions in the S-amlodipine 2.5 mg treatment group were 164.12 ± 10.28 165.72 ± 10.88 and 165.24 ± 10.66 mm of Hg respectively, which after treatment of six weeks changed to 144.9 ± 7.4, 146.04±8.56 and 145.36±8.32 mm of Hg. The baseline values for average diastolic blood pressure in standing, prone, and sedentary positions in the S-amlodipine 2.5 mg treatment group were reported to be 99.63 ± 6.22, 101.13 ± 7.18 and 100.59 ± 6.6 mm of Hg, respectively, which at the end of six weeks treatment changed to 86.0 ± 4.70, 87.18 ± 5.20 and 86.27 ± 5.68 mm of Hg [21]. Another study conducted on the Indian population By Ramya JE, and Meenakshi B has exhibited that S-amlodipine 2.5 mg was equivalent in efficacy and better tolerable compared with racemic from of amlodipine in mild to moderate hypertension at 12 weeks of treatment [22].

Mohanty et al. conducted a study in India comparing the occurrence of edema with S-amlodipine with amlodipine and cilnidipine. They reported that the incidence of peripheral edema with S-amlodipine and cilnidipine was substantially lesser than racemic amlodipine in men (6.7% and 0.0% versus 36.7%, resp.) and women (10.0%and 3.3%versus 43.3%, respectively) (p<0.001 for comparison of both the drugs in either gender) [23]. These results have also been proven in Asian, Far Eastern, and Turkish populations [24].

The S-enantiomer of amlodipine has been reported to possess antihypertensive efficacy with significantly less or minimal peripheral edema establishing it to be a cost-effective treatment option in hypertension. The meta-analysis conducted by Liu et al. has shown that following four weeks of treatment, the weighted mean difference of systolic blood pressure and diastolic blood pressure decrease was -2.84 (95% CI, -6.42 to 0.74) with S-amlodipine and -1.71 (95% CI, -3.48 to 0.06) with racemic amlodipine. After eight weeks of treatment, the weighted mean difference of systolic blood pressure and diastolic blood pressure decrease was -1.13 (95% CI, -5.29 to 3.03) and -1.34 (95% CI, -2.67 to -0.01), respectively. Amongst all the trials included

in the study, S-amlodipine treatment was related to considerably low edema than racemic amlodipine (RD, -0.02; 95% CI, -0.03 to 0.00) [25]. The study has clearly shown that a starting high dose of S-(-) amlodipine enhanced ambulatory hypertension optimization with equivalent tolerability compared with a starting low dose in hypertension [26]. It is important to note that in the systematic review and meta-analysis by Liu et al., it was suggested that no trial was identified that demonstrated the cardiovascular outcomes (incidence of stroke and myocardial infarction). Besides, for the measurement of secondary outcomes such as lowering of BP, the combined results of the studies indicated that (S)-amlodipine 2.5 mg did not show significant changes from racemic amlodipine 5.0 mg [25].

Additionally, edema was reported in 2%to 11%of patients who were given racemic amlodipine, which was a common adverse event linked with dihydropyridine CCBs. However, when only high-quality studies were included for analysis, there was no significant difference. Since medication adherence is an essential element for the effective management of hypertension, the presence of adverse events influences drug use behaviour. Hence, there is a need to assess edema's influence on patient compliance with (S)-amlodipine and racemic amlodipine therapy [25].

A clinical trial conducted in Sri Lanka has proven that patients with uncontrolled hypertension on a prior beta-blocker and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, the addition of S-amlodipine provided better tolerability with decreased occurrence of peripheral edema and equivalent antihypertensive effect at half the dose of conservative amlodipine [27]. Two Korean studies demonstrated that adult Korean patients with hypertension experienced less ankle edema, with equivalent blood pressure reduction and tolerability profile with S-amlodipine than a racemic mixture of amlodipine [28,29]. A study conducted among adult Korean patients comparing S-amlodipine with amlodipine reported no significant differences between the changes in sitting diastolic blood pressure (SiDBP) and sitting systolic blood pressure (SiSBP). The SiDBP response rates were 92.7% in the S-amlodipine group and 88.0% in the amlodipine group. There was no substantial variation in the two groups in the prevalence of adverse events and adverse drug reactions [28]. In an exploratory study among female Korean patients, findings revealed a lowering of 40.24 (110.05) mL in the mean ankle-foot volume following 12 weeks of treatment with S-amlodipine. The mean ankle-foot volume in the amlodipine treated group showed a rise of 30.03 (69.59) mL. Hence, there was a substantial variation in ankle-foot volume change between the two groups (-70.26 mL [95% CI, -134.60 to -5.94], P=0.028). However, at the end of 12 weeks' treatment, there was no substantial mean change in the sitting systolic blood pressure between the two groups, S-amlodipine, and amlodipine (-21.82 [8.76] *vs.*- 26.82 [11.89] mm Hg; P=0.172). The alterations in the mean sitting diastolic blood pressure were also not significant (-14.71 [6.94] *vs.* -10.88 [5.81] mm HG; P=0.091) [29]. When assessed in healthy volunteers, it was noted that the plasma concentration of pharmacologically active S-enantiomer of amlodipine contributed to higher values of the concentration of total amlodipine (41% R enantiomer to 59% S-enantiomer for the AUC) [30].

Pleiotropic effect of S-Amlodipine

While both S-amlodipine and the racemic amlodipine can enhance endothelial function in patients with hypertension, amlodipine has favourable vascular endothelial protection [31]. Another comparative study showed that monotherapy with S-amlodipine was instrumental in reducing left ventricular hypertrophy in 55% of cases and optimization of left ventricular diastolic function in 62.4% of cases of arterial hypertension. Its use also led to a remarkable improvement of brachial artery vasomotor function. Following a 24-week treatment with S-amlodipine in hyperlipidemia patients, atherogenic lipoproteins and total cholesterol was significantly reduced [32].

In a study, the authors have shown that the use of S-amlodipine resulted in substantial improvement in left ventricle structure and function and brachial artery function, and the lowering of atherogenic lipoproteins total cholesterol levels [32].

In a randomized, double-blind, prospective cohort study in individuals with type 2 diabetes mellitus, a comparison between S-amlodipine (2.5 -5 mg/d, n=112) and losartan (50-100 mg/d, n=115) was conducted, and a significant alteration in insulin levels and insulin sensitivity index was observed with both the drugs after three years ($p<0.05$). The study findings have established an equivalent efficacy of s-amlodipine to an angiotensin receptor blockers-losartan in bettering the insulin sensitivity in patients with high blood pressure and abnormal fasting blood glucose levels [33]. Besides, another study has shown that S-amlodipine can prevent accumulation of platelets in high-risk patients like hypertension with type 2 diabetes mellitus [3].

Cost-effectiveness of S-Amlodipine

In a rational comparative LEADER study carried out at 110 centres across China in 10,031 outpatients with high blood pressure treated with S-amlodipine or amlodipine, with 24 months follow-up, the cost analysis revealed that S-amlodipine was linked with a mean cost savings of 2725 (95% CI: 2279-3236) Yuan per patient for the total population and a gain of 0.00392 (95% CI: 0.00020-0.00759) Quality Adjusted Life Years (QALYs) (1.98835 *vs.* 1.98444, respectively). The median total costs (including direct medical and non-medical expenditure and indirect health expenditure) were 5203 (25^{th}-75^{th} percentile (P25-P75): 3080-8230) Yuan and 7262 (P25-P75: 4628-10, 662) Yuan in the s-amlodipine group and the amlodipine group, respectively. It is proven that there is a 100% probability of S-amlodipine being more cost-effective than amlodipine if the decision-makers were ready to pay 150 000 Yuan per QALY achieved. The authors have suggested that S-amlodipine could lower cost by 29% with a similar composite primary cardiovascular and cerebrovascular events incidence rate and reduced incidence of adverse reactions (particularly edema and headache) when compared with amlodipine. However, the study's limitation is that in clinical practice, because of the reduced cost of levoamlodipine maleate, the physicians sometimes recommend prescribing levoamlodipine to patients in the somewhat low economic position and those without health insurance, which may cause some bias. The non-fatal MACCE was a composite event; hence the real utility of diverse specific events may vary widely [20].

A cost-effective retrospective analysis conducted in China compared the disparity between S-Amlodipine *vs.* racemic amlodipine through a respective cost-efficiency analysis. At the end of 4 to 8 weeks' treatment, no statistically significant change in efficacy rate between S-Amlodipine and racemic groups (84.91% *vs.* 77.45%) was seen. The study findings stated that the cost of lowering 1 mm Hg systolic pressure and diastolic pressure in the S-Amlodipine group was 8.1 Yuan (RMB) and 10.5 Yuan (RMB) while the same in the racemic group was 16.9 Yuan (RMB) and 21.7 Yuan (RMB) respectively. The cost of amlodipine is 100% more than that of S-Amlodipine. Following long-term treatment of 6 months, the cost for reducing 1 mm Hg systolic pressure and diastolic pressure in the S-Amlodipine group (124 cases) were 31 Yuan and 43 Yuan, and 50 Yuan and 75 Yuan in the Amlodipine group (104 cases), respectively. This time the price of amlodipine was 1.62 -1.79 times more than that of S-Amlodipine. The study also reported that the adverse reaction of the S-amlodipine group (4.6%) was significantly less than the amlodipine group (10.3%). Hence, this sensitivity analysis in China suggested that S-Amlodipine possessed more economic value [34].

Conclusion

CCBs are one of the first-line drugs in hypertension treatment with proven cardiovascular benefit. However, owing to the adverse event of peripheral edema, amlodipine is also associated with poor medication adherence. The chiral pure form of racemic amlodipine, i.e., S-amlodipine, has equal antihypertensive efficacy at the half dose of racemic amlodipine, which could lower the metabolic load of the drug when used as a single drug and given along with other antihypertensive agents. Besides, the risk of peripheral edema is significantly lower with S-amlodipine use compared with racemic amlodipine. The use of S-amlodipine is not only cost-effective, but it is also suggested to save health care expenditure compared with standard care. Future cost-effectiveness research should be conducted to focus on cardiovascular benefits using S-amlodipine in patients with hypertension, other comorbidities, and associated complications.

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(iii) Author contributions

JK: Conception and design, literature search, data extraction of the relevant studies, drafting and critically revising the article, and final approval of the published version.

UG: Literature search, data extraction of the relevant studies, qualitative assessment of the eligible studies, drafting and critically revising the article, and final approval of the version to be published.

SM: Critical review of the article, data extraction from the relevant article, and final approval of the version to be published.

JT: Contributed towards conception and design, data extraction from the researched articles, qualitative assessment of the selected studies, critically revised the article, and final approval of the version to be published.

SV: Data extraction from selected articles, critical review of the article, and final approval of the version to be published.

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