Literature review

Phillips RA et al., (2001) \(^{27}\) compared the calcium channel blocker amlodipine and angiotensin II receptor blocker losartan, with or without hydrochlorothiazide (HCTZ), were compared for the treatment of mild to moderate hypertension in a multicenter, double-blind, parallel-group clinical trial. Following a 2-week placebo run-in, 440 adults (45-80 years old) were randomized to receive either amlodipine 5 mg once daily or losartan 50 mg once daily. Both treatment groups showed significant reductions from baseline in 24-hour ambulatory BP at the end of treatment, with no difference between them. Adverse events were consistent with the safety profile of each drug. It is concluded that, while both amlodipine and losartan demonstrated a significant benefit for the treatment of mild to moderate hypertension, there were greater reductions in most BP measurements following treatment with amlodipine in comparison to losartan with or without HCTZ.

Massimo V et al., (2003) \(^{28}\) conducted the study for Comparison of the blood pressure-lowering effects and tolerability of Losartan- and Amlodipine-based regimens in patients with isolated systolic hypertension designed as multicenter, prospective, randomized, double-blind, parallel-group study consisted of a 4-week placebo phase and an 18-week active-treatment phase in which 857 patients (65.6% female) were randomized to treatment, 432 in the losartan group and 425 in the amlodipine group shows that patients with ISH, losartan and amlodipine produced comparable clinically relevant reductions in SBP; however, losartan was better tolerated, as evidenced by fewer CAEs and discontinuations compared with amlodipine. Losartan may be considered for the initial treatment of ISH.

Renate T et al., (1998) \(^{29}\) carried out randomized, double-masked, multicenter, clinical study with three parallel treatment groups was conducted to compare the efficacy and tolerability of losartan potassium (losartan), alone or combined with hydrochlorothiazide (HCTZ), and amlodipline in patients with mild-to-moderate hypertension. A 4-week
placebo period was followed by a 12-week treatment period. A total of 936 patients were randomized to 3 treatment regimens: losartan 60 mg once daily with a possible increase to 100 mg once daily (L 60/100, n = 308), losartan 50 mg once daily with a possible addition of HCTZ 12.5 mg once daily (LTXTZ, n = 313), or amlodipine 5 mg once daily with a possible increase to 10 mg once daily (A 6110, n = 314) at week 6. Differences between the treatment groups in patient-reported symptoms were significant, with a higher rate of swelling and edema reported with amlodipine (10%) than with losartan (3%). In this study, losartan appeared to be as effective as amlodipine and to have fewer drug-related side effects.

**Suzzane O et al., (1996)** evaluated Efficacy, tolerability, and effects on quality of life of losartan, alone or with hydrochlorothiazide, versus amlodipine, alone or with hydrochlorothiazide, in patients with essential hypertension demonstrates that regimen of losartan with HCTZ added as needed, when compared with a regimen of amlodipine with HCTZ added as needed, provides comparable efficacy and superior tolerability and less bother to patients with respect to edema.

**John MF et al., (2001)** done a study to assess antihypertensive efficacy and safety of losartan and amlodipine in adult African Americans with mild to moderate hypertension suggest that in African American patients, losartan was significantly more effective than amlodipine in lowering SBP and DBP. Moreover, the losartan/HCTZ combination regimen resulted in significant and clinically meaningful additional reductions in SBP and DBP compared with amlodipine/HCTZ combination.

**Paul RC et al., (2001)** conducted study for evaluating efficacy and safety of angiotensin receptor blockers: a review of losartan in essential hypertension, losartan has been compared with other antihypertensive agents, including enalapril, amlodipine, and nifedipine gastro-intestinal therapeutic system. Losartan has also consistently demonstrated an excellent tolerability profile, with an overall incidence of adverse effects
similar to that of placebo. Subtle pharmacologic differences exist among the agents of the ARB class. However, a recent meta-analysis suggested that no clinically or statistically significant difference in antihypertensive efficacy exists among them.

*Cindy BL et al., (2003)*[^32] study the effect of amlodipine on systolic blood pressure shows that amlodipine monotherapy was effective in reducing SBP. Antihypertensive agents such as amlodipine warrant consideration for the management of patients with inadequately controlled SBP.

*Wilson TW et al., (1998)*[^33] conducted the study to evaluate the antihypertensive efficacy of losartan and amlodipine assessed with office and ambulatory blood pressure monitoring suggested that Losartan alone reduces both office and ABPM readings. The observed changes in office-recorded seating DBP suggest that losartan is less effective than amlodipine or the combination of losartan and hydrochlorothiazide, but ABPM did not confirm this difference. Perhaps changes in office readings measure different attributes of a drug than does ABPM.

*Steven GC et al., (2008)*[^34] conducted study to compare the efficacy and tolerability of combinations of olmesartan medoxom and amlodipine besylate with those of the component monotherapies in patients with mild to severe hypertension shows that: the combination of olmesartan medoxom and amlodipine besylate was effective and well tolerated in the adult population with hypertension.

*Sang HK et al., (2007)*[^35] conducted prospective, randomized, double-blind, parallel-group study in which a total of 189 patients were enrolled (mean age, 53 years; 105 women, 84 men; mean body weight, 65.8 kg). One patient in the amlodipine camsylate group dropped out of the study at week 0 of treatment (this patient did not use any study
medication) and was excluded from the modified intent-to-treat (ITT) analysis. Thus, 188 patients were treated and included in the ITT analysis (94 patients per treatment group; ITT analysis); 161 patients were included in the perprotocol (PP) analysis (n = 80 for amlodipine camsylate, n = 81 for amlodipine besylate) (14 patients in the amlodipine camsylate group and 13 patients in the amlodipine besylate group were excluded from the PP analysis due to consent withdrawal or protocol violation).

Osvaldo K et al., (2005) \(^{37}\) evaluated medium and long term (one year) efficacy, tolerability and metabolic effects of the fixed combination of amlodipine and losartan compared to amlodipine or losartan alone by Brazilian multicenter, randomized, double-blind and comparative trial performed with 198 patients in stage 1 and 2 essential hypertension and concluded that the combination of amlodipine and losartan – the first fixed combination of a calcium channel blocker and an angiotensin II receptor blocker available in the pharmaceutical market, is an excellent option for the treatment of a wide range of hypertensive patients.

Hong BK et al., (2011) \(^{38}\) compared the efficacy and safety of fixed-dose amlodipine/losartan and losartan in hypertensive patients inadequately controlled with losartan: a randomized, double-blind, multicenter study conducted in outpatient hospital clinics. Korean patients with essential hypertension inadequately controlled on losartan 100 mg were administered amlodipine/losartan 5 mg/100 mg combination versus losartan 100 mg. Response rates were significantly higher in the amlodipine/losartan 5 mg/100 mg group versus the losartan 100 mg group (81.4% vs 63.9% at week 4, p < 0.0192; 90.0% vs 66.7% at week 8, p < 0.001). Both treatments were generally well tolerated. Conclusion: Switching to a fixed-dose combination therapy of amlodipine/losartan 5 mg/100 mg was associated with significantly greater reductions in BP and superior achievement of BP goals compared with a maintenance dose of losartan 100 mg in Korean patients with essential hypertension inadequately controlled on losartan 100 mg.
Seok MK et al., (2011)\(^{39}\) conducted no inferiority study compared the clinical efficacy and safety profile of fixed-dose combination of amlodipine/losartan 5/50 mg and amlodipine 10 mg monotherapy in essential hypertensive patients who respond poorly to amlodipine 5 mg monotherapy. It was a double-blind, multicenter, randomized trial of hypertensive patients (N = 185) aged ≥18 years taking amlodipine 5 mg during the run-in treatment period but failed to achieve sitting diastolic blood pressure (DBP) <90 mm Hg.

Results: After 8 weeks, the DBP of both groups decreased from baseline by 8.9 (6.1) and 9.4 (7.5) mm Hg, respectively (difference = −0.5 [6.9] mm Hg, 95% CI: −2.5 to 1.5). Secondary end points of reductions in DBP after 4 weeks (−8.1 [6.7] vs −9.9 [7.3] mm Hg, difference = −1.8 mm Hg, 95% CI: −3.9 to 0.2) and sitting systolic blood pressure after 4 (−10.2 [11.8] vs −12.8 [10.2] mm Hg, difference = −2.6 mm Hg, 95% CI: −5.9 to 0.6) and 8 weeks (−12.2 [11.0] vs −13.4 [11.3] mm Hg, difference = −1.2 mmHg, 95% CI: −4.4 to 2.1) were comparable between the 2 treatment groups.

Praga M et al., (2003)\(^{40}\) compared Antiproteinuric efficacy of losartan with amlodipine in non-diabetic proteinuric renal diseases: a double-blind, randomized clinical trial in which randomly assigned 97 patients with non-diabetic nephropathies and proteinuria >1.5 g/24 h to treatment with losartan (50 mg daily) or amlodipine (5 mg daily) for 20 weeks.

Results: The baseline characteristics in both groups were similar. Proteinuria decreased by 32.4% (95% confidence interval -38.4 to -21.8%) after 4 weeks of treatment and by 50.4% (-58.9 to -40.2%) after 20 weeks in the losartan group, whereas no significant proteinuria changes were observed in the amlodipine group (P < 0.001).

Nicholas JA et al., (2010)\(^{41}\) conducted Randomized, Double-Blind, 12-week, double-blind, multinational study investigated the effects of losartan 0.7 to 1.4 mg/kg per day compared with placebo (normotensive stratum) or amlodipine 0.1 to 0.2 mg/kg per day up to 5 mg/d (hypertensive stratum) on proteinuria (morning-void urinary protein-creatinine ratio, baseline >0.3 g/g) in 306 children up to 17 years of age. Results: Twelve
weeks of treatment with losartan significantly reduced proteinuria compared with amlodipine/placebo: losartan 35.8% versus amlodipine/placebo 1.4%, $P < 0.001$. Adverse event incidence was low and comparable in all groups.

Robert AK et al., (2008) evaluated the efficacy and safety of adding amlodipine to the treatment regimen of patients with hypertension and diabetes who were already receiving either quinapril or losartan as monotherapy. Methods: ADHT was a double-blind, double dummy, 22-week trial conducted in the US. After a washout period of 7–13 days, patients (aged 30–75 y) with hypertension and diabetes were randomized to receive quinapril 20 mg/day plus placebo or losartan 50 mg/day plus placebo for 4 weeks, titrated to 40 mg or 100 mg (if required), respectively, for an additional 4 weeks to achieve their BP goals (<130/80 mm Hg). At week 8, either amlodipine 5 mg/day or placebo was added for an additional 12 weeks, with titration to 10 mg at week 14 if the BP goal was not achieved.

White WB (2001) noted incidence of most adverse cardiovascular events appeared to follow a circadian pattern, reaching a peak in the morning shortly after wakening and arising. The activities of many physiologic parameters, including hemodynamic, hematologic and humoral factors, also fluctuate in a cyclical manner over the 24h. It had been suggested that, during the post-awakening hours, the phases of these cycles synchronize to create an environment that predisposes to atherosclerotic plaque rupture and thrombosis in susceptible individuals, thereby accounting for the heightened cardiovascular risk at this time of day.

Yasuda G et al., (2005) conducted open-label, parallel-prospective, randomized study, 44 patients were treated with losartan and 43 with amlodipine for a 12-week titration phase and a maintenance phase for a maximum of 12 weeks. 24 hours blood pressure and urinary albumin excretion were measured before and during treatment. Losartan decreased (P < 0.001) 24-h urinary albumin excretion from 810
mg/day (95% CI 780-1,140) to 570 (510-910). Amlodipine, however, did not decrease (P = 0.893) albuminuria (790 mg/day [780-1,170] vs. 790 [710-1,260]). Conclusions: These results suggest that in type 2 diabetes with overt nephropathy, 24-h blood pressure regulation alone is inadequate to reduce macroalbuminuria and additional effects of losartan are crucial for antiproteinuric action.

**Park HC et al., (2001)** compared the effects of losartan and amlodipine on proteinuria, as well as on serum and urine TGF-beta1 levels in IgA nephropathy patients with hypertension and proteinuria. Conclusion: Losartan and amlodipine, with similar control of BP, showed different effects on urine protein or TGF-beta1 excretion. Whereas losartan improved both urinary parameters, amlodipine did not. These differences might be important for the management of IgA nephropathy.

**Pablo IG et al., (2001)** compared the effects of an Ang-IIA (losartan) and a calcium-channel blocker (amlodipine) on BP control, renal hemodynamics, TGF-β1, and endothelin-1 (ET-1) in renal transplant patients who had normal graft function and who were treated with CsA and demonstrated that despite similar control of BP with both losartan and amlodipine, the effects on renal hemodynamics and on profibrogenic cytokines were different. This different effect on renal hemodynamics and profibrogenic cytokines between losartan and amlodipine could have potential repercussions for chronic allograft nephropathy.

**Park CG et al., (2011)** determined the dose-response relationship and assess the efficacy and safety of amlodipine or losartan monotherapy and amlodipine camsylate/losartan combination therapy in patients with essential hypertension. Methods: It was an 8-week, randomized, double-blind, factorial design, phase II, multicenter study conducted in outpatient hospital clinics among adult patients aged 18-75 years with essential hypertension. The incidence of adverse events in the group of patients treated with
the amlodipine camsylate/losartan 10 mg/50 mg combination tended to be higher than for any other group (27.9%, 12/43); however, the effect was not statistically significant. Conclusion: Combination amlodipine camsylate/losartan (5 mg/50 mg, 5 mg/100 mg and 10 mg/50 mg) resulted in significantly greater BP lowering compared with amlodipine or losartan monotherapy, and was determined to be generally safe and tolerable in patients with essential hypertension.

**Shimosawa T et al., (2007)** conducted randomized 4-month study, the efficacy and safety were compared between an ARB/diuretics (losartan/hydrochlorothiazide [HCTZ]) combination and the most prescribed combination, ARB/calcium channel blocker (candesartan/amlodipine) in hypertensive patients for whom 8 mg/day of candesartan proved ineffective. The efficacy in reducing BP was similar between the two combination therapies. L/H significantly reduced serum potassium, but within the normal range, and did not increase serum uric acid or serum triglyceride. With L/H, the percentage of patients who attained the BP goal in SBP was higher in elderly patients than in younger patients.

**Gokhale N et al., (2002)** conducted among 719 patients enrolled by 109 doctors to evaluate the efficacy and tolerability of the combination of losartan potassium and amlodipine besylate in Indian patients with mild to moderate hypertension. Out of them 11 patients were dropped out. Of these 708 patients 643 patients received once daily dosage of the combination whereas 10 patients received 1/2 daily, 13 patients received 1 1/2 daily and 42 patients received 1 twice daily dosage of the combination. The mean SBP in the study was 172.89 +/- 19.18 mm Hg baseline. After the 10-day treatment, the mean SBP had significant reduction ie, 13.1% from basal and at the end of day 20 of the treatment, the reduction was 19.13% from the baseline which was significant. Similarly mean DBP was 105.42 +/- 10.85 mm Hg at baseline. The severity of an adverse event was graded on a 3-point scale as mild, moderate and severe. The most common side-effects reported were oedema of feet (5.08%), ankle oedema (1.98%). Remaining adverse events
Literature review

included some cardiovascular events such as palpitations, gastro-intestinal events such as constipation, miscellaneous events, muscular pain, weakness, generalised swelling, etc. CNS events included giddiness, headache, insomnia, etc.

Webb NJ et al., (2011) \(^{50}\) conducted 12-week, double-blind multinational study investigated the effects of losartan 0.7-1.4 mg/kg/day compared with placebo (normotensive patients) or amlodipine 0.1-0.2 mg/kg/day up to 5 mg/day (hypertensive patients) on proteinuria [early morning-void urinary protein/creatinine ratio (UPr/Cr), baseline ≥ 34 mg/mmol] in 30 children of up to 17 years of age with Alport syndrome. Results: Twelve weeks of treatment with losartan significantly reduced proteinuria compared with placebo/amlodipine: losartan -14.7 mg/mmol (interquartile range -49.7 to -5.7 mg/mmol) or 31.6% reduction using a mixed model approach versus placebo/amlodipine 2.3 mg/mmol (-26.0 to 18.1 mg/mmol), P = 0.01 or 2.3% increase using a mixed model approach. Adverse event incidence was low and comparable between losartan and placebo/amlodipine groups.

Watanabe S et al., (2006) \(^{51}\) evaluated the influence of an ARB and a calcium channel blocker on serum adiponectin levels in Japanese patients with hypertension who were treated with losartan or amlodipine for 3 months. Conclusion: In this study, Japanese adults with EHT had significant increased in adiponectin after 3 months of treatment with 50 to 100 mg/d of losartan, but not with 5 to 10 mg/d of amlodipine.

Volpe M et al., (2003) \(^{52}\) compared the effects on trough sitting systolic blood pressure of a regimen of losartan, a selective angiotensin II-receptor antagonist, and an amlodipine-based regimen in patients with ISH by multicenter, prospective, randomized, double-blind, parallel-group study consisted of a 4-week placebo phase and an 18-week active-treatment phase. The primary efficacy measure was change in trough SiSBP from baseline to week 18. Information on the tolerability of study treatments was collected at each visit,
including the investigator's and patient's observations of clinical adverse experiences (CAEs), laboratory adverse experiences, and responses to a symptom questionnaire. Conclusions: In these patients with ISH, losartan and amlodipine produced comparable clinically relevant reductions in Si SBP; however, losartan was better tolerated, as evidenced by fewer CAEs and discontinuations compared with amlodipine. Losartan may be considered for the initial treatment of ISH.

Iino Y et al., (2004) 53 conducted 12-month, multicenter (57 clinical institutions), randomized, open-labeled trial was undertaken to compare the efficacy of the angiotensin II receptor antagonist losartan and the calcium channel blocker amlodipine in patients with proteinuric chronic kidney disease (CKD) and hypertension. A total of 117 patients (79, chronic glomerulonephritis; 14, diabetic nephropathy; 24, other CKD) were randomly allocated into two treatment groups. Losartan and amlodipine exerted the same efficacy for blood pressure (BP) control; however, losartan significantly reduced the 24-h urinary protein excretion at months 3, 6, and 12, with the reduction of 20.7%, 35.2%, 35.8%, whereas amlodipine did not change the amount of proteinuria over the 12-month study period. We conclude that losartan reduced proteinuria in patients with CKD and hypertension. This positive effect may contribute to the renal protective benefit of losartan, and is beyond the magnitude of BP control.