Effect of Enalapril Maleate Therapy With or Without Hydrochlorothiazide on Blood Pressure Control, Compliance and Quality of Life in Hypertensive Patients: an Open-label Naturalistic Phase IV Trial

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ABSTRACT

Introduction: A major risk factor for cardiovascular disease and end-organ damage, hypertension affects approximately 50 million people in North America. Despite the availability of effective antihypertensive agents, hypertension in general is not being managed as well as it could be. **Objective:** To assess BP control, dosage, medication compliance, and quality of life in Canadian hypertensive patients treated with enalapril maleate (EM) or enalapril maleate with hydrochlorothiazide (EMH). **Methods:** This was an open-label, observational, multicenter, Phase IV study in Grade 1 or 2 hypertensive patients (n = 684, mean age 56.5 years) who were newly diagnosed (66.6% of patients), treated but uncontrolled (27.5%) or controlled but unsatisfied (5.9%) with their current medications. Patients initiated treatment with EM 5 mg/day (80.4% of patients) or 10 mg/day (19.6%). EM dose was adjusted, or switched to EMH as necessary. Patient mean BP, number of patients with controlled BP, compliance, and quality of life were measured over 10 weeks (controlled BP defined as a diastolic pressure of < 90 mmHg) and ambulatory BP control was assessed over 24 hours (ambulatory BP control defined as > 70% measurements at < 140/90 mmHg [day] and < 120/80 mmHg [night]). **Results:** After two weeks of therapy, mean BP improved significantly (140.7 ± 14.2/84.8 ± 8.4 mmHg versus 155.5 ± 12.6/93.2 ± 8.4 mmHg at baseline; $p < 0.001$) as did the number of patients with controlled BP (75.7% versus 30.2% at baseline; $p < 0.001$). At 10 weeks, mean BP was 132.2 ± 12.3/81.2 ± 7.8 mmHg and 91.4% of patients were controlled. Patient compliance was high (> 95%) and at study conclusion, 94.4% of patients remained on EM or EMH therapy. Quality of life domains such as emotional health and limitations on activities showed significant ($p < 0.001$) improvement. Ambulatory BP control measurements indicated that 66.6% of patients assessed were controlled over 24 hours. Over the treatment period, 74 patients (10.8%) reported non-serious adverse events related to EM or EMH therapy. **Conclusions:** EM and EMH are effective in controlling BP in patients with mild-to-moderate hypertension. Therapy with EM or EMH treatment leads to excellent compliance and improvement in several quality of life domains.

KEY WORDS:
enalapril maleate, hydrochlorothiazide, blood pressure, hypertension, quality of life, compliance, open-label, observational, effectiveness, real-life, naturalistic

INTRODUCTION

A major risk factor for cardiovascular disease and end-organ damage, hypertension affects approximately 50 million people in North America and one billion people worldwide.[1-3] Mild arterial hypertension represents the majority (75%) of cases and is responsible for most of the resultant morbidity and mortality.[4,5] As the North-American population ages, the prevalence of hypertension and associated morbidity and mortality will continue to increase unless widespread, effective measures are implemented.[1]

Antihypertensive pharmacotherapy is an effective way to reduce blood pressure (BP). Pharmacologic treatment of hypertension has resulted in reductions in the incidence of stroke of 35% to 40%, of myocardial infarction of 20% to 25%, and of heart failure of more than 50%.[1] Despite this, only 68% of hypertensive persons know they have hypertension, 54% receive treatment and 27% are controlled to < 140/90 mmHg.[5,6]

Non-adherence to treatment is an important contributor to suboptimal BP control among hypertensive patients.[2,7] About 16% to 50% of patients discontinue their antihypertensive medication in the initial year of therapy and among those that do continue, adherence to the prescribed regimen is often inadequate.[2] A Canadian study showed that 78% of patients in Saskatchewan with newly diagnosed hypertension continued therapy to the end of the year and only 46% continued to the end of 4.5 years.[4]

Lack of sufficient communication between patient and physician is one driver of non-compliance.[2] Without key information, patients may not realize the serious consequences related to discontinuing their treatment. Adverse events related to antihypertensive medications have also been cited as a major reason for non-compliance.[2] In light of the availability of effective antihypertensive medications with excellent tolerability profiles, this observation is surprising; however, access to these high-quality medications may be limited for economic reasons or physicians' lack of experience with them.[2] Other contributors to non-compliance include complex regimens and multiple-class switches.[7]

Quality of life (QoL) and health-related quality of life (HRQL) relevant to antihypertensive treatment influences compliance and may be affected by medication-associated efficacy and tolerability, the symptoms related to hypertension itself and other factors.[2,8] Since antihypertensive medications demonstrate qualitative and quantitative change in QoL and HRQL to variable degrees depending on the agents chosen, these assessments are increasingly seen as a way to distinguish between the plethora of antihypertensive treatments on the market.[8]

Angiotensin converting enzyme (ACE) inhibitors are an important part of today's therapeutic arsenal for hypertension. Enalapril maleate (Vasotec®, Merck & Co., Inc.) (EM) is a well-known ACE inhibitor on the Canadian market since 1987, and has an excellent safety profile.[9] Enalapril maleate with hydrochlorothiazide (Vaseretic®, Merck & Co., Inc.) (EMH) is a combination of EM and hydrochlorothiazide, a thiazide diuretic.[10]

In order to treat hypertensive patients optimally, not only do traditional measures of efficacy and safety of the antihypertensive agent need to be considered, but also effectiveness of the medication in the real world, with compliance and QoL being important elements of success. The objective of the present study is to assess mean BP control, dosage, adverse events, medication compliance, and QoL in Canadian patients with mild-to-moderate hypertension treated with EM or EMH.

METHODS

The study was a prospective assessment of BP control in patients with Grade 1 or 2 hypertension treated with EM or EMH in Canada in a "real-world" setting. A large group of Canadian general practitioners (n = 165) were each asked to recruit 5 adult patients with Grade 1 or 2 hypertension (as defined by the Canadian Hypertension Education Program [CHEP], 2003[11]) who were either newly diagnosed, uncontrolled or unsatisfied with their current treatment, into a 10-week, open-label, observational multicenter program.

Any patient over 18 years of age with a confirmed diagnosis of Grade 1 or 2 uncomplicated essential hypertension was eligible for the study, provided they were judged to be in otherwise stable health on the basis of medical history and physical examination, had the ability to give legal consent at the time of entry and fell into one of the following patient categories: newly-diagnosed, untreated (with mean BP ranging between 140/90 mmHg and 180/110 mmHg, including patients with isolated systolic hypertension, where systolic BP [SBP] was > 140 mmHg and diastolic BP [DBP] ≤ 90 mmHg); those receiving antihypertensive therapy but whose BP was not controlled (defined as BP in the range of > 140/90 mmHg and ≤ 160/100 mmHg); patients with hypertension controlled (BP ≤ 140/90 mmHg) with a single antihypertensive agent, but unsatisfied or experiencing side effects warranting discontinuation of treatment; and finally those with controlled hypertension (BP ≤ 140/90 mmHg) with two antihypertensive agents, but unsatisfied or experiencing side effects warranting a change of treatment.

TABLE I Quality of Life Domains and Parameters Assessed Over 10 Weeks

QUALITY OF LIFE DOMAIN	PARAMETER
Assessment of general health	Health status ranking, mean score +/- SD
Emotional health over the past month	General feeling, in control, nervousness, energy level, level of tension, health/activities, sad/discouraged
Mental health and fatigue over the past three months	Losing mind, emotionally stable, cheerful, tired
Impact of physical or emotional problems on social activities	Ranking (positive and negative), mean score +/- SD (positive and negative)
Limitations on activities	Vigorous activity, moderate activity, carrying groceries, climbing stairs (several), climbing stairs (one flight), bending/kneeling walking (> 1 mile), walking (> one block), walking (one block), bathing/dressing
Degree of unsteadiness	Unsteadiness, characteristics of unsteadiness
Impact of hypertension on sleep patterns and memory	Trouble staying asleep, wake up tired, poor memory in the last week
Impact on sexual behavior over the past month	*Satisfaction with:* Frequency of sex, strength of sex drive, sexual arousal *Bothered by:* Loss of interest, getting an erection
Patient symptoms in the last week	Dry mouth, headache, limb weakness, blurred vision, shortness of breath, swollen ankles, constipation, bad taste, burning feeling in mouth, blocked/runny nose, nausea, rash, itching, leg cramps, joint pain (hands), shaky hands, racing heart, stomach pain, heartburn, sore throat, dry cough sweating, wheezing, dry eyes, mouth ulcers, sensitive eyes, cold hands/feet, night urination, diarrhea, flushing, heart pounding, fatigue
Impact of physical health on work	Decreased time at work, accomplished less, limited work activities difficulties performing work

Each patient was asked to visit their physician for a total of four visits. Visits were scheduled at 4-week intervals (± 3 days) with the exception of Visit 2, which was scheduled 2 weeks ± 3 days from the first visit (Visit 1). At any time during the study, unscheduled visits were permitted to ensure patient safety, to assess adverse events, or for any other reason.

Over the course of the study, mean BP, patient reported adverse events, and the use of cardiovascular-related concomitant medications were measured and recorded by physicians. Details of all concomitant medications including the name of the drug, the indication and the dose per day, as well as the start and end dates for each medication were also recorded at Visits 2, 3 and 4. Current cardiovascular medications being used by the patients at Visit 1 were also recorded.

All patients recruited for the study received orally administered EM 5 mg or 10 mg qd at Visit 1. The investigators were asked to determine a mean BP target to achieve for each patient. In order to account for compelling comorbidities (*e.g.,* diabetes, renal disease) and other factors which require more aggressive targets,[1,11] the target mean BP could be different than the mean BP value determined to be within the controlled levels as defined previously. During subsequent visits, physicians either adjusted the EM dose or prescribed EMH based on BP values observed as well as patient's BP target for BP control. At the conclusion of each visit (except Visit 4) the physician dispensed study medication consisting of a box of 30 tablets of EM (5, 10 or 20 mg) or EMH (10/25 mg) to patients with instructions to return with the remaining medication at the next visit. Compliance was assessed by relating the remaining tablets to the number that should remain, based on a one tablet per day dosing regimen, and by direct questioning of the patient by the physician.

The efficacy analysis was carried out on both the full analysis and the per protocol population which were defined in the following manner: full analysis set (intention-to-treat, consisting of all patients receiving at least one dose of study medication) and per protocol set (patients were excluded from the per protocol population for reasons of diagnosis, trial procedure compliance and confounding criteria [*i.e.,* violation of exclusion criteria], or insufficient efficacy data).

TABLE 2 **Baseline Characteristics**

CHARACTERISTIC	FULL ANALYSIS (*n* = 684)	
AGE (YEARS)		
Mean ± SD	56.5 ± 12.6	
Min - max	22 - 95	
GENDER (%)		
male	54.2	
RACE (%)		
Caucasian	93.7	
Black	1.2	
Asian	2.1	
Hispanic	0	
Other	3.1	
HEIGHT (CM)	FEMALES	MALES
Mean ± SD	160.1 ± 7.0	173.6 ± 8.1
Min - max	143.0 - 180.0	146.0 - 200.7
WEIGHT (KG)	FEMALES	MALES
Mean ± SD	77.1 ± 17.0	89.1 ± 17.0
Min - max	37.2 - 140.7	37.7 - 181.6
DIAGNOSIS		
Essential hypertension:		
Grade I (*n* [%])	377 (55.5)	
Grade II (*n* [%])	302 (44.5)	
TIME SINCE DIAGNOSIS (MONTHS)		
Mean ± SD	31.7 ± 59.3	
Min - max	0 - 600	
PATIENT CATEGORIES		
New diagnosis (*n* [%]) (> 140/90 mmHg - < 180/110 mmHg)	451 (66.6)	
Treated/uncontrolled (*n* [%]) (> 140/90 mmHg - < 160/100 mmHg)	186 (27.5)	
Controlled with single agent/unsatisfied (*n* [%]) (< 140/90 mmHg)	30 (4.4)	
Controlled with two agents/unsatisfied (*n* [%]) (< 140/90 mmHg)	10 (1.5)	
BLOOD PRESSURE (MMHG)		
Mean ± SD	155.5 ± 12.6/93.2 ± 8.4	
Min - max	89 - 193/59 - 113	

The QoL domains/parameters listed in Table 1 were also assessed at Visit 1 and at the conclusion of the study at Visit 4 through a 60-question questionnaire designed specifically for patients with hypertension.[12] The QoL questions were adapted from various published QoL instruments.[13-18] This questionnaire also contained elements that assessed the extent of symptoms/adverse events in patients recruited for the study. The majority of the questions demanded a graded Likert response.

Prior to Visit 4, patients were invited to participate in an ambulatory BP monitoring (ABPM) subprogram that permitted an assessment of 24-hour control of BP.

The analysis of effectiveness (% change in mean BP control) involved two-tailed tests with a significance level of 5%. Subpopulation analyses were conducted to explore key subgroups (*i.e.*, patients with diabetes, Black patients, patients with dyslipidemia and patients with BMI > 27).

RESULTS

The data for the per protocol population was similar to the data for the full analysis population. For this reason, only the data for the full analysis population is presented herein.

The full analysis (intention-to-treat) population consisted of 684 patients at Visit 1, 670 at Visit 2, 645 at Visit 3 and 607 at Visit 4. As shown in Table 2, the mean age of the patients in the full analysis population at baseline was 56.5 ± 12.6 years and the average weight was 77.1 ± 17.0 kg (females) and 89.1 ± 17.0 kg (males). The vast majority of patients were Caucasian (93.7%) and slightly over half were male (54.2%). More patients had Grade 1 hypertension (55.5%) than Grade 2 (44.5%). The majority of patients (66.6%) were newly diagnosed, while 27.5% were treated but their BP was uncontrolled. A small fraction of the patients (5.9%) were controlled with one or two antihypertensive agents but were unsatisfied with their treatment. Mean BP at baseline for the full analysis population was 155.5 ± 12.6/93.2 ± 8.4 mmHg.

In this study, the definition of controlled BP was ≤ 140 mmHg (systolic) and ≤ 90 mmHg (diastolic). Although they were aware of this definition, investigators were also given the liberty to set lower patient BP targets. More than half of physicians (54.5%) set their patients' SBP targets below 140 mmHg (135.5 ± 5.9 mmHg) and 68.7% set diastolic targets below 90 mmHg (84.7 ± 4.9 mmHg).

Table 3 indicates that significantly ($p < 0.001$) more patients had controlled mean BP at Visit 4 (91.4%) compared to Visit 1 (30.2%). The decrease in BP occurred rapidly after initiation of the study therapy and 70% of the total DBP, and 64% of the SBP decrease, were apparent at Visit 2 (approximately 2 weeks post-baseline visit). Patient compliance with the study regimen was consistently > 95% from Visit 2 to 4.

Figure 1 presents the number of patients using EM (5, 10 and 20 mg) and EMH at each of the physician visits. Although the absolute number of patients considered at each Visit decreases over the course of the 10-week study (681, 668, 643 and 606 patients at Visits 1, 2, 3 and 4, respectively), the trend towards decreasing use of the lower doses

TABLE 3 **Blood Pressure Control and Patient Compliance Over the 10-week Study Period**

Blood pressure parameters	Visit 1 (*n* = 681)	Visit 2 (*n* = 668)	Visit 3 (*n* = 643)	Visit 4 (*n* = 606)	*P* value
Mean BP ± SD (mmHg) (Systolic ± SD / Diastolic ± SD)	155.5 ± 12.6 / 93.2 ± 8.4	140.7 ± 14.2 / 84.8 ± 8.4	136.8 ± 13.8 / 83.0 ± 8.2	132.2 ± 12.3 / 81.2 ± 7.8	< 0.001 / < 0.001
Min - max (Systolic / Diastolic)	89 - 193 / 59 - 113	103 - 200 / 51 - 110	97 - 189 / 60 - 117	92 - 176 / 55 - 113	
Number of patients with controlled BP* (*n* [%])					
Systolic	69 (10.1)	366 (54.8)	421 (65.5)	473 (78.1)	< 0.001
Diastolic	206 (30.2)	506 (75.7)	532 (82.7)	554 (91.4)	< 0.001
Mean change in SBP from baseline ± SD (mmHg)					
All patients	N/A	-14.9 ± 13.6	-18.7 ± 14.4	-23.2 ± 14.6	N/A
Grade 1 patients†	N/A	-13.1 ± 12.6	-15.4 ± 12.8	-19.6 ± 13.4	N/A
Grade 2 patients†	N/A	-16.9 ± 14.4	-22.8 ± 15.3	-27.6 ± 14.9	N/A
Mean change in DBP from baseline ± SD (mmHg)					
All patients	N/A	-8.4 ± 8.1	-10.1 ± 8.6	-12.0 ± 8.6	N/A
Grade 1 patients†	N/A	-7.8 ± 7.5	-9.2 ± 7.7	-10.7 ± 7.6	N/A
Grade 2 patients†	N/A	-9.1 ± 8.7	-11.3 ± 9.6	-13.6 ± 9.5	N/A
Mean patient compliance (%)	N/A	(*n* = 672) 96.7	(*n* = 644) 95.7	(*n* = 604) 98.2	N/A

*Defined as a diastolic pressure of ≤ 90 mmHg and a systolic pressure of ≤ 140 mmHg
†Refers to patient diagnosis of hypertension at baseline

of EM and increasing use of the higher doses and EMH is evident with time. With each visit, the percentage of patients receiving EM 5 mg decreases, EM 10 mg increases then decreases, EM 20 mg increases and EMH increases (Figure 1b). At study conclusion, 84.4% of the patients were prescribed EM or EMH for continuing BP control and the most frequently indicated medications were EM 5 mg (26.5% of patients) and EM 10 mg (28.4% of patients).

As shown in Figure 2, between Visit 2 and 4, the percentage of patients controlled with EM 5 mg increases between baseline and Visit 2 and then decreases through to study conclusion. The percentage of patients controlled with EM 10 mg increases between Visit 1 and 4 and those controlled with EM 20 mg and EMH increases between Visit 2 and 4.

Of the patients participating in the ABPM substudy, 66.6% had a controlled BP over the 24-hour assessment period. Controlled BP was defined as > 70% of ABPM measurements < 140/90 mmHg during the day, and < 120/80 mmHg at night.

As shown in Table 4, the mean score for overall QoL assessment of general health improved significantly for men ($p < 0.001$) between Visit 1 and 4. The mean score also improved for women but the change was not significant.

As presented in Table 5, the following significant improvements were also found for other QoL measures. Improvement in the majority of the emotional health categories for both men and women between Visits 1 and 4 was established including: general feeling, feeling of being in control, nervousness, energy level, level of tension and feeling of being sad/discouraged ($p < 0.001$). Improvement was also seen again for women in two (feeling of "losing mind" and feeling "tired") of the categories assessed for mental health and fatigue ($p < 0.001$). With respect to limitations on activities, fewer patients felt that their antihypertensive treatment regimen affected their ability to perform vigorous activity "a lot" at Visit 4 compared to Visit 1 ($p < 0.001$). Patients (men and women) also experienced improvement in sleep patterns over the course of the study: more men reported that the antihypertensive treatment had "no impact" on their ability to stay asleep and more women felt that the study medication had no impact on "waking up tired" at Visit 4 compared to Visit 1 ($p < 0.001$). With respect to the impact of hypertension on work, improvement was seen for all parameters assessed between Visit 1 and 4 ($p < 0.001$). Fewer patients reported unsteadiness at Visit 4 compared to Visit 1 ($p < 0.001$). In terms of symptoms experienced in the week prior to the Visit assessment, improvement ($p < 0.001$) was seen for the following

TABLE 4 Quality of Life: Assessment of General Health

	Number of Patients (*n* [%])†				
	Visit 1		Visit 4		*P* value*
Criteria	Males	Females	Males	Females	
Health status (*n*)	366	306	323	273	
Excellent (*n* [%])	32 (8.7)	32 (10.5)	45 (13.9)	18 (6.6)	
Very good (*n* [%])	118 (32.2)	87 (28.4)	109 (33.7)	107 (39.2)	
Good (*n* [%])	157 (42.9)	143 (46.7)	133 (41.2)	112 (41.0)	
Fair (*n* [%])	52 (14.2)	37 (12.1)	31 (9.6)	34 (12.5)	
Poor (*n* [%])	7 (1.9)	7 (2.3)	5 (1.5)	2 (0.7)	
Mean score ± SD‡	2.68 ± 0.89	2.67 ±0.90	2.51 ± 0.90	2.62 ± 0.81	M < 0.001
					F = 0.076

**P* value with respect to the statistical significance of the change in mean scores for male (M) or female (F) patients between Visit 1 and 2
†Percentages of male and female patients are expressed in terms of the total number of males and females participating in the questionnaire at Visits 1 and 4
‡Mean score based on a rating of 1 for excellent to 5 for poor

parameters between Visit 1 and Visit 4: headache (men and women), limb weakness (women only), shortness of breath (women only), swollen ankles (women only), joint pain (women only), racing heart (both men and women), heartburn (men only), dry cough (women only), cold hands/feet (women only), night urination (women only), heart pounding (women only) and fatigue (women only).

Over the course of the study 79 patients (11.5% of the Visit 1 population) withdrew from the study. Adverse events were the major reason for withdrawal, accounting for 39 of the 79 withdrawals. As shown in Table 6, 74 (10.8%) reported events where related to EM/EMH therapy, and 60 (9.6%) unrelated, during the 10-week study period. The most common adverse events were cough (44 patients), dizziness (28 patients) and fatigue (17 patients). Only 7 patients (1.0% of the patient population) reported serious adverse events and all of these were unrelated to EM or EMH.

An assessment of concomitant cardiovascular medication use was carried out at Visits 2, 3 and 4, reflecting the use of non-study medication between visits. This was assessed in two ways: as an indication of additions or discontinuations of concomitant medications since the last visit (in the physician-completed Case Report Form) and by physician completion of a concomitant medication form which recorded details of the medication including dose, indication, etc. Over the course of the study, 8 (1.2% of the full analysis population), 5 (0.7%) and 8 (1.2 %) patients were indicated as having added or discontinued concomitant cardiovascular medications at Visits 2, 3, and 4 respectively (data not shown).

DISCUSSION

The results of the present study demonstrate that EM 5 mg, 10 mg, 20 mg and EMH 10/25 mg provide effective control of BP in patients with mild-to-moderate hypertension in a naturalistic setting. Through aggressive prescribing strategies involving EM dose increases and/or switching to EMH, the percentage of patients with controlled BP increased significantly over the 10-week study period. EM/EMH use also led to improved QoL between Visit 1 and 4, with the improvement reaching statistical significance for several parameters.

One of the key findings in this study was physician tendency to increase the EM dose or to switch to EMH not only in uncontrolled patients, but also in patients who had controlled BP. Such an appropriate titration is not commonly reported: the authors of a recent study of 800 hypertensive men in five U.S. Veteran's Affairs departments found that BP was over 160/90 mmHg in 40% of the men studied and concluded that the prescribers were not sufficiently aggressive in their antihypertensive treatment. Another study reported that 87% of hypertensive patients assessed remained on their initial dose of ACE inhibitor.[19] The recently published ANBP2 study included mainly Grade 1 and Grade 2 hypertensive patients.[20] This study set BP lowering goals of achieving a reduction of SBP of at least 20 mmHg to less than 160 mmHg, with a further reduction to less than 140 mmHg if tolerated, and a reduction of DBP by at least 10 mmHg to less than 90 mmHg, with a further reduction to less than 80 mmHg if tolerated. The ACE Inhibitor enalapril and the

FIGURE 1A **Number of Patients Using EM 5 mg, 10 mg, 20 mg or EMH (10/25 mg): Visit 1 to 4**

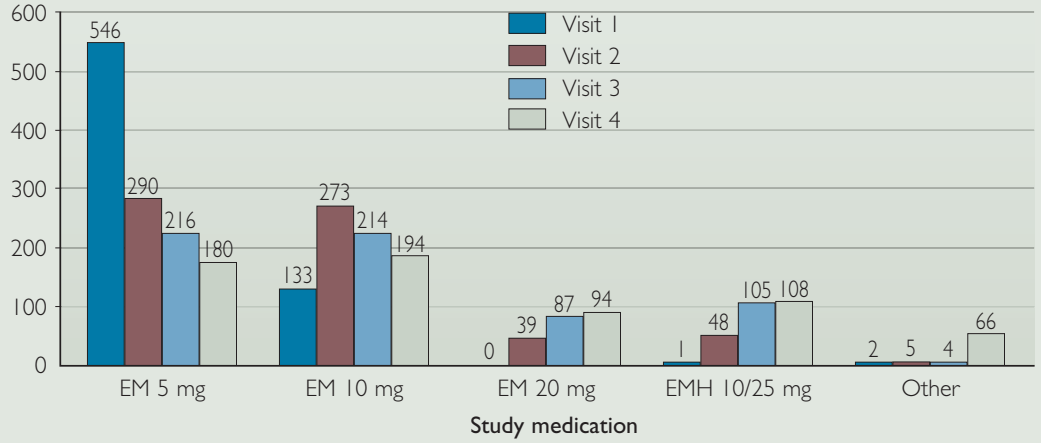
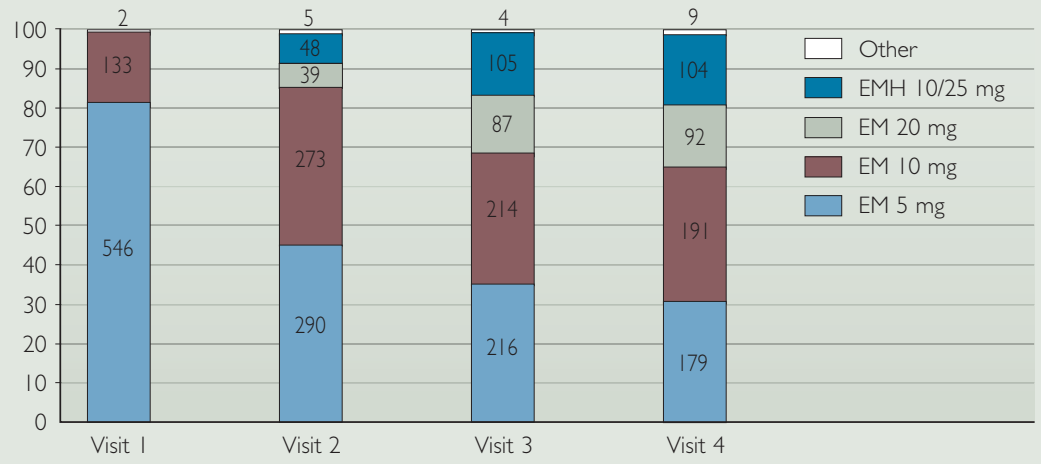


FIGURE 1B **Percentage of Patients Using EM 5 mg, 10 mg, 20 mg or EMH (10/25 mg): Visit 1 to 4**



diuretic hydrochlorothiazide were recommended as initial therapy. In this trial, physicians applied a strategy that focused on BP lowering goals and used a variety of doses to achieve the result. At the end of the trial, BP was decreased by 26/12 mmHg in both groups.

In the present study, physician set lower BP targets than originally and adopted associated prescribing strategies in both controlled and uncontrolled patients and clearly had a positive effect on BP control; however, it raises questions about the criteria used by physicians when they make decisions to titrate or to switch to another medication. Guidelines may influence their decision-making but only to a limited extent. According to a recent report, 47.7% of antihypertensive prescriptions filled are non-compliant with Joint National Committee (JNC) recommendations.[21] Furthermore, many North American physicians are unaware of the existence of the JNC guidelines.[19]

Knowingly or unknowingly, physicians in the present study were part of a trend towards setting more aggressive BP targets and appropriate prescribing for hypertensive patients as mapped out in both the CHEP (2003) guidelines as well as the American Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7).[1,11] Similar to the criteria for controlled BP set in the current trial, the CHEP 2003 guidelines maintain that BP targets for patients with diastolic and systolic hypertension should be < 140/90 mmHg (and < 140 for isolated systolic hypertension).[11] However, for patients with hypertension and diabetes, renal disease and proteinuria (> 1 g per day), both CHEP and JNC 7 guidelines specify BP targets of < 130/80 mmHg, < 130/80 mmHg and < 125/75 mmHg, respectively. In addition, hypertensive patients (without diabetes, renal disease or proteinuria), who measure their own BP at home are advised to use < 135/85 mmHg as a target value.

TABLE 5 Quality of Life Domains and Parameters with Significant ($p < 0.001$) Improvement Over 10 Weeks

QUALITY OF LIFE DOMAIN	PARAMETER	VISIT 1	VISIT 4
Females			
Emotional health over the past month	General feeling (n = 308/n = 275)	3.05 ± 1.03	2.79 ± 0.96
	In control (n = 307/n = 274)	2.15 ± 1.14	1.89 ± 0.90
	Nervousness (n = 307/n = 274)	4.45 ± 1.25	4.86 ± 1.12
	Energy level (n = 309/n = 274)	2.87 ± 1.14	2.59 ± 1.05
	Level of tension (n = 309/n = 273)	3.66 ± 1.20	4.04 ± 1.05
	Sad/discouraged (n = 308/n = 274)	5.07 ± 1.26	5.29 ± 1.09
Mental health and fatigue over the past three months	Losing mind (n = 308/n = 275)	1.78 ± 1.20	1.58 ± 1.00
	Tired (n = 309/n = 275)	2.94 ± 1.28	2.65 ± 1.19
Impact of hypertension on sleep patterns and memory	Wake up tired (no impact) (n = 309/n = 273)	90 (29.4)	90 (33.0)
Patient symptoms in the last week	Headache (n = 308/n = 273)	2.16 ± 1.10	1.74 ± 0.93
	Limb weakness (n = 307/n = 272)	1.79 ± 1.00	1.55 ± 0.87
	Shortness of breath (n = 309/n = 274)	1.79 ± 0.94	1.61 ± 0.85
	Swollen ankles (n = 308/n = 274)	1.55 ± 0.97	1.37 ± 0.78
	Joint pain (hands) (n = 308/n = 273)	1.99 ± 1.19	1.75 ± 1.13
	Racing heart (n = 307/n = 272)	1.71 ± 0.95	1.51 ± 0.77
	Dry cough (n = 307/n = 274)	1.52 ± 0.80	1.88 ± 1.09
	Cold hands/feet (n = 308/n = 275)	1.86 ± 1.11	1.61 ± 0.96
	Night urination (n = 309/n = 275)	2.29 ± 1.15	2.07 ± 1.03
	Heart pounding (n = 309/n = 274)	1.67 ± 1.00	1.44 ± 0.77
	Fatigue (n = 309/n = 275)	2.49 ± 1.24	2.13 ± 1.11
Males			
Emotional health over the past month	Energy level (n = 366/n = 327)	2.58 ± 1.11	2.31 ± 0.91
	General feeling (n = 366/n = 327)	2.84 ± 1.03	2.50 ± 0.97
	Level of tension (n = 365/n = 327)	3.93 ± 1.18	4.25 ± 1.10
Impact of hypertension on sleep patterns and memory	Trouble staying asleep (no impact) (n = 365/n = 327)	143 (39.2)	153 (46.8)
Patient symptoms in the last week	Headache (n = 367/n = 325)	1.65 ± 0.88	1.45 ± 0.71
	Racing heart (n = 366/n = 326)	1.49 ± 0.77	1.31 ± 0.63
	Heartburn (n = 365/n = 325)	1.54 ± 0.83	1.37 ± 0.68
Females and males			
Limitations on activities	Vigorous activity (n = 673/n = 594)		
	A lot	185 (27.5)	134 (22.6)
	A little	253 (37.6)	216 (36.4)
	Not at all	235 (34.9)	244 (41.1)
Degree of unsteadiness	Unsteadiness (n = 632/n = 549)	129 (20.4)	79 (14.4)
Impact of physical health on work	Decreased time at work (n = 673/n = 600)	145 (21.5)	97 (16.2)
	Accomplished less (n = 672/n = 599)	219 (32.6)	159 (26.5)
	Limited work activities (n = 671/n = 598)	174 (25.9)	129 (21.6)
	Difficulties performing work (n = 668/n = 600)	200 (29.9)	145 (24.2)

In the present study, physicians set more aggressive BP target for patients with diabetes (mean 130.64 ± 5.8/81.26 ± 3.79 mmHg) compared to patients without diabetes (mean 136.11 ± 5.62/85.16 ± 4.79 mmHg). Use of these more appropriate targets clearly had a positive effect: the mean BP of diabetic patients decreased from 154 ± 14.2/90.9 ± 9.0 mmHg to 131.7 ± 12.4/79.6 ± 9.0 mmHg between Visit 1 and 4, respectively ($p < 0.001$). Furthermore, subgroup analysis of diabetic patients (n = 80) had a significant improvement ($p < 0.001$) in the percentage of patients with controlled BP between Visit 1 and 4 (from 38.8% to 90.7%, respectively). Although not completely meeting the CHEP/JNC 7 target of < 130/80 mmHg set for diabetic hypertensive patients, the BP values attained at study conclusion were very close to these standards, indicating that the prescribing practices used in this trial allowed achieving those goals even in patients suffering from diabetes.

TABLE 6 **Adverse Events Over the Study Period**

OUTCOME	AES NOT RELATED‡	AES RELATED†
Number of patients with one or more adverse event (*n* [%])	66 (9.6)	74 (10.8)
Mean age ± SD (Years)	56.4 ± 15.8	56.8 ± 12.5
Gender (% female) (*n* [%])	37 (56.1)	36 (48.6)
Intensity of adverse event (*n* [%])		
Mild	45 (6.6)	42 (6.1)
Moderate	36 (5.2)	37 (5.4)
Severe	2 (0.3)	3 (0.4)
Serious	7 (1.0)	0
Adverse events (*n* [%])*		
Cough	2 (0.3)	42 (6.1)
Dizziness	15 (2.2)	13 (1.9)
Fatigue	7 (1.0)	10 (1.5)
Headache	5 (0.7)	5 (0.7)
Nausea	3 (0.4)	6 (0.9)
Diarrhea	4 (0.6)	2 (0.3)
Rash	3 (0.4)	1 (0.1)
Hypotension	0	1 (0.1)
Other	80 (11.7)	32 (4.7)

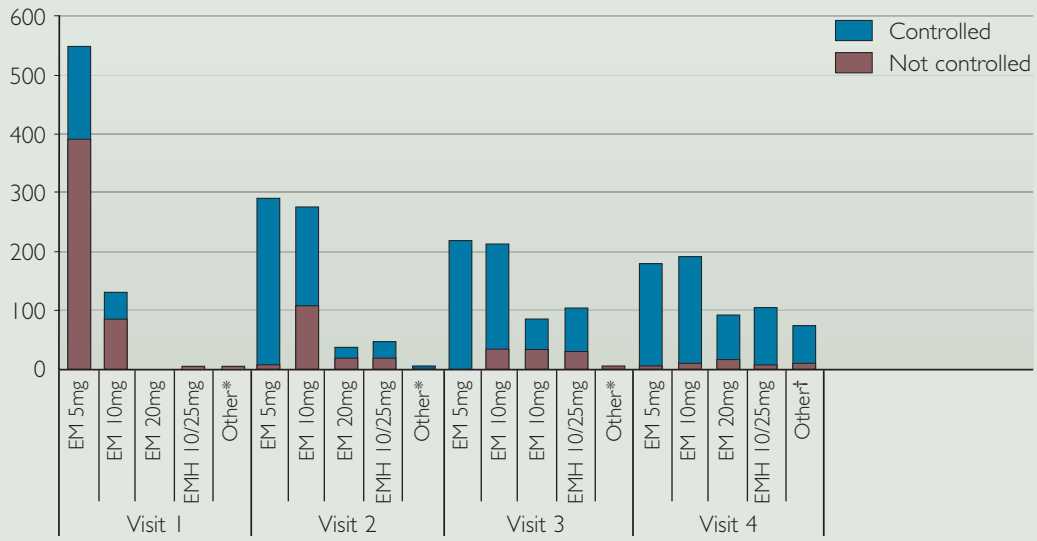
*Percentages based on the total number of patients in the study (*n* = 686)
†Related was defined as probably and definitely related to the test drug
‡Not related was defined as definitely not and probably not related to the test drug

The significant improvement in BP in both the general study population and specifically among patients with hypertension and diabetes, may have been due to the appropriate use of the EM/EMH continuum of care within the study. Ability to adjust EM dose between 5 and 20 mg per day and, when necessary switch to EMH (10/25 mg per day) appears to have been an effective approach to the management of a population of hypertensive patients that included diabetics (11.7%). The benefits of combination drugs (particularly those including a thiazide diuretic) such as better efficacy, lower doses of each component (due to the additive effects of these antihypertensive drugs), better tolerance and better compliance have been well documented.[4,7] The ACE inhibitor/thiazide diuretic combination in particular has been called a "useful combination" by CHEP.[11] The availability and increasing use of the combination product, EMH, over the 10-week study may have contributed to the excellent BP control achieved.

The mean decrease in DBP and SBP that occurred between baseline and Visit 2 was greater among patients with Grade 2 hypertension (-9.1±8.7 and -16.9±14.4 mmHg, respectively) as compared to patients with Grade 1 hypertension (-7.8±7.5 and -13.1±12.6 mmHg, respectively). The mean decrease in DBP and SBP by Visit 4 was also larger in the Grade 2 versus the Grade 1 group. These results suggest a stronger treatment effect in the Grade 2 group, which may have been related to the significantly ($p < 0.001$) higher doses of medication taken by this group at each Visit as compared to the Grade 1 patients. Despite this, the percentages of patients with controlled BP in both Grade 1 and Grade 2 subgroups were very similar indicating that the EM/EMH continuum of care offers enough flexibility to effectively treat patients with different grades of hypertension. More importantly, the time to reach the target BP was very short. This is in line with the observations of the recently published trial VALUE,[22] in which hypertensive patients who are at high cardiovascular risk may benefit significantly from treatments that lower BP in a relatively short time (weeks rather than months).

The excellent safety profile of EM and EMH may have contributed to the high level of sustained compliance in this study (> 95% Visit 2 to 4). Although other factors such as lack of information and the symptoms of hypertension may also affect compliance, adverse events of antihypertensive medication have been reported to account for most non-compliance.[2,8] The good tolerability of EM/EMH is underlined by the results related to cough. Dry, persistent non-productive cough is often associated with ACE inhibitor treatment, affecting up to 30% of patients.[23] In this study however, the incidence of cough decreased between Visit 1 and 4 (QoL assessment) and only 6.4% of patients reported it as an adverse event.

FIGURE 2 Percentage of Patients Using EM 5 mg, 10 mg, 20 mg or EMH (10/25 mg): Visit 1 to 4 by Level of Control (controlled, controlled but not at target, and uncontrolled*)



*Includes any other dosage of EM and/or EMH
†Includes beta-blockers, diuretics, AIIA, ARB, CCB, ACEI, and any other dosage of EM and/or EMH

The effectiveness of EM/EMH therapy was further demonstrated in an ABPM sub-study where BP was assessed for a 24-hour period. Of the patients participating in this sub-study, 66.6% had controlled BP during the ABPM assessment period where control was defined as > 70% of ABPM measurements < 140/90 mmHg during the day and < 120/80 mmHg at night. This data showed that EM/EMH maintains effective BP control over a 24-hour period. The ABPM results also indicate that "white coat" hypertension (*i.e.*, BP that is elevated during an office visit but is otherwise normal)[24] was not observed in our study.

The improvement in QoL related to the EM/EMH regimen established in this study may have been due to the agents' excellent tolerability as well as effects on the symptoms of hypertension. Although hypertension is often considered to be asymptomatic, some investigators have seen increases in symptoms subjectively reported by patients who suffer from a rising BP.[8] The beneficial impact of EM/EMH on the underlying symptoms of hypertension could directly explain the improvements noted in patient reported symptoms and indirectly explain other QoL improvements.

Some differences between QoL findings for male and female patients over the course of the study were observed. For example, the improvement in mean QoL (assessment of general health) score between Visit 1 and 4 was significant for men ($p < 0.001$) and not for women. With respect to symptoms reported over the last week, statistically significant improvement between Visit 1 and 4 was evident for women for many items (*e.g.*, dry mouth, limb weakness, shortness of breath) whereas improvement for men was not significant. Such gender differences have also been found in the literature: women tend to report lower QoL than men as well as more symptoms.[8]

LIMITATIONS

One limitation of the present study may have been the use of DBP as the measure of control. At baseline 13.8% of the full analysis population was at target DBP while only 4.1% at SBP goals and 2.2% at both SBP and DBP targets. These data suggest that the use in the present study of DBP ≤ 90 mmHg as the definition of controlled BP may have overestimated the number of patients who were actually controlled. It has been reported that high SBP is a strong predictor of lack of BP control and patients with higher initial SBP have been found to need more intensive therapy in order to meet their BP targets.[5] The traditional emphasis on DBP may lead to undertreatment of certain patients: some have normal DBP but elevated SBP.[5] SBP is a stronger risk marker than DBP in the prediction of negative CV outcomes.[5]

The prevalence of concurrent medical conditions and use of concomitant medication may have affected the results. Subpopulation analyses of major

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co-morbidity categories (*e.g.*, diabetes and dyslipidemia) indicated that BP control improvement was similar to the overall patient population. About a third (34%) of patients were taking one or more antihypertensive medications at baseline and over the course of the study, 8 (1.2%), 5 (0.7%) and 8 (1.2%) patients took concomitant medication at Visits 2, 3 and 4, respectively. Although a latent effect of the baseline antihypertensive medication may have had an effect on the results, the concomitant medication taken over the course of the study was unlikely to have had an important effect due to the small numbers involved.

CONCLUSIONS

With EM 5 mg, 10 mg, 20 mg and EMH 10/25 mg once daily, physicians have the flexibility to optimally manage BP in patients with Grade 1 and 2 hypertension. Although the present study does not identify a specific optimal dose of EM or EMH for newly diagnosed or uncontrolled patients, it does however show that appropriate EM/EMH titration and physician judgment allow for excellent BP control and consistently high compliance (> 95%). In addition, EM/EMH treatment also led to improved patient QoL over the course of the study, in many cases with the improvement reaching statistical significance. In North America and elsewhere, policy-makers and prescribers may benefit patients and society by considering compliance and QoL in addition to the traditional efficacy and safety information to discriminate between antihypertensive agents.

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