Effectiveness and Safety of Losartan in the Management of Essential Hypertension: A Prospective Cohort Study

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ABSTRACT

Background: Combination therapy is often required to effectively manage hypertension.

Objectives: To assess the effectiveness of a treat-to-target approach with dose titration from 50 mg losartan to 50 mg losartan/12.5 mg hydrochlorothiazide (HCTZ) and 100 mg losartan/25 mg HCTZ in treating adult patients with essential grade I or II hypertension.

Methods: Open-label, prospective, 14-week, multicenter study of hypertensive patients enrolled from 253 Canadian sites. Patients were initially treated with losartan 50 mg/day. If target BP was not achieved after 6 or 10 weeks, patients were titrated to 50 mg losartan/12.5 mg HCTZ and then to 100 mg losartan/25 mg HCTZ.

Results: 1,340 patients were enrolled, of which 1,319 were in the final study sample and 1,175 completed the study. Of these, 607 (46.0%) patients were controlled on 50 mg losartan, 468 (35.5%) were titrated to 50 mg losartan/12.5 mg HCTZ and 244 (18.5%) required titration to 100 mg losartan/25 mg HCTZ. After 14 weeks, significant mean reductions in SBP and DBP of 22.1 and 11.7 mmHg, respectively, were reported and 81.4% of patients with previously uncontrolled BP achieved target. Frequently reported adverse events included nervous system disorders (n = 36 [2.7%]), especially headaches and dizziness, and general disorders (n = 15 [1.1%]), predominantly fatigue.

Conclusions: A treat-to-target dose titration regimen of 50 mg losartan, 50 mg losartan/12.5 mg HCTZ and 100 mg losartan/25 mg HCTZ is effective and safe in the management of grade I or II essential hypertension.

KEY WORDS:
hypertension, angiotensin receptor antagonist, hydrochlorothiazide, losartan

INTRODUCTION

According to the Canadian Heart Health Survey, it is estimated that 22% of adult Canadians (26% of men and 18% of women) between the ages of 18 to 74 years and more than 50% of Canadians over 65 years of age are hypertensive.[1,2] It is estimated that only 13% of this population is diagnosed and treated to target blood pressure (BP).[2] For patients with diabetes, BP is estimated to be within normal ranges in only 9% of patients. The current Canadian guidelines for the management of hypertension emphasize the need to control BP to recommended target levels.[3,4] Treatment targets are dependent upon the patient's global atherosclerotic risk, presence of target organ damage, and comorbidity.[3,4] Specifically, it is recommended to reduce systolic blood pressure and diastolic blood pressure (SBP/DBP) to less than 140/90 mmHg in most patients including the elderly. The recommended target SBP/DBP is less than 130/80 mmHg for patients with diabetes or renal dysfunction[3,4] and even lower for cardiac patients.[5] The 2006 Canadian Hypertension Education Program (CHEP) recommendations for the management of hypertension include lifestyle modifications and drug therapy for patients with an average SBP/DBP of 160/100 mmHg and no macrovascular target organ damage or other cardiovascular risk factors.[4] For patients with average DBP ≥ 90 mmHg or SBP ≥ 140 mmHg and macrovascular target organ damage or other cardiovascular risk factors, antihypertensive therapy is strongly recommended.[4]

Controlling hypertension is of great importance considering that, in patients between 40 and 70 years old, the risk of cardiovascular disease doubles with each increase in SBP/DBP of 20/10 mmHg above 115/75 mmHg.[6,7] The data in the literature have shown that combination therapy is often necessary to achieve target BP and maintenance.[8-16] Common treatments for hypertension include diuretics, angiotensin-I converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers (CCBs), and angiotensin-II receptor blockers (ARBs).[4,17,18]

Losartan potassium is a selective, competitive, reversible angiotensin AT1 receptor antagonist that blocks the effects of angiotensin II.[19-22] Losartan has been used for the treatment of hypertension in Canada since 1995. In phase II and III clinical studies, losartan has been proven to be an effective, once-daily antihypertensive with a good tolerability and safety profile.[9,15,23-28] The results of controlled clinical trials provide evidence of efficacy and safety under ideal conditions. The generalization of these results to "real-life" effectiveness, safety and tolerance is often problematic because the controlled conditions of clinical trials do not reflect real-life clinical practice. There is therefore an ongoing need for data that better represent the real-life setting. Phase IV studies, when properly designed better emulate the "real-life" setting. The present study addressed this need by enrolling patients treated by a random sample of Canadian family physicians and general practitioners. This study evaluated the effectiveness of a two-step BP target-based approach for the management of hypertension by incorporating titration from losartan 50 mg/day to combination losartan 50 mg/day with hydrochlorothiazide (HCTZ) 12.5 mg/day and then to losartan 100 mg/day combined with HCTZ 25 mg/day.

METHODS

Study Design

This was an open-label, multicenter, prospective cohort study. All potentially eligible patients signed an informed consent form before any study procedure, including all eligibility assessments, were performed. Follow-up duration was 14 weeks with clinic assessments at baseline, 6, 10 and 14 weeks. At baseline, patients underwent a review of their medical history and a brief physical examination. At all visits, BP measurements and concomitant medications were recorded. Investigator physicians were instructed to ascertain BP according to their routine procedures using the average of three measurements obtained on the same arm with the same device during a five minute period. During the follow-up visits at 6, 10 and 14 weeks, details regarding adverse events and adherence to treatment were documented. Investigators were asked to follow-up with their patients 14 days after the last dose of study medication in order to record adverse events. During the final study visit, the physical examination was repeated.

Eligibility Criteria

A random, geographically representative sample of Canadian general practitioners and family physicians was invited to participate in the study. The following inclusion criteria were applied to identify potentially eligible study subjects:

i. Age of at least 18 years,
ii. With the exception of hypertension, in otherwise good health,
iii. Diagnosis with grade I or II essential hypertension and fulfilling at least one of the following requirements:
   a. Newly diagnosed, antihypertensive treatment naïve with 140/90 mmHg ≤ SBP/DBP ≤ 180/110 mmHg;
   b. Isolated systolic hypertension, defined 140 mmHg ≤ SBP ≤ 180 mmHg and DBP < 90 mmHg;
   c. If diagnosed with type II diabetes mellitus, then 130/80 mmHg ≤ SBP/DBP ≤ 180/110 mmHg;
   d. Currently on antihypertensive therapy with uncontrolled BP, defined as 140/90 mmHg ≤ SBP/DBP ≤ 160/100 mmHg;
iv. Controlled hypertension, defined as SBP/DBP

< 140/90 mmHg, while on therapy with no more than two antihypertensive agents but requiring treatment change due to adverse event or low patient satisfaction.

The following exclusion criteria were applied:

i. Well-controlled BP, defined as SBP < 140 mmHg and DBP < 90 mmHg, and satisfied or not experiencing adverse events with the current treatment,
ii. Known secondary hypertension of any aetiology,
iii. Intolerance to any component of losartan or HCTZ,
iv. History or suspicion of angioedema,
v. Pregnant women or a woman of childbearing potential who was sexually active and not using an effective method of birth control,
vi. Patients with any of the following conditions were also excluded from the study:
   a. History of cardiac insufficiency (class III and IV),
   b. History of myocardial infarction or stroke within the last 6 months,
   c. Percutaneous coronary angioplasty or coronary artery bypass within the last 3 months,
   d. Confirmed renal or hepatic dysfunction and/or electrolyte imbalance on the basis of the case history or a recent laboratory test (serum creatinine > 150 mmol/L or creatinine clearance < 30 mL/min, AST or ALT > 2 times above the normal range, serum potassium < 3.5 or > 5.5 mEq/L),
vii. Participation in an investigational drug program or clinical trial within 30 days of baseline,
viii. Being on any of the following cardiac medications at baseline and not being able to discontinue their use during the course of the study: beta-blockers, diuretics, ACE inhibitors, ARBs, CCBs.

Treatment

All eligible and enrolled patients were initially treated with 50 mg losartan potassium (COZAAR®) once daily for 6 weeks. At the 6 and 10-week visits, patients who were not at target BP while on 50 mg losartan were titrated to 50 mg losartan with 12.5 mg HCTZ (HYZAAR®). At the 10-week visit, further titration to 100 mg losartan with 25 mg HCTZ (HYZAAR®DS) was applied for patients who were not at target while on 50 mg losartan/12.5 mg HCTZ.

Outcome Measures

The primary effectiveness outcome measure of the study was the absolute change in SBP and DBP between the baseline and the final study visit at week 14 of treatment. Secondary efficacy outcome measures were the change in SBP and DBP at 6 and 10 weeks of follow-up and the proportion of patients achieving target BP. Absolute changes in BP measurements were calculated as $\Delta SBP = SBP_0 - SBP_F$ and $\Delta DBP = DBP_0 - DBP_F$. Where: SBP_0 = SBP at Baseline; SBP_F = SBP at the Follow-up Visit; DBP_0 = DBP at Baseline; DBP_F = DBP at the Follow-up Visit. Target BP was defined as SBP/DBP ≤ 140/90 mmHg for non-diabetic patients and SBP/DBP ≤ 130/80 mmHg for patients with type II diabetes.

Other outcome measures included adherence to treatment and safety. Adherence to treatment was ascertained by questioning the patient regarding missed doses of treatment. Safety was assessed by the incidence of treatment-related (definitely or probably related) adverse events as reported by the patients at each study visit and for 14 days after the last dose of study medication. The causal relationship between an adverse event and the study drug was determined by the treating physician. Adverse events were coded and reported according to terminology in the Medical Dictionary for Regulatory Activities (MedDRA version 8.1).[29]

Statistical Methods

Descriptive statistics were produced for all study variables including patient characteristics, treatment and outcome variables. For continuous variables the mean, standard deviation (SD) and 95% confidence interval (CI) of the mean were reported. For categorical variables, frequency distributions were reported.

The statistical significance of the change in BP measurements between baseline and the 6, 10 and 14 week visits was assessed with the Student's t test for paired samples. Stratified analyses were conducted for strata defined according to the final treatment used in the titration process, specifically: i) 50 mg losartan, ii) titration to 50 mg losartan/12.5 mg HCTZ and iii) titration to 100 mg losartan/25 mg HCTZ. A second stratified analysis was conducted for patient strata defined according to the severity of hypertension measuring SBP at baseline as grade I (SBP: 140–159 mmHg), grade II/III (SBP: 160–179 mmHg/SBP: 180–209 mmHg) or controlled with the current treatment.

The proportion of patients achieving target BP at 6, 10 and 14 weeks was calculated using the number of patients who were in the study at the beginning of the time interval as the denominator. A Kaplan-Meier survival function was used to describe the overall rate of achieving target BP during the study and to estimate time to BP control.

All patients who received study medication and returned for one or more follow-up visits were included in the effectiveness analysis. In line with the real-life nature of the study, these included patients who did not complete all visits of the study and who had protocol violations. No imputations or replacement of missing data were applied. Patients who discontinued prior to the first follow-up visit at week 6 were excluded from the effectiveness analysis because the change in BP could

not be calculated. Patients who received at least one dose of the study medication were included in the safety analysis.

RESULTS

In total, 1,340 patients were enrolled in the study, of which 20 (1.5%) were not included in the final study sample because they did not take any of the study medications. One other patient was excluded because withdrawal occurred before the second study visit at week 6. Of the 1,319 patients in the final study sample, 1,175 (89.1%) completed all three follow-up visits. Of the 144 (10.9%) patients who were discontinued or withdrew during the study, 55 (4.2%) were lost to follow-up, 52 (3.9%) withdrew due to an adverse event, 21 (1.6%) due to protocol violation, 11 (0.8%) withdrew consent and 5 (0.4%) were discontinued by the physician due to lack of efficacy. Of the 1,319 patients in the final study sample, 118 (8.9%) had controlled BP with their current antihypertensive drug(s) at study entry but were either experiencing adverse events or were not satisfied with their treatment. The remaining 1,201 patients were enrolled because their BP was not controlled.

Table 1 describes the demographics of the 1,319 patients in the study sample. During the study, 607 (46.0%) achieved BP control on losartan 50 mg and did not require further titration, 468 (35.5%) were titrated to 50 mg losartan/12.5 mg HCTZ and 244 (18.5%) were titrated to 100 mg losartan/25 mg HCTZ. The mean (SD) age of the patients enrolled in the study was 58 (12) years. Patients who were controlled on 50 mg losartan daily were younger than the other two patient groups ($p = 0.054$). The majority (73.5%) of the patients enrolled were over the age of 50 years, with the largest proportion (32.7%) being between 50 and 59 years old. There were 51.7% males and the vast majority (87.6%) of the study patients were Caucasian. At baseline, there were 786 (59.6%) patients with grade I hypertension, 398 (30.2%) with grade II hypertension, 17 (1.3%) with grade III hypertension and 118 (8.9%) had controlled BP. The prevalence of type II diabetes mellitus was significantly higher in patients who were titrated to 100 mg losartan/25 mg HCTZ daily when compared to the other two patient groups ($p < 0.001$). This group also had the highest prevalence of hypercholesterolemia; however, this difference was not statistically significant ($p = 0.192$).

There were 816 (61.9%) patients who were treatment naïve at study entry. The most frequent cardiovascular medications used prior to participation in the study were ACE inhibitors (15.8%) and diuretics (14.8%). When compared to the other two groups, patients that were titrated to 100 mg losartan/25 mg HCTZ /day were significantly less likely to be treatment naïve ($p < 0.001$) and more likely to be treated with diuretics ($p = 0.005$) and CCBs ($p = 0.001$) at baseline.

The mean (SD) SBP at baseline for all patients was 153.4 (12.4) mmHg (Table 2). Patients who were controlled with 50 mg losartan had significantly lower mean SBP at baseline ($p = 0.001$) when compared to the other two subject groups (Figure 1). The baseline mean (SD) DBP for the study sample as a whole was 91.3 (8.8) mmHg and was similar for the three subject groups ($p = 0.379$) (Table 3). At the 6, 10 and 14-week visits, the patients who were controlled on losartan 50 mg/day had significantly lower mean SBP when compared to the other two patient groups ($p < 0.001$). For these patients, the mean DBP was also significantly lower at each follow-up assessment visit when compared to the other two groups ($p < 0.001$ at weeks 6 and 10; $p = 0.011$ at week 14) (Figure 1).

The data in Tables 4 and 5 summarize the change in SBP and DBP measurements, respectively, from baseline to each study follow-up visit. These results show that, by the sixth week of treatment, significant reductions were observed for the study sample as a whole and for all patient groups. The patients that were controlled with 50 mg losartan had significantly higher reductions in both SBP and DBP at the 6-week assessment when compared to the other patient groups. However, by the final assessment at week 14, the changes in SBP and DBP from baseline for all groups were similar and statistically significant ($p < 0.001$). The patients with grade II/III hypertension had significantly higher mean reductions in SBP ($p < 0.001$) and DBP ($p < 0.05$) at all visit assessments when compared to those with grade I hypertension (Tables 4 and 5).

By the final study visit at week 14, patients with grade II/III hypertension experienced a mean reduction in SBP of -31.3 mmHg (95% CI: -32.6 to -30.0) and in DBP of -12.9 mmHg (95% CI: -13.9 to -12.0) compared to changes in SBP of -18.9 mmHg (95% CI: -19.8 to -18.1) and DBP of -11.2 mmHg (95% CI: -11.8 to -10.6) for patients with grade I hypertension. All changes in SBP and DBP from baseline were statistically significant ($p < 0.05$) for both of these groups of patients.

There were 1,201 patients with uncontrolled BP at study entry. By the end of the study follow-up at week 14, 978 (81.4%) of these patients had achieved target BP as defined by the NCEP guidelines, specifically SBP/DBP ≤ 140/90 mmHg for non-diabetic patients and SBP/DBP ≤ 130/80 mmHg for patients with diabetes mellitus. The cumulative proportions of individuals achieving target BP at 6, 10 and 14 weeks were 41.9%, 68.4% and 81.4%, respectively. Kaplan-Meier-based survival analysis shows that the estimated mean time to target BP was 8.9 weeks (95% CI: 8.66 – 9.09) with a median of 10 weeks (95% CI: 9.63 – 10.37). The results of this analysis and Cox's proportional hazard models, summarized in Figure 3, show that the first step of the titration process increased the likelihood of achieving

TABLE I **Demographics and Baseline Patient Characteristics**

	Final Titration Groups			
	Losartan 50 mg	**Losartan 50 mg/ HCTZ 12.5 mg**	**Losartan 100 mg/ HCTZ 25 mg**	**Groups Combined**
Number of Patients (N)	607	468	244	1319
Age (yrs): mean (SD)	56.7 (12.3)	58.1 (12.6)	58.8 (11.5)	57.6 (12.3)
Gender, N (%)				
Female	292 (48.1)	228 (48.7)	117 (47.8)	637 (48.3)
Male	315 (51.9)	240 (51.3)	127 (51.8)	682 (51.7)
Baseline Hypertension Severity, N (%)				
Grade I (SBP 140-159 mmHg)	382 (62.9)	273 (58.3)	131 (53.7)	786 (59.6)
Grade II (SBP 160-179 mmHg)	146 (24.1)	155 (33.1)	97 (39.8)	398 (30.2)
Grade III (SBP 180-209 mmHg)	3 (0.5)	10 (2.1)	4 (1.6)	17 (1.3)
Controlled Hypertension (not satisfied or experiencing adverse effects)	76 (12.5)	30 (6.4)	12 (4.9)	118 (8.9)
Comorbidities, N (%)				
Dyslipidemia / Hypercholesterolemia	220 (36.2)	156 (33.3)	98 (40.2)	474 (35.9)
Type II Diabetes	69 (11.4)	60 (12.8)	53 (21.6)	182 (13.8)
Prior Hypertension Medication: N (%)				
Treatment naïve	408 (67.2)	284 (60.7)	124 (50.8)	816 (61.9)
Beta-Blockers	33 (5.4)	32 (6.8)	16 (6.6)	81 (6.1)
Diuretics	77 (12.7)	66 (14.1)	52 (21.3)	195 (14.8)
ACE Inhibitors	82 (13.5)	78 (16.7)	48 (19.7)	208 (15.8)
Angiotensin Receptor Blockers (ARBs)	30 (4.9)	34 (7.3)	22 (9.0)	86 (6.5)
Calcium Channel Blockers (CCBs)	26 (4.3)	36 (1.7)	27 (11.1)	89 (6.8)

DBP: diastolic blood pressure; HCTZ: hydrochlorothiazide; SBP: systolic blood pressure.

TABLE 2 Mean Systolic Blood Pressure by Hypertension Severity, Treatment Group and Visit

Baseline Hypertension Severity / Final Treatment Group	Baseline				Week 6				Week 10				Week 14			
	N	Mean (SD)	95% CI Lower	Upper	N	Mean (SD)	95% CI Lower	Upper	N	Mean (SD)	95% CI Lower	Upper	N	Mean (SD)	95% CI Lower	Upper
All Groups																
Losartan 50 mg	607	151.0 (12.6)	150.0	152.0	574	131.2 (10.6)	130.3	132.0	524	128.6 (8.9)	127.8	129.4	506	129.0 (10.0)	128.1	129.8
Losartan 50 mg/ HCTZ 12.5 mg	468	155.1 (12.1)	154.0	156.2	468	144.8 (12.1)	143.7	145.9	455	135.0 (11.0)	134.0	136.0	430	132.7 (10.5)	131.7	133.7
Losartan 100 mg/ HCTZ 25 mg	244	156.2 (11.0)	154.8	157.6	244	152.9 (12.8)	151.3	154.5	244	148.3 (11.1)	147.0	149.7	239	136.4 (13.3)	134.7	138.1
Total	1319	153.4 (12.4)	152.7	154.1	1286	140.3 (14.4)	139.5	141.1	1223	134.9 (12.5)	134.2	135.6	1175	131.8 (11.3)	131.2	132.5
Grade I																
Losartan 50 mg	382	149.6 (5.3)	149.1	150.1	365	131.2 (9.7)	130.2	132.2	337	128.6 (8.8)	127.7	129.6	322	129.0 (9.4)	128.0	130.0
Losartan 50 mg/ HCTZ 12.5 mg	273	150.1 (5.5)	149.5	150.8	273	143.2 (11.7)	141.8	144.6	266	134.5 (10.7)	133.2	135.8	255	131.6 (9.8)	130.4	132.8
Losartan 100 mg/ HCTZ 25 mg	131	150.4 (5.2)	149.6	151.3	131	149.8 (11.3)	147.8	151.7	131	146.0 (10.2)	144.2	147.7	128	134.5 (12.2)	132.3	136.6
Total	786	149.9 (5.3)	149.5	150.3	769	138.6 (13.0)	137.7	139.5	734	133.8 (11.6)	133.0	134.7	705	130.9 (10.3)	130.2	131.7
Grade II / III																
Losartan 50 mg	149	166.1 (6.8)	165.0	167.2	134	135.2 (11.5)	133.2	137.1	116	132.2 (7.2)	130.9	133.5	113	131.9 (9.7)	130.0	133.7
Losartan 50 mg/ HCTZ 12.5 mg	165	167.7 (7.6)	166.6	168.9	165	149.4 (10.9)	147.7	151.0	159	137.1 (10.9)	135.4	138.8	148	135.3 (11.2)	133.5	137.1
Losartan 100 mg/ HCTZ 25 mg	101	166.3 (6.8)	165.0	167.7	101	157.7 (12.5)	155.2	160.2	101	151.8 (10.9)	149.6	153.9	101	139.1 (14.4)	136.3	142.0
Total	415	166.8 (7.2)	166.1	167.5	400	146.7 (14.5)	145.3	148.2	376	139.5 (12.5)	138.2	140.8	362	135.3 (12.1)	134.1	136.5
Controlled																
Losartan 50 mg	76	128.3 (8.4)	126.4	130.2	75	123.9 (9.3)	121.7	126.0	71	122.7 (8.7)	120.7	124.8	71	124.1 (11.5)	121.4	126.9
Losartan 50 mg/ HCTZ 12.5 mg	30	131.6 (6.3)	129.2	134.0	30	134.5 (11.6)	130.1	138.8	30	128.7 (10.8)	124.7	132.7	27	128.6 (10.5)	124.4	132.7
Losartan 100 mg/ HCTZ 25 mg	12	133.2 (6.5)	129.1	137.3	12	146.7 (17.6)	135.5	157.9	12	145.6 (14.0)	136.7	154.5	10	134.5 (11.9)	125.9	143.0
Total	118	129.6 (7.9)	128.2	131.1	117	128.9 (13.2)	126.5	131.3	113	126.7 (12.1)	124.5	129.0	108	126.2 (11.6)	124.0	128.4

HCTZ: hydrochlorothiazide; CI: confidence interval.

TABLE 3 Mean Diastolic Blood Pressure by Hypertension Severity, Treatment Group and Visit

Baseline Hypertension Severity / Final Treatment Group	Baseline				Week 6				Week 10				Week 14			
	N	Mean (SD)	95% CI Lower	Upper	N	Mean (SD)	95% CI Lower	Upper	N	Mean (SD)	95% CI Lower	Upper	N	Mean (SD)	95% CI Lower	Upper
All Groups																
Losartan 50 mg	607	91.0 (8.6)	90.3	91.7	574	80.2 (7.2)	79.6	80.8	524	79.0 (6.7)	78.5	79.6	506	79.5 (7.1)	78.9	80.1
Losartan 50 mg/ HCTZ 12.5 mg	468	91.7 (8.9)	90.9	92.5	468	86.6 (8.9)	85.8	87.4	455	81.6 (8.0)	80.9	82.4	430	80.3 (7.6)	79.5	81.0
Losartan 100 mg/ HCTZ 25 mg	244	91.6 (9.2)	90.5	92.8	244	88.5 (9.2)	87.3	89.6	244	87.0 (9.1)	85.8	88.1	239	81.3 (8.7)	80.2	82.4
Total	1319	91.3 (8.8)	90.9	91.8	1286	84.1 (9.0)	83.6	84.6	1223	81.6 (8.2)	81.1	82.1	1175	80.1 (7.6)	79.7	80.6
Grade I																
Losartan 50 mg	382	91.2 (7.7)	90.4	92.0	365	80.2 (6.9)	79.5	80.9	337	78.9 (6.7)	78.2	79.7	322	79.6 (7.2)	78.8	80.4
Losartan 50 mg/ HCTZ 12.5 mg	273	91.3 (8.7)	90.3	92.3	273	87.1 (8.7)	86.0	88.1	266	81.7 (7.9)	80.8	82.7	255	80.4 (7.3)	79.5	81.3
Losartan 100 mg/ HCTZ 25 mg	131	90.8 (8.8)	89.3	92.4	131	89.0 (9.9)	87.3	90.7	131	87.5 (9.0)	86.0	89.1	128	81.3 (8.5)	79.8	82.8
Total	786	91.2 (8.3)	90.6	91.7	769	84.2 (9.0)	83.5	84.8	734	81.5 (8.2)	80.9	82.1	705	80.2 (7.5)	79.6	80.7
Grade II / III																
Losartan 50 mg	149	93.4 (8.7)	92.0	94.8	134	80.6 (7.8)	79.3	81.9	116	79.6 (6.9)	78.3	80.9	113	79.4 (6.7)	78.2	80.7
Losartan 50 mg/ HCTZ 12.5 mg	165	93.2 (8.5)	91.9	94.5	165	85.8 (9.2)	84.4	87.2	159	81.6 (7.6)	80.4	82.8	148	80.1 (7.2)	78.9	81.3
Losartan 100 mg/ HCTZ 25 mg	101	93.2 (9.4)	91.3	95.0	101	88.0 (8.5)	86.3	89.7	101	86.3 (8.8)	84.6	88.1	101	81.2 (9.0)	79.5	83.0
Total	415	93.3 (8.8)	92.4	94.1	400	84.6 (9.0)	83.7	85.5	376	82.3 (8.2)	81.4	83.1	362	80.2 (7.6)	79.4	81.0
Controlled																
Losartan 50 mg	76	85.1 (9.9)	82.9	87.4	75	79.5 (7.4)	77.8	81.2	71	78.7 (6.1)	77.2	80.1	71	79.3 (7.5)	77.5	81.1
Losartan 50 mg/ HCTZ 12.5 mg	30	86.9 (11.3)	82.7	91.2	30	86.2 (9.1)	82.8	89.6	30	80.9 (10.4)	77.0	84.8	27	79.8 (11.3)	75.3	84.2
Losartan 100 mg/ HCTZ 25 mg	12	87.3 (9.1)	81.5	93.1	12	86.8 (8.7)	81.3	92.4	12	86.1 (11.4)	78.9	93.3	10	82.3 (8.6)	76.1	88.4
Total	118	85.8 (10.1)	84.0	87.7	117	82.0 (8.6)	80.4	83.5	113	80.0 (8.3)	78.5	81.6	108	79.7 (8.7)	78.0	81.3

HCTZ: hydrochlorothiazide; CI: confidence interval.

TABLE 4 Absolute Change in Systolic Blood Pressure by Hypertension Severity, Treatment Group and Visit

Baseline Hypertension Severity / Final Treatment Group	Week 6 to Baseline				Week 10 to Baseline				Week 14 to Baseline			
	N	Mean (SD)	95% CI Lower	Upper	N	Mean (SD)	95% CI Lower	Upper	N	Mean (SD)	95% CI Lower	Upper
All Groups												
Losartan 50 mg	574	-19.4 (13.4)	-20.5	-18.3	524	-21.5 (12.8)	-22.6	-20.4	506	-21.1 (13.9)	-22.3	-19.8
Losartan 50 mg/ HCTZ 12.5 mg	468	-10.3 (13.7)	-11.6	-9.1	455	-20.0 (14.2)	-21.3	-18.7	430	-22.3 (14.1)	-23.6	-20.9
Losartan 100 mg/ HCTZ 25 mg	244	-3.3 (13.0)	-4.9	-1.6	244	-7.8 (12.2)	-9.4	-6.3	239	-19.9 (15.2)	-21.9	-18.0
Total	1286	-13.0 (14.8)	-13.8	-12.2	1223	-18.2 (14.2)	-19.0	-17.4	1175	-21.3 (14.3)	-22.1	-20.5
Grade I												
Losartan 50 mg	365	-18.4 (10.4)	-19.4	-17.3	337	-20.8 (9.9)	-21.9	-19.8	322	-20.4 (10.1)	-21.5	-19.3
Losartan 50 mg/ HCTZ 12.5 mg	273	-6.9 (12.0)	-8.3	-5.5	266	-15.7 (11.3)	-17.0	-14.3	255	-18.5 (10.9)	-19.9	-17.2
Losartan 100 mg/ HCTZ 25 mg	131	-0.7 (11.4)*	-2.6	1.3	131	-4.5 (10.3)	-6.3	-2.7	128	-15.9 (12.9)	-18.2	-13.7
Total	769	-11.3 (13.2)	-12.2	-10.4	734	-16.0 (12.0)	-16.9	-15.2	705	-18.9 (11.0)	-19.8	-18.1
Grade II / III												
Losartan 50 mg	134	-30.5 (12.1)	-32.6	-28.4	116	-33.2 (8.8)	-34.8	-31.5	113	-33.6 (11.2)	-35.7	-31.5
Losartan 50 mg/ HCTZ 12.5 mg	165	-18.4 (12.3)	-20.2	-16.5	159	-30.4 (11.7)	-32.2	-28.6	148	-32.3 (12.5)	-34.3	-30.3
Losartan 100 mg/ HCTZ 25 mg	101	-8.6 (11.6)	-10.9	-6.3	101	-14.5 (9.7)	-16.5	-12.6	101	-27.2 (14.2)	-30.0	-24.4
Total	400	-20.0 (14.7)	-21.4	-18.5	376	-27.0 (12.8)	-28.3	-25.7	362	-31.3 (12.8)	-32.6	-30.0
Controlled												
Losartan 50 mg	75	-4.5 (12.2)	-7.3	-1.7	71	-5.3 (11.6)	-8.1	-2.6	71	-3.9 (13.6)	-7.1	-0.7
Losartan 50 mg/ HCTZ 12.5 mg	30	2.9 (13.5)*	-2.2	7.9	30	-2.9 (12.7)*	-7.6	1.8	27	-2.7 (12.2)*	-7.5	2.2
Losartan 100 mg/ HCTZ 25 mg	12	13.5 (17.8)	2.2	24.8	12	12.4 (14.4)	3.2	21.5	10	1.8 (14.4)*	-8.5	12.1
Total	117	-0.8 (14.3)*	-3.4	1.8	113	-2.8 (13.2)	-5.3	-0.3	108	-3.1 (13.3)	-5.6	-0.5

*All changes from baseline were statistically significant ($p < 0.05$) unless noted (*). HCTZ: hydrochlorothiazide; CI: confidence interval.

target BP by 63% (Odds Ratio = 1.63; 95% CI: 1.43–1.87; $p < 0.001$) and the second titration step further increased the likelihood of achieving target BP by 153% (Odds Ratio = 2.53; 95% CI: 2.14–3.15; $p < 0.001$). The results summarized in Figure 4 show an estimated mean time to target BP of 8.9 weeks (95% CI: 8.67–9.16) with a median of 10 weeks (95% CI: 9.58–10.42) for patients with grade I hypertension at baseline and 10.2 weeks (95% CI: 9.82–10.48) for those with grade II and III hypertension at baseline.

The majority (93.4%) of patients reported more than 90% adherence to the study treatment. The distribution of missed doses was similar between the three study groups. There were 134 non-serious adverse events (NSAEs) reported by 102 (7.7 %) patients that were definitely or probably due to the study treatment as per the judgement of the treating physician. There was one NSAE of severe intensity, reported as facial edema and pruritis of the hands, that was definitely related to the study drug and 5 that were probably related that were reported as headache (two patients), loss of consciousness, heart palpitations and hyponatraemia. The most frequently reported NSAEs were nervous system disorders for 36 (2.7%) patients, specifically headaches and dizziness, followed by general disorders for 15 (1.1%) patients, predominantly fatigue. There were no serious adverse events reported that were attributed to the study drug.

TABLE 5 Absolute Change in Diastolic Blood Pressure by Hypertension Severity, Treatment Group and Visit

Baseline Hypertension Severity / Final Treatment Group	Week 6 to Baseline				Week 10 to Baseline				Week 14 to Baseline			
	N	Mean (SD)	95% CI Lower	Upper	N	Mean (SD)	95% CI Lower	Upper	N	Mean (SD)	95% CI Lower	Upper
All Groups												
Losartan 50 mg	574	-10.6 (8.3)	-11.3	-9.9	524	-11.9 (8.4)	-12.7	-11.2	506	-11.5 (8.7)	-12.3	-10.8
Losartan 50 mg/ HCTZ 12.5 mg	468	-5.1 (8.3)	-5.9	-4.4	455	-10.0 (9.1)	-10.8	-9.1	430	-11.4 (8.7)	-12.2	-10.6
Losartan 100 mg/ HCTZ 25 mg	244	-3.1 (7.9)	-4.1	-2.1	244	-4.7 (7.7)	-5.6	-3.7	239	-10.4 (9.0)	-11.5	-9.3
Total	1286	-7.2 (8.8)	-7.7	-6.7	1223	-9.8 (9.0)	-10.3	-9.2	1175	-11.2 (8.8)	-11.7	-10.7
Grade I												
Losartan 50 mg	365	-10.9 (7.4)	-11.7	-10.1	337	-12.5 (7.5)	-13.3	-11.7	322	-12.0 (7.5)	-12.8	-11.2
Losartan 50 mg/ HCTZ 12.5 mg	273	-4.2 (7.8)	-5.1	-3.3	266	-9.6 (9.4)	-10.7	-8.5	255	-10.9 (8.4)	-11.9	-9.8
Losartan 100 mg/ HCTZ 25 mg	131	-1.8 (8.3)	-3.3	-0.4	131	-3.3 (6.9)	-4.5	-2.1	128	-9.7 (8.3)	-11.2	-8.2
Total	769	-7.0 (8.6)	-7.6	-6.4	734	-9.8 (8.8)	-10.4	-9.2	705	-11.2 (8.0)	-11.8	-10.6
Grade II / III												
Losartan 50 mg	134	-12.5 (9.1)	-14.0	-10.9	116	-13.8 (8.7)	-15.4	-12.2	113	-13.9 (9.6)	-15.7	-12.1
Losartan 50 mg/ HCTZ 12.5 mg	165	-7.4 (7.9)	-8.6	-6.2	159	-11.4 (8.2)	-12.6	-10.1	148	-12.9 (8.9)	-14.3	-11.4
Losartan 100 mg/ HCTZ 25 mg	101	-5.2 (6.8)	-6.5	-3.8	101	-6.8 (7.5)	-8.3	-5.3	101	-11.9 (9.4)	-13.8	-10.1
Total	400	-8.5 (8.6)	-9.4	-7.7	376	-10.9 (8.6)	-11.8	-10.0	362	-12.9 (9.3)	-13.9	-12.0
Controlled												
Losartan 50 mg	75	-5.7 (9.2)	-7.9	-3.6	71	-6.2 (9.7)	-8.5	-3.9	71	-5.6 (9.6)	-7.9	-3.3
Losartan 50 mg/ HCTZ 12.5 mg	30	-0.7 (11.2)*	-4.9	3.4	30	-6.0 (10.8)	-10.1	-2.0	27	-8.2 (10.1)	-12.2	-4.2
Losartan 100 mg/ HCTZ 25 mg	12	-0.5 (9.3)*	-6.4	5.4	12	-1.2 (11.5)*	-8.5	6.1	10	-4.0 (10.3)*	-11.4	3.4
Total	117	-3.9 (10.0)	-5.7	-2.1	113	-5.6 (10.2)	-7.6	-3.7	108	-6.1 (9.8)	-8.0	-4.2

*All changes from baseline were statistically significant ($p < 0.05$) unless noted (*). HCTZ: hydrochlorothiazide; CI: confidence interval.

DISCUSSION

The present study used a prospective design to assess the effectiveness and safety of a treat-to-target, titration-based regimen from 50 mg losartan to 50 mg losartan/12.5 mg HCTZ to 100 mg losartan/25 mg HCTZ in the management of patients with essential hypertension. The sample of patients had a high incidence of comorbidities, specifically dyslipidemia and diabetes, and is therefore representative of the target population with multiple risk factors who requires aggressive management of their hypertension. In the present 14-week study, the two-step titration-based treatment produced an 81.4% BP control rate as well as clinically and statistically significant reductions in both SBP and DBP of 22.1 mmHg and 11.7 mmHg, respectively. These blood pressure reductions were clinically important and would result in reduced cardiovascular risk, which demonstrate real-life therapeutic effectiveness of these titration step interventions in hypertension management. A median time to target BP of 10 weeks was observed. At the final study visit, all patient subgroups had achieved mean SBP/DBP targets with confidence intervals below 140/90 mmHg. Adherence to treatment was high and the low incidence of predominantly mild adverse events contributes to the evidence for the tolerability and safety of the study drugs. The results of the present study are in general agreement with those published in the literature, demonstrating clinical effectiveness of losartan in the management of hypertension.[9,23-27,30]

Prospective clinical trials have also shown that losartan produces a reduction in the risk of mortality and morbidity and/or increases target organ protection.[23]

In order to achieve target BP, many patients require combination treatment.[8,13,31,32] It is generally recommended to combine antihypertensive agents that have alternate mechanisms of action in order to inhibit any compensatory regulatory mechanisms (*i.e.,* water and sodium retention, activation of the sympathetic nervous system or activation of the renin-angiotensin system) that may be initiated in response to the partnered agent. Low-dose diuretics have long been recognised for their safety and effectiveness in the treatment of hypertension.[6,15-17,33] The combination of an ARB with a diuretic is recognised in Canada by CHEP as one of the most effective multi-drug antihypertensive regimens.[4]

The results of the present study, which demonstrate effectiveness of this combination strategy, are in general agreement with those reported in a recent meta-analysis that assessed the combined antihypertensive efficacy of available ARB-class drugs with HCTZ.[34] This meta-analysis showed that the addition of HCTZ to the existing ARB therapy produced an additional 40% to 60% reduction in BP, and that approximately 40% more patients achieved target BP after addition of HCTZ compared to doubling of the initial ARB dose. The overall response rate to ARB/HCTZ combination therapy was reported as between 56% to 70%. Lacourcière and Poirier showed that doubling both losartan and HCTZ doses led to a significant reduction of both SBP and DBP.[15] Furthermore, the addition of HCTZ to losartan did not affect the number of drug-related adverse experiences compared to the administration of losartan alone or compared to placebo. In the present study, the two-step titration strategy also resulted in significant reductions in BP, with 81% of patients achieving target BP by 14 weeks with high tolerability and safety of the study drugs.

In the present study, patients who required titration to combination therapy or to higher doses of losartan and the diuretic were older, had higher prevalence of diabetes and were less likely to be treatment naïve. This would suggest that subjects not achieving target BP with the lower dose losartan had either more advanced disease or had different disease profile that contributed to more resistant hypertension. This observation has important implications for clinical practice and suggests that these patient groups who are at high risk for cardiovascular disease should be monitored closely and should be candidates for more aggressive and rapid combination therapy when target BP in not achieved with monotherapy.

Rates of adherence to treatment vary according to the drug and the disease, but common patterns are often observed. For example, it is estimated that nearly half of the patients prescribed drugs for chronic diseases do not correctly take their medication. In the case of hypertension, a condition that does not present discomforting symptoms, adherence is a challenging aspect of therapy.[35] Thus, antihypertensive drugs that have minimal side effects, and consequently increased likelihood of adherence, would be preferred.[36] In this study, the high adherence with the recommended treatment regimen supports the potential benefit of losartan and losartan combined with HCTZ from a population perspective. High tolerability and safety of losartan has been demonstrated in previous clinical studies.[37,38] The safety results of the present study are in agreement with those in the literature demonstrating a high tolerance and a low incidence of predominantly mild adverse events in this patient population.

The potential limitations of the present study include the single cohort, open-label design. However, this design was required in order to assess the effectiveness of the titration-based regimen in the management of hypertension within a non-controlled real-life setting. The simulation of a real-life setting and generalizability of the study results are the predominant strengths of the present study. By allowing physicians and patients to be unblinded with respect to their treatment, the real-life setting is better replicated with valid generalization to routine clinical practice. In addition, by selecting patients from a random sample of general practitioners across Canada, generalization of the results to the Canadian target population is possible.

CONCLUSION

By the end of the 14-week treatment period, over 80% of patients that had uncontrolled BP at study entry achieved target BP, as defined by NCEP guidelines. In addition, the two-step regimen produced clinically important reductions in both SBP and DBP. The results of this study have shown that a stepwise treat-to-target titration-based approach using 50 mg losartan, 50 mg losartan/12.5 mg HCTZ and 100 mg losartan/25 mg HCTZ is safe and effective for the management of hypertension in this patient population.

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