Review Article

S-Amlodipine: An Isomer with Difference—Time to Shift from Racemic Amlodipine

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Received 19 November 2017; Accepted 8 April 2018; Published 20 May 2018

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Calcium channel blockers are among the first-line drugs for treatment of hypertension (HTN). S-amlodipine (S-AM), an S-enantiomer of amlodipine, is available in India and in other countries like China, Korea, Russia, Ukraine, and Nepal. Being clinically researched for nearly two decades, we performed an in-depth review of S-AM. This review discusses clinical evidence from total 42 studies (26 randomized controlled trials, 14 observational studies, and 2 meta-analyses) corroborating over 7400 patients treated with S-AM. Efficacy and safety of S-AM in HTN in comparison to racemic amlodipine, used as monotherapy and in combination with other antihypertensives, efficacy in angina, and pleiotropic benefits with S-AM, are discussed in this review.

1. Introduction

Management of hypertension (HTN) involves different therapeutic approaches. Among the medications for treating HTN, calcium channel blockers (CCBs) are one of the first-line agents as recommended by recent Joint National Committee 8 (JNC-8) guidelines [1]. Besides efficacy, occurrence of adverse effects (AEs) plays an important role in maintaining adherence with medications [2]. Occurrence of peripheral edema is the major reason for poor adherence with amlodipine. The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) [3] reported peripheral edema in 23% patients receiving amlodipine. This suggests that nearly 1 out of 4 patients treated with amlodipine may develop peripheral edema. Conventionally used amlodipine is a mix of S- and R-enantiomers. Development of separate enantiomers improves pharmacokinetics (PK) and avoids undesirable AEs [4]. From R- and S-isomers of amlodipine, S-enantiomer has nearly 1000 times greater affinity for the receptor site. Further, S-amlodipine (S-AM) has less variable PK, lower intrasubject variation, and longer half-life [5]. S-AM is equally efficacious at half-dose with better tolerability and lesser incidence of peripheral edema than racemic amlodipine (Amlo) [6].

S-AM is marketed world-wide. The central drugs standards control organization (CDSCO), India, approved S-AM on 16 August 2002 for its use in HTN [7]. Globally, S-AM has been approved and is being used in countries like China [8], Korea [9], Ukraine [10], Philippines [11], and Nepal [12]. Besides these, S-AM is marketed in nearly 47 countries [13]. Since S-AM approval in China (1999) [14] and in India (2002) [7], it has been studied extensively. As being researched for nearly two decades, we performed an in-depth review of clinical evidence of S-amlodipine and provided key summary with identification of areas for further research.
2. Search Methodology and Literature Details

We performed search using terms “S-Amlodipine” or “levamlodipine” across electronic databases like PUBMED, Google Scholar, and clinical trials registry, http://www.clinicaltrials.gov. Additionally, a general search at Google search engine was performed. Clinical studies including randomized trials and observational and postmarketing studies before June 2017 were included in the review. Journals articles available only as print copies were also included in the review. For non-English literature articles, information available from the abstracts was captured.

After an extensive search, we included total 42 studies. In these, 26 were RCTs (20 monotherapy and 6 combination studies), 14 were observational studies (13 monotherapy studies and 1 combination study) and two were meta-analyses. From these, a maximum number of studies (n = 18) were from China followed by 11 from India, 6 from Korea, 3 each from Russia and Ukraine, and one from Sri Lanka. Combined from all the studies, over 7400 patients had received S-AM either alone or in combination with other antihypertensives. In these studies, racemic amlodipine was the major comparator in 26 studies and in two meta-analyses as well. As monotherapy and/or combination therapy, other comparator molecules from 10 studies were lercanidipine (Lercan), nifedipine sustained release (Nifed-SR), cilnidipine (CLD), ramipril (Rami), enalapril (Enala), losartan (Los), telmisartan (Telmi), and indapamide. In five observational studies, there was no comparator to S-AM. In two combination studies, the combination treatment was compared to S-AM monotherapy.

3. S-Amlodipine in Hypertension

For its use in HTN, S-AM has been evaluated in various RCTs (total 22) and observational studies (total 9) either as monotherapy (total 25) or in combination (total 6 RCTs only). Two meta-analyses were performed in 2010 and 2015 with 15 and 8 studies of S-AM (levamlodipine), respectively. Major findings from the RCTs, observational studies, and meta-analyses are summarized in Tables 1, 2, and 3, respectively. Most of these studies were comparing S-AM (2.5 to 5 mg) to racemic amlodipine (5 to 10 mg) and found near equal antihypertensive efficacy with lower incidence of side effects. Two RCTs especially evaluated ankle (peripheral) edema with S-AM in comparison to Amlo and reported significantly lower incidence of edema with better tolerability of S-AM [15, 16]. Besides racemic amlodipine, S-AM was compared to lercanidipine [17, 18] and ramipril [19] in three trials. S-AM had nearly similar efficacy and tolerability to lercanidipine. However, its efficacy and safety were better than that of ramipril (Table 1). A study from Chen et al. [20] needs a special mention as they compared higher-dose (5 mg) to the lower-dose (2.5 mg) of S-AM (Table 1). After 8-week treatment, 24-hour ambulatory systolic BP (SBP) reduction was significantly greater in 5 mg group than in 2.5 mg of S-AM (between group difference: 2.1 mmHg, p = 0.02). However, 24-hour diastolic BP (DBP) reduction was similar (between group difference: 0.9 mmHg, p = 0.17). Interestingly, the incidence of overall AEs was similar (20.0% versus 17.0%, resp., p = 0.05) in both groups and proportion of individual AEs was nearly equal in both doses. This perpetuates that S-AM can be safely used of high-dose of 5 mg per day with incremental efficacy.

All nine observational studies were monotherapy trials (Table 2). In these, racemic amlodipine was comparator in four studies, lercanidipine in one, and cilnidipine in one trial. Four studies were single arm trials with no comparator. Four studies without any comparator, the safety and efficacy of S-amlodipine (SESA) studies, were the postmarketing trials that reported significant BP reduction with significantly less or no occurrence of pedal edema in Indian hypertensive patients (Table 2) [21–24]. Occurrence of edema with S-AM in comparison to Amlo and cilnidipine was evaluated in another observational study from India. Incidence of peripheral edema with S-AM and cilnidipine was significantly lower than racemic amlodipine in males (6.7% and 0.0% versus 36.7%, resp.) and in females (10.0% and 3.3% versus 43.3%, resp.) (p < 0.001 for both drug comparisons in either gender) (Table 2) [25].

S-AM was also assessed in combination with other antihypertensives like atenolol [26, 27] and telmisartan [28, 29] and in patients receiving both angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB) and beta blocker (BB) [16]. In studies of combination with atenolol and ACEI/ARB + BB, S-AM had similar antihypertensive efficacy compared to racemic amlodipine (Table 1). However, in two separate studies, combination of S-AM and telmisartan (40–80 mg) was associated with greater BP reduction compared to monotherapy of telmisartan 80 mg or S-AM 2.5 mg (Table 1). Tolerability of telmisartan-based combinations was reported to be similar or better than the comparative monotherapy treatments (Table 1).

In a meta-analysis (Table 3) of 15 trials, Liu et al. [30] reported similar effect of S-AM (2.5 mg) on BP compared to racemic amlodipine (5 mg). From three high-quality RCTs included in the meta-analysis, weighted mean difference (WMD) of SBP and DBP was −2.84 (95% confidence interval (CI), −6.42 to 0.74) and −1.71 (95% CI, −3.48 to 0.06), respectively, after 4-week treatment (one RCT) whereas it was −1.13 (95% CI, −5.29 to 3.03) and −1.34 (95% CI, −2.67 to −0.01), respectively, after 8-week treatment (two RCTs). Further, S-Amlo was associated with significantly less edema than racemic amlodipine (risk difference, −0.02; 95% CI, −0.03 to 0.00). Another meta-analysis performed recently by Zhao and Chen [31] involving 1456 patients from eight studies reported that levamlodipine (S-AM) was efficacious (odds ratio (OR) 2.19, 95% CI 1.61–2.97; p < 0.01) and safer (OR 0.51, 95% CI 0.34–0.77; p < 0.01) than racemic amlodipine. Thus, available evidence from RCTs, observational studies, and meta-analyses finds equivalent BP lowering efficacy of S-AM against racemic amlodipine with better tolerability. Incidence of pedal edema is found to be significantly lesser with S-AM than racemic amlodipine.

4. S-Amlodipine in Angina

The antianginal effects of racemic amlodipine are known. Systemic vasodilation with reduction afterload reducing cardiac workload and dilatation of coronary vasculature and...
| Author (year)          | Country | S-AM (mg) | Comparator (mg) | n     | Duration (weeks) | Antihypertensive efficacy | AEs               |
|-----------------------|---------|-----------|-----------------|-------|------------------|----------------------------|---------------------|
| Liu et al. (2001) [44]| China   | 2.5       | Amlo (5)        | 30/30 | 4                | Equivalent                 | NA                  |
| Fang (2002) [45]      | China   | 2.5       | Amlo (5)        | 140/140 | 40              | Equivalent                 | NR                  |
| Cheng et al. (2002) [46]| China     | 2.5–5   | Amlo (5–10)     | 60/60 | 5                | Equivalent                 | No difference, milder with S-AM |
| Hiremath and Dighe (2002) [47]| India    | 2.5       | Amlo (5)        | 25/25 | 6                | Mean change of SBP/DBP (S-AM Vs Amlo) | None               |
| Kerkar (2003) [48]    | India   | 2.5       | Amlo (5)        | 25/25 | 6                | Mean change of SBP/DBP (S-AM Vs Amlo) | None               |
| Pathak et al. (2004) [49]| India     | 2.5       | Amlo (5)        | 97/91 | 6                | Mean change of SBP/DBP (S-AM Vs Amlo) | None               |
| Zhang (2006) [50]     | China   | 2.5–5     | Amlo (5–10)     | 36/36 | 8                | S-AM: 165.30/98.22 to 132.70/81.87 Amlo: 164.30/99.30 to 134.10/85.61 | Number: 1 vs 6 |
| Bae et al. (2008) [51]| Korea   | 2.5       | Amlo (5)        | 58/60 | 8                | SBP: −24.27 ± 11.55 vs −25.24 ± 12.47 DBP: −14.73 ± 8.9 vs −14.56 ± 9.28 S-AM non-inferior to Amlo | No significant differences |
| Zhu et al. (2008) [52]| China   | 2.5–5     | Amlo (5–10)     | 44    | 8                | Mean change in SBP: 156.26 to 131.50 vs 158.23 to 131.74 DBP: 98.48 to 83.28 vs 99.18 to 83.19 | None               |
| Author (year)       | Country | S-AM (mg) | Comparator (mg) | n      | Duration (weeks) | Antihypertensive efficacy | AEs                  |
|---------------------|---------|-----------|-----------------|--------|------------------|--------------------------|------------------------|
| Youn et al. (2010)  | Korea   | 2.5       | Lercanit        | 32/29  | 8                | Mean change              | sSBP: −20.5 ± 13.6 vs −19.93 ± 14.5 sDBP: −14.03 ± 8.07 vs −12.93 ± 8.68  |
|                     |         |           |                 |        |                  |                          | None                   |
| Kim et al. (2011)   | Korea   | 2.5       | Rami (2.5–5)    | 68/70  | 8                | Mean change              | SBP: −18.1 ± 7.91 vs −14.3 ± 11.96 (p = 0.047)              |
|                     |         |           |                 |        |                  |                          | DBP: −12.7 ± 7.02 vs −9.6 ± 7.38 (p = 0.023)                |
|                     |         |           |                 |        |                  |                          | BP normalization rate: 81.3% vs 61.4% (p = 0.017)               |
|                     |         |           |                 |        |                  |                          | 5.8% vs 14.2% (p = 0.012)                                |
| Shengye (2012)      | China   | 2.5–5     | Amlo (5–10)     | 90/90  | 8                | Equivalent               | Milder with S-AM       |
| Oh et al. (2012)    | Korea   | 2.5–5     | Amlo (5–10)     | 17/17* | 12               | Mean change              | sSBP: −21.82 ± 8.76 vs −26.82 ± 11.89 (p = 0.172)                     |
|                     |         |           |                 |        |                  |                          | sDBP: −14.71 ± 6.94 vs −10.88 ± 5.81 (p = 0.091)                  |
|                     |         |           |                 |        |                  |                          | Significant improvement in ankle edema with S-AM (AFV difference: −70.26 mL, p = 0.028) |
| Zhao (2013)         | China   | NA        | Nifed-SR        | 61/61  | NA               | Significant reduction in BP in both groups Overall response rate: 91.8% vs 80.33% (p < 0.05) |
|                     |         |           |                 |        |                  |                          | Lower with S-AM: 6.56% vs 18.03% (p < 0.05)                        |
| Parvathi et al. (2014) | India  | 2.5       | Amlo (5)        | 54/54  | 12               | SBP change: −32.4 vs −26.9 DBP change: −13.4 vs −12.0          |
|                     |         |           |                 |        |                  |                          | Edema significantly lower with S-AM: mean change AC: 0.26 vs 0.02 (p < 0.009) |
| Chen et al. (2017)  | China   | 2.5       | S-AM (5)        | 263/260| 8                | SBP: 6.0 vs 8.1 (p = 0.02) DBP: 3.8 vs 4.7 (p = 0.17) Target BP achievement: SBP: 81.8% vs 90.8% DBP: 84.0% vs 94.2% SBP&DBP: 75.7% vs 87.3% (p = 0.003) |
|                     |         |           |                 |        |                  |                          | 17.0% vs 20.0 (p = 0.05)                               |
| Author (year) | Country | S-AM (mg) | Comparator (mg) | n   | Duration (weeks) | Antihypertensive efficacy | AEs |
|--------------|---------|-----------|----------------|-----|-----------------|---------------------------|-----|
| Combination Studies (n = 6) | | | | | | | |
| Rajanandh et al. (2013) | India | 2.5 | Amlo (5) | 32/32 | 24 | Mean change | No difference: 21.9% vs 31.3% |
| Maksimova et al. (2013) | Russia | 2.5 | Amlo (5) | Total: 31 | LSM reduction | Number: 8 vs 16 |
| Hu and Xiao (2013) | China | NA | Indapamide | 83 | 12–24 | At 12 and 24 weeks | |
| Ihm et al. (2016) | Korea | 2.5 | S-AM 2.5 | 63/63/61 | 8 | Mean NP change in groups: 2.5/40 & 5/40 vs S-AM 2.5 |
| Park et al. (2016) | Korea | 2.5 & 5 | T (80) | 61/60/62 | 8 | No differences: 18.6%, 20.0% vs 22.6% |
| Galappatthy et al. (2016) | Sri Lanka | 2.5–5 | Amlo (5–10) | 76/70 | 16 | Responders Rate: Similar- 98.57% vs 98.68% |

AC: ankle circumference, ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker, AEs: adverse effects, AFV: ankle-foot volume, Amlo: racemic amlodipine, ARR: absolute risk reduction, AT: atenolol, BB: beta blocker, BP: blood pressure, DBP: diastolic BP, DBPV: DBP variability, FDC: fixed-dose combination, HR: heart rate, LSM: least square mean, Nifed-SR: nifedipine sustained release, NA: not available, NR: not reported, RRR: relative risk reduction, RR: risk reduction, S-AM: S-amlodipine, SBP: systolic BP, SBPV: SBP variability, and T: telmisartan; * only females; † chlorthalidone 12.5 mg was added to treatments if BP remained uncontrolled with study medications.
| Author (year)         | Country   | S-AM (mg) | Comparator (mg) | n      | Duration (weeks) | Antihypertensive efficacy | AEs                      |
|----------------------|-----------|-----------|-----------------|--------|-----------------|---------------------------|--------------------------|
| SESA (2003) [21]    | India     | 2.5–5     | -               | 1859   | 4               | 2.5 mg: 161/100 to 129/84  | Rate: 1.61%              |
|                      |           |           |                 |        |                 | 5 mg: 179/107 to 137/86   | Edema: 0.75%             |
|                      |           |           |                 |        |                 | p < 0.0001 for both       |                          |
| SESA-II (2005) [22] | India     | 2.5–5     | -               | 2230   | 4               | SBP: −26.65                | Reduction in pedal edema:|
|                      |           |           |                 |        |                 | DBP: −13.30                | 93% cases, RRR: 95.4%     |
|                      |           |           |                 |        |                 | HR: −3.51                  |                          |
| SESA-IV (2007) [23] | India     | 2.5–5     | -               | 1076   | 4               | SBP: −24.27 (p < 0.0001)   | Edema: 1.77%             |
|                      |           |           |                 |        |                 | DBP: −13.28 (p < 0.0001)   |                          |
|                      |           |           |                 |        |                 | HR: −4.87 (p < 0.0001)     |                          |
| SESA-IVA (2007) [24]| India     | 2.5–5     | -               | 30     | 4               | 2.5 mg: 150.48/92.28 to    | None                     |
|                      |           |           |                 |        |                 | 128.57/80.86               |                          |
|                      |           |           |                 |        |                 | 5 mg: 165.78/95.55 to 132/82.22 |                          |
|                      |           |           |                 |        |                 | p < 0.0001 for both        |                          |
| Bobroff et al. (2007) [57] | Ukraine | 2.5–10   | Amlo (5–10) | 60/38  | 12              | In both groups, significant reduction in | Peripheral edema; 1.6%   |
|                      |           |           |                 |        |                 | Average daily BP          | versus 78%               |
|                      |           |           |                 |        |                 | Daytime BP                |                          |
|                      |           |           |                 |        |                 | Nighttime BP              |                          |
| Basu (2007) [58]    | India     | 5         | Amlo (10)       | 10/10  | 4               | SBP: 154.4 to 130.4 versus  | None                     |
|                      |           |           |                 |        |                 | 130.4 to 132.4             |                          |
|                      |           |           |                 |        |                 | DBP: 99.1 to 77.5 versus   |                          |
|                      |           |           |                 |        |                 | 82.7 to 78.4               |                          |
|                      |           |           |                 |        |                 | Target of <140/90: 83.3% versus |                          |
|                      |           |           |                 |        |                 | 84.2%                      |                          |
| Sierkova et al. (2009) [59] | Ukraine | NA       | Amlo           | 31/32  | NA              | Equal BP reduction with 2 times | Lesser with S-AM        |
|                      |           |           |                 |        |                 | lower dose of S-AM          |                          |
| Koval et al. (2013) [18] | Russia  | NA       | Lercani       | NA     | NA              | Similar efficacy in reducing BP in | Lower with lercanidipine |
|                      |           |           |                 |        |                 | HTN with obesity          |                          |
| Mohanty et al. (2016) [25] | India   | 2.5–5    | Amlo (5–10) and CLD (10–20) | 60/60/60 | 12              | NR                        | Incidence of Edema M: 6.7% vs 36.7% and 0.0% F: 10.0% vs 43.3% and 3.3% |

AEs: adverse effects, Amlo: racemic amlodipine, BP: blood pressure, CLD: cilnidipine, DBP: diastolic BP, F: females, HR: heart rate, HTN: hypertension, Lercani: lercanidipine, M: males, MAP: mean arterial pressure, NA: not available, RRR: relative risk reduction, S-AM: S-amlodipine, SESA: safety and efficacy of S-Amlodipine, and SBP: systolic BP.
Table 3: Meta-analyses of S-amlodipine in hypertension.

| Author (year)          | Country | S-AM (mg) | Comparator (mg) | n   | Duration (weeks) | Antihypertensive efficacy | AEs                      |
|------------------------|---------|-----------|-----------------|-----|-----------------|----------------------------|--------------------------|
| Liu et al. (2010) [30] | China   | 2.5       | Amlo (5)        | 15  | 4–40            | All trials: Similar efficacy | Similar; RD: all trials: −0.04; High quality: −0.04 |
|                        |         |           |                 |     |                 | Only high-quality trials: WMD for decrease in SBP/DBP at 4 weeks: −2.84/−1.71 8 weeks: −1.38/−1.33 |                         |
| Zhao and Chen (2015) [31] | China   | NA        | Amlo            | 8   | 732/724        | Significantly better efficacy of S-AM than Amlo: OR 2.19 (p < 0.01) | Significantly lower rate of AEs: OR 0.51 (p < 0.01) |

AEs: adverse effects, Amlo: racemic amlodipine, BP: blood pressure, DBP: diastolic BP, NA: not available, OR: odds ratio, RD: risk difference, S-AM: S-amlodipine, and SBP: systolic BP.
reduction in cardiac oxygen consumption underlie the relief in anginal cases. Being an isomer of amloidipine, S-AM has also shown efficacy in angina. In SESA-Angina study (2005) [32] conducted in India, patients of ischemic heart disease (IHD) with history of angina and positive stress test (n = 25) were included. No other concomitant treatments were allowed during the treatment period of 8 weeks. S-AM (2.5–5mg/d) treatment was associated with significant reduction in average number angina attacks in every 15 days (p < 0.0001) and significant improvement in anginal symptoms (94.1%). After treatment, there was significant increase in exercise capacity (p < 0.0001) and nonsignificant increase in time required for 1.5mm ST-segment depression (p = 0.1764) and maximum workload achieved (p = 0.1170). No AEs were reported in any patient. This emphasizes efficacy and safety of S-AM in management of angina.

5. S-Amlodipine and Pleiotropic Benefits

5.1. Effect on Arterial Stiffness and Endothelial Function. Efficacy of S-AM for change in arterial stiffness and endothelial function was assessed in four RCTs [33–36] and in one observational study [37]. In a 12-week randomized study, Liangjin et al. (2013) [33] compared levamlodipine (S-AM, 2.5–5 mg, n = 40) to nifedipine sustained release (Nifed-SR, 10 mg, n = 40) for its effect on BP variety ratio (BPVR) and CIMT. Compared to baseline, systolic and diastolic BPVR was significantly better with S-AM than Nifed-SR at 12 weeks. CIMT was reduced significantly with S-AM (p < 0.05) but not with Nifed-SR (Table 4). There was significant correlation of BPVR with CIMT in S-AM group. Changes in lipid parameters and C-reactive protein were nonsignificant in both groups.

One RCT [34] reported significant improvements in flow mediated dilatation [FMD] after 6-week treatment with S-AM and racemic amloidipine. Continued treatment for 12 weeks was found to lower serum cholesterol equally in both groups. Guo et al. [35] reported significant improvements in the central BP components, brachial-ankle pulse-wave velocity (PWV), ambulatory arterial stiffness index (AASI), and the variability of ambulatory BP in both S-AM and racemic amloidipine treatment. However, both treatments were not associated with significant changes in CIMT. Thus, the benefits with S-AM on vascular function are similar to those exerted by racemic amloidipine. In another 6-week, randomized, crossover trial, Si et al. [36] reported that FMD%, nitric oxide (NO) and endothelial nitric oxide synthase (eNOS) levels were significantly improved in both groups with no between treatment differences. Increase in NO levels in cultured human umbilical vein endothelial cells was significant with both treatments but more marked in Amlo. Authors concluded that, with S-AM, probably antihypertensive effect is the cause of improved vascular function and S-AM may exert its protective effect on endothelial function by unknown mechanism. However, a 6-month study which assessed effects of S-AM (5–10 mg/d) and enalapril (10–20 mg/d) combination compared to enalapril alone on endothelial dysfunction in patients with chronic pulmonary heart disease (CPHD) and HTN (n = 65) observed that S-AM added to enalapril is associated with further improvements in endothelial function than enalapril alone in HTN. This was probably because of more pronounced reduction in endothelin-1 (ET-1) level after treatment with two drugs (3.86 ± 0.24 to 1.95 ± 0.19 pg/mL, p < 0.05) compared to enalapril alone (3.32 ± 0.27 to 1.83 ± 0.21 pg/mL, p < 0.05). Therefore, though there remains uncertainty about possible mechanisms, S-AM may exert some protection effect on endothelium by improving eNOS levels and reducing ET-1 levels [37].

5.2. Effect on Structure and Function of Left Ventricle and Brachial Artery. Iskenderov and Saushkina (2013) [38] assessed S-AM (n = 61) and Amlo (n = 66) in stages 1-2 HTN patients using left ventricular (LV) and brachial artery structural and functional parameters. After 24-week treatment, S-AM was associated with comparable BP reduction to Amlo, but the mean dose was significantly lower (7.5 ± 0.8 versus 11.6 ± 1.4 mg/day; p < 0.01). Significant improvement in LV structure and function and brachial artery function were reported. Reductions in atherogenic lipoproteins and total cholesterol were also significant with S-AM.

5.3. Efficacy in Renal Transplant Patients. Tang et al. (2003) [39] observed that, in kidney transplant patients with HTN (n = 20), S-AM (2.5 to 5 mg) treatment for 2 months was associated with significant reduction in SBP (p < 0.01), DBP (p < 0.01), and blood nitrogen (p < 0.05) with no increase of serum creatinine (p > 0.05). Normalization of BP was reported in 85% of patients.

5.4. Efficacy in Insulin Resistance. In a randomized, double-blind, prospective cohort study in type 2 diabetes (T2D) patients, Xiao et al. [40] compared effects of S-AM (2.5–5 mg/d, n = 112) and losartan (50–100mg/d, n = 115) after treatment for 36 months (156 weeks). They had followed patients at first, second, and third year of the study. Difference in the reduction in SBP and DBP at the end of 12 months was statistically significant between two groups. However, there were no significant differences between the groups when assessed at the end of 24 or 36 months. Change in fasting insulin levels (mIU/L) and insulin sensitivity index (ISI) was significant with both S-AM and losartan by the end of 3 years (p < 0.05). This establishes equivalent efficacy of S-AM to an ARB, losartan in improvement of insulin sensitivity in patients with HTN and impaired fasting glucose.

5.5. Effect on Platelet Aggregation. In patients of HTN and T2D, Li et al. (2013) [41] studied effect of levamlodipine on platelet aggregation and expression of matrix metalloproteinase (MMP) 9 and MMP 2. In 32 patients treated, platelet aggregation maximal assessed by coagulation instrument TYXN-91A reduced significantly (p < 0.05) from 47.77 ± 11.92 (pretreatment) to 40.78 ± 13.97 (posttreatment). Platelet inhibition rate was 13.50 ± 25.23%. There was no effect on levels of MMP 9 and MMP 2. This study highlights that S-AM has potential to prevent platelet aggregation in high-risk patients like HTN with T2D.
| Author (year)          | Country | S-AM (mg) | Comparator (mg) | n  | Duration (weeks) | Antihypertensive efficacy | Pleiotropic effect                                      |
|-----------------------|---------|-----------|----------------|----|-----------------|---------------------------|--------------------------------------------------------|
| **Effect on Arterial stiffness and Endothelial function** |         |           |                |    |                 |                            |                                                        |
| **RCTs**              |         |           |                |    |                 |                            |                                                        |
| Liangjin et al. (2013) [33] | China   | 2.5–5     | Nifed-SR (10)  | 40/40 | 12               |                           |                                                        |
|                       |         |           |                |    |                 | S-AM: 14.7 ± 3.1 to 12.1 ± 2.7 (p < 0.05) |                                                        |
|                       |         |           |                |    |                 | Nifed-SR: 14.8 ± 2.9 to 13.7 ± 3.2 (p > 0.05) |                                                        |
|                       |         |           |                |    |                 | DBPVR (mmHg) S-AM: 10.2 ± 1.8 to 8.5 ± 1.9 (p < 0.05) |                                                        |
|                       |         |           |                |    |                 | Nifed-SR: 10.2 ± 1.9 to 9.8 ± 2.5 (p > 0.05) |                                                        |
|                       |         |           |                |    |                 | CIMT (per mm) S-AM: 1.24 ± 0.41 to 1.08 ± 0.28 (p < 0.05) |                                                        |
|                       |         |           |                |    |                 | Nifed-SR: 1.23 ± 0.31 to 1.22 ± 0.33 |                                                        |
| Zhang et al. (2003) [34] | China   | 2.5       | Amlo (5)       | 60  | 6               | NA                        | S-AM: 4 ± 4 to 3 ± 4 (p = 0.01) Amlo: 6.7% to 6.8% (p = 0.01) |
|                       |         |           |                |    |                 |                           | Significant improvements in central BP components baPWV |
|                       |         |           |                |    |                 |                           | ambulatory arterial stiffness index variability of ambulatory BP (all P < 0.0001) |
|                       |         |           |                |    |                 |                           | CIMT: No significant changes                            |
| Guo et al. (2012) [35] | China   | NA        | Amlo           | 126/106 | 24              |                           |                                                        |
|                       |         |           |                |    |                 | S-AM: 153.88/94.03 to 132.59/81.96 (p < 0.001 for both) |                                                        |
|                       |         |           |                |    |                 | Amlo: 152.21/93.3 to 133.22/82.47 (p < 0.001 for both) |                                                        |
|                       |         |           |                |    |                 | FMD%: 5.7 to 8.0 (Amlo) and 73 (S-AM) (p < 0.01 for both) |                                                        |
|                       |         |           |                |    |                 | NMD%: 13.6 to 12.9 (Amlo) and 14.1 (S-AM) (p < 0.01 for both) |                                                        |
|                       |         |           |                |    |                 | NO μmol/L: 42 to 62 (Amlo) and 59 (S-AM) (p < 0.01 for both) |                                                        |
|                       |         |           |                |    |                 | eNOS μL: 20 to 26 (Amlo) and 24 (S-AM) (p < 0.01 for both) |                                                        |
| Si et al. (2014) [36] [crossover trial, 2-week washout] | China   | 2.5       | Amlo (5)       | 24  | 6 × 6           |                           |                                                        |
|                       |         |           |                |    |                 | SBP: 162 to 132 (Amlo) and 131 (S-AM) (p < 0.01 for both) |                                                        |
|                       |         |           |                |    |                 | DBP: 95 to 81 (Amlo) and 82 (S-AM) (p < 0.01 for both) |                                                        |
|                       |         |           |                |    |                 | HR: 76 to 72 (Amlo) and 73 (S-AM) (p < 0.05 for both) |                                                        |
Table 4: Continued.

| Author (year) | Country     | S-AM (mg) | Comparator (mg) | n   | Duration (weeks) | Antihypertensive efficacy | Pleiotropic effect |
|--------------|-------------|-----------|-----------------|-----|------------------|---------------------------|-------------------|
| Nestorovich (2013)
  [37] [S-AM + Enalapril versus enalapril] | Ukraine     | 5–10      | E (10–20)       | 33/32 | 24               | NR                        |                   |
|               |             |           |                 |      |                  | Combination therapy had greater changes in Maximal speed ($V_{max}$) of bloodstream in BA (i) initial (22.8 and 176 cm/sec) (ii) after reactive hyperaemia (41.7 and 31.6 cm/sec), Speed of retrograde wave: (i) initial (19.6 and 143.4 cm/sec) (ii) after reactive hyperaemia (25.9 and 20.2 cm/sec) (iii) post-occlusive dilatation (5.2% and 3.4%) Changes in endothelin-1 levels (i) Combination: 3.86 ± 0.24 to 1.95 ± 0.19 pg/mL, $p < 0.05$ (ii) Enalapril alone: 3.32 ± 0.27 to 1.83 ± 0.21 pg/mL, $p < 0.05$ |
| Iskenderov and Saushkina (2013)
  [38] | Russia      | -         | Amlo            | 61/66 | 24               | Comparable BP reduction at lower dose of S-AM | S-AM was associated with Complete regression of LVH: 51% cases Normalization of LV diastolic function: 62.4% cases Significant improvement in BA vasomotor function Significant reduction in atherogenic lipoproteins and TC |
| Iskenderov and Saushkina (2013)
  [38] | Russia      | -         | Amlo            | 61/66 | 24               | Comparable BP reduction at lower dose of S-AM | S-AM was associated with Complete regression of LVH: 51% cases Normalization of LV diastolic function: 62.4% cases Significant improvement in BA vasomotor function Significant reduction in atherogenic lipoproteins and TC |
| Tang et al. (2003)
  [39] | China       | 2.5–5     | Amlo            | 20   | 8                | Significant reduction in SBP ($p < 0.01$) DBP ($p < 0.01$) BUN ($p < 0.05$) | Normalization of BP in 85% cases Improved renal function |
| Xiao et al. (2016)
  [40] | China       | 2.5–5     | Losartan (50–100) | 112/115 | 156           | BP reduction was significant and similar in both groups | In both groups, significant reduction in fasting insulin Increase in insulin sensitivity index |
| Li et al. (2013)
  [41] | China       | NA        | -               | 32   | NA               | NA                        | Reduced platelet aggregation maximal (%): 47.77 ± 11.92 to 40.78 ± 13.97 ($p < 0.05$) Platelet inhibition rate (%): 13.5 ± 25.23 No effect on MMP levels |

AEs: adverse effects, Amlo: racemic amlodipine, BA: brachial artery, baPWV: brachial artery pressure wave velocity, BP: blood pressure, BUN: blood urea nitrogen, CIMT: carotid intima media thickness, DBP: Diastolic BP, DBPVR: DBP variety ratio, eNOS: endothelial nitric oxide synthase, FMD: flow-mediated dilatation, HR: heart rate, LV: left ventricle, LVH: left ventricular hypertrophy, MMP: matrix metalloproteinase, NA: not available, Nifed SR: nifedipine sustained release, NMD: nitroglycerine-mediated dilatation, NO: nitric oxide, NR: not reported, OR: odds ratio, RD: risk difference, S-AM: S-amlodipine, SBP: systolic BP, SBPVR: SBP variety ratio, and TC: total cholesterol.
6. S-Amlodipine and Pedal Edema

CCBs are associated with a considerable risk of peripheral oedema that may reduce patient compliance or necessitate switching to a different drug. It has been now well-established that S-AM is associated with lower incidence of pedal edema and improved compliance to therapy as evident from studies discussed above. Of note is a recent RCT from Galappatthy et al. (2016) [16] where the incidence of leg edema was the primary outcome assessed. Patients uncontrolled with BB and ACEI/ARB (n = 172) were randomized to S-AM 2.5–5 mg (n = 86) and racemic amlodipine 5–10 mg (n = 86). With S-AM, absolute risk reduction of new edema was 15.1%, relative risk reduction was 32.47%, and number needed to treat was seven (NNT = 7). In SESA trial, edema was resolved in 98.72% patients after switching from racemate amlodipine to S-AM [21]. In SESA-II study done in 2230 patients with HTN, incidence of pedal edema was reported in 41.90% patients who were taking racemic amlodipine before switching over to S-AM [22]. When patients were switched over to S-AM, resolution of pedal edema was noted in 93.07%. Overall incidence of pedal edema was 1.92% with S-AM and the relative risk reduction of pedal edema after S-AM switch was 95.4%. Thus, the evidence convincingly suggests minimal incidence of edema with S-AM compared to racemate amlodipine. The confirmatory evidence is observed in a meta-analysis of 15 RCT of S-AM where Liu et al. [30] reported that S-AM (n = 907) was associated with significantly less edema than racemic amlodipine (n = 897) (risk difference [RD], −0.02; 95% CI, −0.03 to 0.00; test for overall effect: Z = 2.20; p = 0.03).

Higher incidence of pedal edema is likely to result in higher degree of discomfort. Therefore, use of chirally pure S-AM would be advantageous due to lower incidence of edema which could result in improved adherence to therapy and hence optimum BP control. Amlodipine causes mainly precapillary vasodilatation without proportional increase of postcapillary blood flow, which leads to peripheral edema. Although R-amlodipine does not have calcium channel blocking properties, it reduces activity of postural vasopressor reflex, which increases the pressure in capillary vessels that activates egress of fluid into surrounding tissues. Studies have shown that nitric oxide (NO) released by the inducible nitric oxide synthase is responsible for development of edema. R (+) amlodipine is involved in local NO formation through the kinin pathway and this may lead to loss of the precapillary reflex vasoconstriction and development of edema when racemate mixture is used. S-AM at any concentration was not found to release NO and does not affect postural vasopressor reflex [42].

7. S-Amlodipine and Cost-Effectiveness

From China, Hu et al. (2014) [43] conducted a retrospective cost-effectiveness analysis from two multicentre RCTs of S-AM (2.5 mg/d, n = 110) and Amlo (5 mg/d, n = 104). With 4–8 weeks of treatment, efficacy rate of both drugs was similar (84.91% and 77.45%, resp.). Cost figures observed for 1 mmHg reduction with S-AM and Amlo were 8.1 Yuan (∼1.2 $) and 10 Yuan (∼1.5 $) for SBP and 16.9 Yuan (∼2.5 $) and 21.7 Yuan (∼3.2 $) for DBP, respectively. Reported AEs were 4.6% and 10.3% in two groups, respectively. Thus, study suggests S-Amlo is more cost-effective than racemic amlodipine.

8. Summary

Compared to racemic amlodipine, S-AM had equivalent antihypertensive efficacy at half-dose. Evidence suggests efficacy of S-AM in 24-hour ambulatory BP reduction, including day-time and night-time BP reduction. It was also found to be effective in nocturnal HTN showing its effectiveness in nondippers. Meta-analyses showed equivalent efficacy of S-AM compared to racemic amlodipine with similar or lower rates of AEs. Significantly lower incidence of peripheral edema suggests a better tolerability of S-AM and absolute risk reduction of 15.1% in peripheral edema is seen. Otherwise, overall incidence of AEs was nearly similar with two treatments. Compared to clindidine, incidence of edema was found to be nearly similar with S-AM, whereas it was significantly lesser in both drugs when compared to racemic amlodipine. Higher-dose S-AM (5 mg) was more effective and equally safe as that of lower-dose (2.5 mg). In combination with telmisartan, atenolol, and enalapril, S-AM showed greater antihypertensive effect with better safety and tolerability. Besides HTN, S-AM was found effective and safe in angina. It lowers numbers of attacks and improves symptoms. S-AM had shown BP lowering efficacy in renal transplant cases with no significant adverse effect on functional renal parameters.

Besides being potent antihypertensive, S-AM showed various pleiotropic benefits. These include improvement in endothelial function, slowing of CIMT progression or reversal of increased CIMT, improvement in arterial stiffness, regression of LVH and improvement in LV diastolic function, improvement in lipid profile, improvement in insulin sensitivity, and reduction in platelet aggregation.

Analysis from China identified S-AM as the cost-effective therapy with economic savings compared to racemic amlodipine.

9. Limitations

Although we did extensive search of literature, there is likely chance of missing on non-English literature not covered under the databases searched. Most of the non-English articles were available as abstracts only.

10. Conclusion

An equivalent antihypertensive efficacy to racemic amlodipine with lesser or negligible peripheral edema proves S-amlodipine as a cost-effective treatment option in HTN. It is effective, safe, and well-tolerated in combination with other antihypertensives as well. Besides HTN, its efficacy in angina makes it suitable agent in patient with both comorbidities. Pleiotropic benefits like improvement in endothelial function and insulin sensitivity show its promise in patients with comorbidities like diabetes. Given its positive effects on BP,
endothelial function, platelet aggregation, insulin sensitivity, and atherogenic lipids, S-AM is likely to lower the adverse cardiovascular outcomes. The evidence from this review clearly suggests that S-amloidepine may be considered as one of the first-choice antihypertensive in patients with HTN including those with heightened cardiovascular risk. Future research should focus on cardiovascular outcomes with S-AM in patients with HTN and other comorbidities.

Conflicts of Interest
The authors declare no conflicts of interest.

Acknowledgments
The authors are thankful to medical team of Emcure Pharmaceuticals Ltd., Pune, India, for their assistance in procuring the literature evidence and assistance in conceptualization of this article. They also thank Dr. Vijay M. Katekhaye, Quest MedPharma Consultants, Nagpur, India, for his assistance in drafting and editing this manuscript.

References
[1] P. A. James, S. Oparil, B. L. Carter et al., "2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC8)," Journal of the American Medical Association, vol. 311, no. 5, pp. 507–520, 2014.
[2] K. Rahimi, C. A. Emdin, and S. MacMahon, "The Epidemiology of Blood Pressure and Its Worldwide Management," Circulation Research, vol. 116, no. 6, pp. 925–935, 2015.
[3] B. Dahlöf, P. S. Sever, N. R. Poulter et al., "Prevention of cardiovascular events with an antihypertensive regimen of amloidepine adding perindopril as required versus atenolol adding bendroflumethiazide as required in the, the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial," The Lancet, vol. 366, no. 9489, pp. 895–906, 2005.
[4] Y. K. Agrawal, H. G. Bhatt, H. G. Raval, P. M. Oza, and P. J. Gogoi, "Chirality - A new era of therapeutics," Mini-Reviews in Medicinal Chemistry, vol. 7, no. 5, pp. 451–460, 2007.
[5] L. Pathak, "Chiral switches in the management of hypertension," BMJ (South Asia edition), vol. 21, pp. 668–669, 2005.
[6] H. P. Thacker, "S-Amlodipine - The 2007 Clinical Review," J Indian Med Assoc, vol. 105, pp. 180–190, 2007.
[7] http://www.cdsco.nic.in/writereaddata/list_of_drugs_approved_during_2000.html
[8] "Levamolpedine besylate," http://appl.sfdia.gov.cn/datasearcheng/face3/base.jsp?tableId=85&tableName=TABLE85&amp;title=Database%20of%20approved%20Active%20Pharmaceutical%20Ingredients%20(API)%20and%20API%20manufacturers%20in%20China&amp;bcId=136489132266591324609420000667.
[9] "Korea Innovative Pharmaceutical Company Directory," Korea Health Industry Development Institute, Ministry of Health & Welfare. Ahngook Pharm, http://www.khidiuae.org/images/Korea%20Innovative%20Company.pdf.
[10] "SAMLOPIN., Instructions for medical use. Approved. The Order of Ministry of Health of Ukraine," http://www.gladpharm.com/images/mod_catalog_prod_files/2431/Samlopin_tabl_insert_eng_03.06.2016.pdf.
[11] "Amlobes – S(-)-amlodipine besylate 5 mg tablet," VerHeiLen GmbH - Farma Iberica, http://farmaberica.com/products/amlobes/
[12] R. Paudel, P. Kishore, P. Mishra, S. Palitana, and B. C. Dwari, "Urticular Skin Reaction Induced by Oral Clonidine," Journal of Pharmacy Practice and Research, vol. 36, no. 3, pp. 218–219, 2006.
[13] "Chiral Drugs – S-Amlodipine, Calcium channel Blocker," Asomex, http://www.chiralemcura.com/pop/S-amlodipine_globalpresence.html.
[14] "Levamolpedine Beslate Accounts for Half of Chinese Anti-hypertension Drug Market," 2017, http://www.en-cphi.cn/news/show-20651.htm.
[15] G.-C. Oh, H.-Y. Lee, H.-J. Kang, J.-H. Zo, D.-J. Choi, and B.-H. Oh, "Quantification of Pedal Edema During Treatment With S(-)-Amlodipine Nicotinate Versus Amlodipine Besylate in Female Korean Patients With Mild to Moderate Hypertension: A 12-Week, Multicenter, Randomized, Double-Blind, Active-Controlled, Phase IV Clinical Trial," Clinical Therapeutics, vol. 34, no. 9, pp. 1940–1947, 2012.
[16] P. Galappatthy, Y. C. Waniganayake, M. I. M. Sabeer, T. J. Wijethunga, G. K. S. Galappatthy, and R. A. Ekanayaka, "Leg edema with S-amloidepine vs conventional amloidepine given in triple therapy for hypertension: A randomized double blind controlled clinical trial," BMC Cardiovascular Disorders, vol. 16, no. 1, article no. 168, 2016.
[17] J. S. Youn, Y. S. Ahn, Y. J. Hwang, H. M. Jung, W. J. Kim, and M. G. Lee, "Phase IV Clinical Trial for the Comparison of Efficacy and Safety between S-(-)-Amlodipine Nicotinate and Lercanidipine HCI in patients with hypertension," Korean Hypertension, vol. 16, pp. 18–30, 2010.
[18] SN. Koval, IA. Bozhko Sneurouskaya, and SV. Salnikova, Comparative Efficacy and Tolerability of Lercanidipine and S-isomer of Amlodipine in Patients with Essential Hypertension Associated with Abdominal Obesity. Arterial Hypertension, [ABSTRACT], Arterial Hypertension, 2013.
[19] M. S. Kim, M. H. Jeong, M. G. Lee et al., "The Phase 4 Randomized, Public, Parallel, Comparative, Clinical Trial to Compare Efficacy and Safety of S(-)-Amlodipine Nicotinate with Ramipril in Hypertensive Patients," Journal of the Korean Society of Hypertension, vol. 17, no. 3, pp. 103–113, 2011.
[20] Q. Chen, Q. Huang, Y. Kang et al., "Efficacy and tolerability of initial high vs low doses of S(-)-amlodipine in hypertension," The Journal of Clinical Hypertension, vol. 19, no. 10, pp. 973–982, 2017.
[21] "Safety and Efficacy of S-Amlodipine: SESA study," in JAMA-India, vol. 2, pp. 87–92, 2003.
[22] "The SESA-II Study: Safety and Efficacy of S (-) Amlodipine in the Treatment of Hypertension," in Indian Medical Gazette, pp. 529–533, SESA-II Study group, 2005.
[23] "SESA IV: Results of a Multicentric Post-marketing Surveillance Study on Safety and Efficacy of S-amlodipine in the Treatment of Hypertension," in Cardiology Today, vol. XI, pp. 1–4, SESA-IV Study group, 2007.
[24] K. Singh, "Safety and Efficacy of S(-)Amlodipine in the Management Stage-I and Stage-II Hypertension: The SESA-IVA Experience at Imphal," Indian Medical Gazette, pp. 230–234, 2007.
[25] M. Mohanty, K. P. Tripathy, S. Sarkar, and V. Srivastava, “Comparative Analysis On Incidence Of Pedal Oedema Between Amlodipine, Cilnidipine And S-Amlodipine In Mild To Moderate Hypertensive Individuals Of Either Sex,” IOSR Journal of Dental and Medical Sciences, vol. 15, pp. 24–34, 2016.

[26] M. G. Rajanandh, A. S. Parihar, and K. Subramaniyan, “Comparative Effect of Racemic Amlodipine and its Enantiomer with Atenolol on Hypertensive Patients-A Randomized, Open, Parallel Group Study,” Journal of Experimental and Clinical Medicine(Taiwan), vol. 5, no. 6, pp. 217–221, 2013.

[27] M. A. Maksimova, Y. V. Lukina, and S. Y. Martsevich, “The role of S-amlodipine in arterial hypertension therapy with combination of calcium channel blockers and beta-blockers,” in Ration Pharmacother Cardiol, vol. 9, pp. 236–240, 2013.

[28] S.-H. Ihm, H.-K. Jeon, T.-J. Cha et al., “Efficacy and safety of two fixed-dose combinations of S-amlodipine and telmisartan (CKD-828) versus S-amlodipine monotherapy in patients with hypertension inadequately controlled using S-amlodipine monotherapy: An 8-week, multicenter, randomized, double-blind, Phase III clinical study,” Drug Design, Development and Therapy, vol. 10, pp. 3817–3826, 2016.

[29] C. G. Park, T. H. Ahn, E. J. Cho et al., “Comparison of the Efficacy and Safety of Fixed-dose S-Amlodipine/Telmisartan and Telmisartan in Hypertensive Patients Inadequately Controlled with Telmisartan: A Randomized, Double-blind, Multicenter Study,” Clinical Therapeutics, vol. 38, no. 10, pp. 2185–2194, 2016.

[30] F. Liu, M. Qiu, and S. Zhai, “Tolerability and effectiveness of (S)-amlodipine compared with racemic amlodipine in hypertension: A systematic review and meta-analysis,” Current Therapeutic Research, vol. 71, no. 1, pp. 1–29, 2010.

[31] Z. G. Zhao and Y. Chen, “Efficacy and Safety of Amlodipine vs. Levamlodipine for Mild to Moderate Hypertension: A Systematic Review, in Evaluation and Analysis of Drug-use in Hospitals of China,” vol. 15, pp. 318–321, 2015, https://www.cabdirect.org/cabdirect/abstract/2063216081.

[32] J. S. Hiremath, “The SESA-Angina Study — Safety and Efficacy of S (-) Amlodipine in Angina,” Indian Medical Gazette, pp. 403–408, 2005.

[33] G. Liangjin, Z. Hanlin, L. Yaqian, S. Menga, and H. Yan, “Effect of Levamlodipine besylate and nifedipine sustained-release tablets on blood pressure variety ratio and carotid intima media thickness in patients with primary hypertension,” Modern Journal of Integrated Traditional Chinese, p. 22, 2013.

[34] H. Zhang, KS. Liu, RG. Gao, C. Liu, and HY. Xue, “Effects of l-amlodipine and amlodipine on vascular endothelial function and serum cholesterol in patients with essential hypertension,” Chinese Journal of New Drugs and Clinical, 2003.

[35] J. Guo, Y. Gong, and Y. Li, ”858 The effectiveness of s(-)-amlodipine on vascular function,” Journal of Hypertension, vol. 30, p. e251, 2012.

[36] D. Si, Y. He, C. Yang et al., “The effects of amlodipine and S(-)-amlodipine on vascular endothelial function in patients with hypertension,” American Journal of Hypertension, vol. 27, no. 1, pp. 27–31, 2014.

[37] S. V. Nestorovich, “Correction of endothelial dysfunction under the influence of treatment complex of S (-) Amlodipine and ACE-inhibitor Enalapril in patients with chronic pulmonary heart disease with arterial hypertension,” Journal of Scientific & Innovative Research, p. 716, 2013.

[38] B. G. Iskenderov and S. V. Saushkina, “Organoprotective and metabolic effects of S-amlodipine in patients with arterial hypertension,” Kardiologiya, vol. 33, no. 10, pp. 24–29, 2013.

[39] S. D. Tang, J. Qi, W. Han, and Z. L. Ming, “P-257 Levamlodipine Therapy for Hypertension After Kidney Transplantation,” American Journal of Hypertension, p. 16, 2003.

[40] W.-Y. Xiao, N. Ning, M.-H. Tan et al., “Effects of antihypertensive drugs losartan and levamlodipine besylate on insulin resistance in patients with essential hypertension combined with isolated impaired fasting glucose,” Hypertension Research, vol. 39, no. 5, pp. 321–326, 2016.

[41] J. Li, L. Fu, G.-J. Lao, C. Yang, M. Ren, and L. Yan, “Effects of Levamlodipine on Platelet Aggregation and Expression of MMP-9 / MMP-2 in Patients with Type 2 Diabetes and Hypertension,” Journal of Sun Yat-Sen University (Medical Sciences), vol. 35, pp. 35–270, 2014.

[42] X.-P. Zhang, Z. Q. Kit, S. Mital, S. Chahwala, and T. H. Hintze, “Paradoxical release of nitric oxide by an L-type calcium channel antagonist, the R+ enantiomer of amlodipine,” Journal of Cardiovascular Pharmacology, vol. 39, no. 2, pp. 208–214, 2002.

[43] S. Hu, Y. Zhang, J. He, and L. Du, “A Retrospective Cost-Effectiveness Analysis of S-Amlodipine in China,” Value in Health, vol. 17, no. 7, p. A758, 2014.

[44] G. S. Liu, K. Wang, and M. H. Zhag, “Comparative effect of amlodipine and levamlodipine on nocturnal hypertension in hypertensive patients,” Bulletin of Medical Postgraduate, p. 6, 2001.

[45] Z. G. Fang, “Clinical evaluation of levamlodipine in treatment of 140 patients with essential hypertension,” Chinese New Drugs Journal, p. 12, 2002.

[46] Y.-Z. Cheng, Wu. X-G, X-Y. Chen, and W. Fu, “Clinic study of the efficacy and adverse reactions levamlodipine besylate in treatment of hypertension,” Chinese Journal Medicinal Guide, p. 03, 2002.

[47] M. S. Hiremath and G. D. Dhige, “A Randomized, Double-blind, Double-dummy, Multicentric, Parallel Group, Comparative Clinical Trial of S-amlodipine 2.5 mg versus Amlodipine 5 mg in the Treatment of Mild to Moderate Hypertension,” JAMA-India, vol. 8, pp. 86–92, 2002.

[48] PG. Kerkar, “Clinical Trial of S-Amlodipine 2.5 mg versus Amlodipine 5 mg the Treatment of Hypertension,” Indian Journal of Clinical Practice, p. 13, 2003.

[49] L. Pathak, M. S. Hiremath, P. G. Kerkar, and V. G. Manade, “Clinical Trial of S-Amlodipine 2.5 mg Versus Amlodipine 5 mg in the treatment of Mild to Moderate Hypertension - A Randomized, Double-blind Clinical Trial,” Journal of the Association of Physicians of India, vol. 52, pp. 197–202, 2004.

[50] L. Zhang, “Study of Action and Adverse Drug Reaction of Levamlodipine Besylate and Amlodipine Besylate,” Chinese Journal of Pharmacoepidemiology, p. 06, 2006.

[51] J.-H. Bae, J.-E. Jun, M.-M. Lee, C.-H. Kim, M-S. Hyon, K. H. Choe et al., “Double-blind, Randomized, Multi-center Trial for the Comparison of Efficacy and Safety between S-Amlodipine Besylate and Amlodipine Besylate in Patients with Hypertension,” Korean Hypertension J, vol. 14, pp. 28–36, 2008.

[52] Y. Zhu, Z. Hua, K. Shi, Z. Tan, L. Gong, and Y. Zhuo, “Effect and safety of levamolodipine maleate tablets on patients with mild-to-moderate hypertension,” Chinese Journal of Clinical Pharmacy, p. 02, 2008.

[53] Y. Shengye, “Efficacy Observation of Amlodipine and Levamlodipine for Mild to Moderate Hypertension,” Chinese Journal of Medicinal Guide, p. 09, 2012.
[54] G-H. Zhao, “Clinical efficacy of levamlodipine besylate in treatment of primary hypertension,” in *Cardiovascular Disease Prevention and Control*, vol. 9, 2013.

[55] T. Parvathi, J. E. Ramya, and B. Meenakshi, “Prospective Study to Compare the Efficacy and Tolerability of S-Amlodipine 2.5 mg versus Racemic Amlodipine 5 mg in Mild to Moderate Hypertension. Research And Reviews?: Journal Of Pharmacology And Toxicological Studies,” *Journal Of Pharmacology And Toxicological Studies*, vol. 2, pp. 26–33, 2014.

[56] X. Hu and C. Xiao, ”Effects of irbesartan combined with levamlodipine or indapamide regimen on blood pressure variation in patients with primary hypertensive,” *Clinical Cardiology*, p. 03, 2013.

[57] V. A. Bobroff, O. I. Davydova Medvedenko, and L. V. Klimenko, ”Application of S-amlodipine in treatment of patients with mild to moderate arterial hypertension,” *Health of Ukraine*, vol. 12, pp. 1–5, 2007.

[58] D. Basu, ”Comparative Study to Evaluate the Effect of S-Amlodipine versus Amlodipine on Office and Ambulatory Blood Pressure in Mild to Moderate Hypertensives,” *Indian Medical Gazette*, pp. 493–497, 2007.

[59] V. K. Sierkova, N. V. Kuz'minova, and I. S. K. Alshantti, ”Comparative estimation of efficiency and safety of racemic amlodipine and its S-enantiomer in hypertensive patients,” *Lik Sprava*, no. 3-4, pp. 39–44, 2009.