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RESEARCH ARTICLE

ANTIHYPERTENSIVE EFFECTIVENESS OF A FIXED-DOSE COMBINATION OF RAMIPRIL/HYDROCHLOROTHIAZIDE IN THE GULF REGION: RESULTS FROM THE PACHA REGISTRY.

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Abstract

Ramipril/hydrochlorothiazide (HCTZ) combined therapy can be used for the treatment of hypertension. We determined the percentage of patients who achieved optimum blood pressure control according to 2007 ESH recommendations after 3 months treatment with fixed-dose combination (FDC) ramipril/HCTZ and assessed tolerance to treatment. This non-interventional, prospective, multicentre, observational study was conducted in three Gulf countries (United Arab Emirates, Kuwait and Qatar). Patients with uncontrolled hypertension were treated with FDC ramipril/HCTZ (10/12.5 mg or 10/25 mg) for 3 months. Systolic (SBP) and diastolic (DBP) blood pressure were measured at baseline and after 1 and 3 months of treatment. Primary endpoint was the number of patients who achieved the target blood pressure of <140/90 mmHg (or <130/80 mmHg in diabetics) after 3 months of treatment. Secondary endpoints were the reduction in mean SBP and DBP in different patient subgroups and overall safety.

A total of 409 patients were included in the efficacy analysis. The majority of patients (n=324, 79.2%) were given FDC ramipril/HCTZ 10/12.5 mg, while 85 (20.8%) received ramipril/HCTZ 10/25 mg. Ninety-four (23%) of these 409 patients had diabetes. There was no significant difference in the daily dose of ramipril/HCTZ FDC between patients with and without diabetes (78.7% of patients with diabetes and 79.4% of patients without received ramipril/HCTZ 10/12.5 mg; p = 0.89).

After three months of treatment, 260 (63.6%; 95%CI: 58.9-68.3) patients achieved the blood pressure target and 149 (36.4%) did not. The proportion of patients achieving the blood pressure target was significantly higher at three months than at one month (p<0.001).

The proportion of patients achieving the blood pressure target was considerably higher in non-diabetic patients than in those with diabetes (81.3% vs 4.3% respectively; p<0.001), irrespective of the ramipril/HCTZ dose. In conclusion, 10/12.5 mg and 10/25 mg FDC ramipril/HCTZ was effective at reducing both SDP and DBP to below guideline target levels in hypertensive patients, including those with

diabetes, within 3 months of treatment. Ramipril/HCTZ was well tolerated.

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Introduction:-

Hypertension, defined by the American Heart Association (AHA) as a systolic/diastolic blood pressure (SBP/DBP) $\geq 140/90$ mmHg (Mancia et al., 2007), is one of the most common diseases in the world. In 2000, it was estimated that over 972 million people worldwide were suffering from hypertension and that the global prevalence is set to increase to over 1.56 billion by 2025 (Hajjar et al., 2006, Chockalingam et al., 2006). Hypertension is more common in low- to middle-income countries (Chockalingam et al., 2006) and has a higher incidence in people over the age of 65 years than in younger persons (WHO, 2002). Other risk factors for hypertension include male gender, race/ethnicity (higher risk in African Americans), obesity and lifestyle factors such as inactivity, alcohol, stress and eating too much sodium or too little potassium (Ezzati et al., 2002). Hypertension is the leading cause of cardiovascular disease worldwide (Hajjar et al., 2006), including cerebrovascular stroke, and has been ranked as the third most important factor for disability-adjusted life years (Chockalingam et al., 2006, Ezzati et al., 2002, World Health Report, 2002).

Because of its associated morbidity and mortality and its cost to society, hypertension is an important public health challenge (Riaz and Batuman 2016). Over the past few decades, a concerted effort on the part of healthcare professionals has led to a decrease in mortality and morbidity rates from multiple organ damage arising from years of untreated hypertension (Riaz and Batuman 2016). Treating hypertension has been associated with a 20–25% reduction in the risk of myocardial infarction, a 35–40% reduction in the risk of stroke and a >50% reduction in the risk of heart failure (Neal et al., 2000). Despite these promising results, approximately 30% of adults are still unaware that they have hypertension, up to 40% of people with hypertension are not receiving treatment and, of those treated, only about one-third achieve adequate blood pressure control (Hajjar et al., 2006, Chobanian et al., 2003).

Five major classes of agents are recommended for the control of hypertension: thiazide diuretics, calcium channel antagonists (CCA), angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor antagonists (ARB) and β -blockers. The seventh JNC report in 2003 recommended treatment that includes a thiazide diuretic, either alone or in combination with another class of drug having a complementary mode of action, as initial therapy for uncomplicated stage II hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg) (Chobanian et al., 2003). This report and the AHA and ESC (European Society of Hypertension) 2007 guidelines on the management of hypertension state that most patients will require two or more drugs to achieve the blood pressure target and that when the blood pressure is >20/10 mmHg above the goal, physicians should consider prescribing a bitherapy from the outset (Mancia et al., 2007, Chobanian et al., 2003). In comparison with monotherapy, fixed-combination tablets and multiple tablet treatment regimens have been associated with a 55% and 26% increased likelihood of blood pressure control, respectively (Gu et al., 2012). The majority of currently available fixed-dose combinations include a diuretic (Kalra et al., 2010).

Ramipril is the most frequently prescribed ACEi and has underlying mechanisms by which it prevents cardiovascular events and decreases the risk of stroke and transient ischaemic attacks, cardiovascular death and myocardial infarction, independent of the reduction in blood pressure (Bosch et al., 2002, Yusuf et al., 2000). Ramipril can be used in combination with different drugs but is mostly used with hydrochlorothiazide (HCTZ), a diuretic that increases renal excretion of sodium and chloride (Messerli et al., 2011). In a double-blind comparative study in patients with mild to moderate hypertension the proportion of responders was significantly higher with combined ramipril/HCTZ therapy than with ramipril alone (Heidbreder, 1992). Although such clinical studies show that the majority of treated patients effectively achieve satisfactory blood pressure control with ramipril/HCTZ, it is important to monitor effectiveness of such treatments in real-world conditions in order to ensure that blood pressure targets are met. This is of particular relevance in developing countries such as those in the Middle East where little such data is available.

The present study was carried out in three countries in the Gulf region (Kuwait, Qatar and United Arab Emirates) with the objectives of evaluating the percentage of patients who achieved optimum blood pressure control according to ESH 2007 guidelines with fixed-dose combination (FDC) ramipril/HCTZ (10/12.5 mg or 10/25 mg) within a time

limit of three months, both overall and in subgroups of patients at particular risk, and of assessing the overall safety of treatment (Mancia et al., 2007).

Materials and Methods:-

Study design:-

This regional, non-interventional, prospective, multicentre, observational study (PACHA registry) was conducted in patients with hypertensive treated with FDC ramipril/HCTZ in private and governmental hospitals and clinics in the United Arab Emirates (UAE), Kuwait and Qatar between 16th November 2012 and 11th December 2014.

The study was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) including all subsequent amendments, with international guidelines, with national laws and regulations of the countries in which the study was performed and in compliance with the guidelines for Good Epidemiology Practice.

Study objectives:-

The primary objective of the study was to determine the number of patients in different subgroups who achieved the target blood pressure of <140/90 mmHg (or <130/80 mmHg in patients with diabetes) after three months of treatment according to the 2007 ESH guidelines (1). Secondary objectives were to determine mean SBP and DBP after three months in different subgroups of patients defined according to their risk factors for hypertension and to assess the overall safety of FDC ramipril/HCTZ.

Study population:-

Cardiologists, interns, GPs and diabetologists treating patients with hypertension in private and governmental hospitals and clinics in the three participating countries were selected by random sampling. Each investigator was asked to include one patient who met the inclusion criteria per consultation session with the aim of recruiting approximately 20 consecutive patients each over a 6-month period. This method of consecutive recruitment was chosen to limit any selection bias.

Adult patients (age >18 years) whose blood pressure was not controlled according to 2007 ESH guidelines (<140/90 mmHg or <130/80 mmHg in patients with diabetes) and for whom the participating physician had decided to prescribe FDC ramipril/HCTZ were eligible for the study. It was required that the patients had failed to respond adequately to previous treatment with anti-hypertensive monotherapy for at least four weeks and <12 months. Patients were required to be eligible for anti-hypertensive treatment according to international guidelines and suitable for treatment with FDC ramipril/HCTZ as specified in the local Summary of Product Characteristics. Patients were excluded if they had a history of impaired renal function, defined as serum creatinine >1.5 mg/dL in men and >1.3 mg/dL in women, previous or current liver impairment, a history of angioedema or secondary hypertension. In addition, pregnant or breast-feeding women were excluded as were patients with known hypersensitivity to Ramipril, HCDZ or any of their excipients, and patients with any other contraindication to the use of FDC ramipril/HCTZ.

Written informed consent and a signed data release consent form were obtained from all patients or the patients' legal representatives prior to inclusion. All patients included in the study were recorded in a specific study log under an anonymous patient identity number to ensure data privacy.

Treatment:-

The dose of FDC ramipril/HCTZ (10/12.5 mg or 10/25 mg) was chosen by the treating physician according to the prescribing information and the level of blood pressure control required. Treatment was continued for a period of three months. The prescription of treatment was the sole responsibility of the patient's physician.

Data collection:-

Blood pressure was measured at each study visit according to the participating physician's standard practice. All adverse events (AEs) and serious AEs that occurred during the study were recorded and their relationship to the study drugs determined.

All data were collected on paper clinical report forms (CRFs) at three visits (baseline, one month and three months). Entry of data into a computerised database and subsequent analysis were performed by a contract research

organisation (DATACLin, Giza, Egypt). In case of missing data or inconsistencies in the data, queries were addressed to the relevant participating physician.

Statistical analysis:-

The target sample size was determined through *a priori* power calculations. According to Heidbreder et al. (18), 72% [95%CI: + 11.56%] of patients taking FDC ramipril/HCTZ achieved blood pressure control after at least ten weeks of treatment. In our study, we assumed that at least 60% of patients would achieve blood pressure control after twelve weeks. In order to determine such a proportion with a 95% confidence interval (95%CI) of 5%, a sample of 637 patients would be required. Considering an anticipated drop-out rate of 15%, then 733 should be recruited, which was rounded up to 750 patients.

Three study populations were defined. The enrolled population was defined as all patients included in the study, and this was used for the safety analysis. The eligible population was defined as all enrolled subjects who satisfied the eligibility criteria, and was used for the descriptive analysis of the study population. The analysis population was defined as all eligible subjects with no protocol violations and for whom an evaluable blood pressure measure was available at three months; this population was used for the efficacy analysis.

Continuous variables were presented as mean and median values, with standard deviation (SD) and range (minimum, maximum) and categorical variables presented as frequency counts and percentages. Repeated measures within groups were compared using the paired *t*-test and repeated measures ANOVA and study groups were compared using an independent *t*-test and one way ANOVA. Categorical data were compared using the χ^2 test. All statistical tests were two-tailed and a probability threshold of 0.05 was considered as statistically significant.

Results:-

Study population:-

A total of 30 sites in the three countries (UAE 23 sites, Qatar 3 sites and Kuwait 4 sites) enrolled patients, with an average of 14-20 patients per site. Overall, 472 patients with hypertension were enrolled, 336 (71.2%) in the UAE, 76 (16.1%) in Kuwait and 60 (12.7%) in Qatar. These 472 patients constituted the enrolled population and were used for the safety analysis. Forty-five of these patients (9.5%) did not fulfil the eligibility criteria for the study, and the remaining 427 (90.5%) patients constituted the eligible population (Figure 1).

Of these 427 patients, 392 (91.8%) were prescribed a daily FDC of ramipril/HCTZ 10/12.5 mg at baseline and 35 (8.2%) patients were prescribed a FDC of 10/25 mg. The efficacy analysis was performed on 409 (86.7%) patients (analysis population) who fulfilled the eligibility criteria and for whom blood pressure measurements at baseline and three months were available. Eighteen (3.8%) patients were excluded from the efficacy analysis due to missing blood pressure measurements at three months.

The study populations and reasons for exclusion from the eligible or analysis populations are summarised in Figure 1.

Demographic and clinical characteristics of the study population:-

The baseline demographic and clinical characteristics of the 427 patients who were prescribed ramipril/HCTZ are presented in Table 1. Mean age ($\pm$ SD) was 44.9 ± 8.2 years, mean body mass index (BMI) $\pm$ SD was 28.44 ± 3.94 kg/m² and three-quarters of the patients (74.2%) were male. Almost two-thirds (63.7%) of the patients were Asian.

At inclusion, mean SBP $\pm$ SD was 157.3 ± 13.1 mmHg and mean DBP $\pm$ SD was 98.5 ± 7.3 mmHg. Two-thirds of the patients (65.6%) had a family history of hypertension. Hypertension was diagnosed <1 year prior to study entry in 139 (32.6%) patients, <5-10 years in 50 (11.7%) 10-<15 years in 28 (6.6%) patients and ≥ 15 years in 14 (3.3%) patients (Table 1). All patients were being treated with antihypertensive monotherapy at inclusion. The most commonly reported monotherapies at baseline were CCA (29.7%), ARB (25.3%), ACEi (22.2%) and β -blockers (20.6%) (Table 1). The mean duration of antihypertensive monotherapy was 6.4 ± 3.0 months prior to study entry. Ninety-seven patients (22.7%) had diabetes mellitus and 51 (11.9%) were obese. Eighty-three patients (19.4%) were current smokers (Table 1). One-hundred and fifty-four patients (36.1%) were taking lipid-lowering agents and 34.2% were taking antidiabetics (Table 1).

Study Treatment:-

A total of 409 patients were included in the efficacy analysis. The majority of patients (n=324, 79.2%) were given FDC ramipril/HCTZ 10/12.5 mg, while 85 (20.8%) received ramipril/HCTZ 10/25 mg. Ninety-four (23%) of these 409 patients had diabetes. There was no significant difference in the daily dose of ramipril/HCTZ FDC between patients with and without diabetes (78.7% of patients with diabetes and 79.4% of patients without received ramipril/HCTZ 10/12.5 mg; $p = 0.89$). The proportion of patients receiving the higher dose of ramipril/HCTZ 10/25 mg increased as a function of the severity of hypertension (14.2% in Grade I hypertension, 20.9% in Grade II and 44.9% in Grade III).

At the interim analysis after one month of treatment, 143 patients (35.0%; 95%CI: 30.3-39.6) achieved the blood pressure target while 266 (65.0%) did not. Three-hundred and twenty-four patients (79.2%) continued on the same daily FDC of ramipril/HCTZ (10/12.5 mg) prescribed at baseline and 35 (8.6%) continued on a daily FDC of 10/25 mg. In 50 patients (12.2%), who were initially treated with ramipril/HCTZ 10/12.5 mg, the daily FDC was increased to 10/25 mg to try and achieve better blood pressure control.

Blood pressure control at three months:-

After three months of treatment, 260 (63.6%; 95%CI: 58.9-68.3) patients achieved the blood pressure target and 149 (36.4%) did not. The proportion of patients achieving the blood pressure target was significantly higher at three months than at one month ($p < 0.001$).

Blood pressure control according to FDC ramipril/HCTZ dose and the presence of comorbid diabetes is presented in table 2. A total of 324 patients received ramipril/HCTZ 10/12.5 mg and 213 (65.7%) of these achieved the target blood pressure, while 47/85 patients (55.3%) who received ramipril/HCTZ 10/25 mg achieved the target ($p=0.075$). The proportion of patients achieving the blood pressure target was considerably higher in non-diabetic patients than in those with diabetes (81.3% vs 4.3% respectively; $p < 0.001$), irrespective of the ramipril/HCTZ dose (Table 2).

Blood pressure control as a function of the presence of different risk factors and other potential explanatory variables is presented in Figure 2. For example, the proportion of patients achieving adequate blood pressure control was significantly lower in the high risk age group (men aged over 55 years and women over 65 years) compared to younger, lower-risk patients (41.9% vs. 66.1%; $p=0.002$). On the other hand, the proportion of patients with controlled blood pressure did not differ between men and women. The number of patients who achieved the blood pressure target was inversely associated with the severity of hypertension (71.6% in Grade I, 61.0% in Grade II and 42.9% in Grade III; $p < 0.001$). No association was observed between the extent of blood pressure control and the time since diagnosis of hypertension. The proportion of patients achieving blood pressure targets was significantly lower in patients with hypercholesterolemia compared to those without (52.9% vs 69.0%; $p = 0.001$) and in patients with hypertriglyceridemia compared to those without (53.1% vs 65.5%; $p = 0.041$). Conversely, obesity, smoking status, cardiovascular disorders, and BMI and duration of hypertension had no significant effect on the extent of blood pressure control.

Evolution of blood pressure, heart rate and weight between inclusion and three months:-

Systolic and diastolic blood pressure at inclusion and three months, the mean percent reduction and the absolute reduction in blood pressure in the different subgroups are presented in Table 3.

There was a significantly greater decrease in SBP in the ramipril/HCTZ 10/25 mg subgroup compared to patients treated with ramipril/HCTZ 10/12.5 mg (absolute mean reduction of 32.0 ± 16.3 mmHg vs. 24.1 ± 11.0 mmHg respectively, $p=0.002$). On the other hand, there was no significant difference between the two subgroups with regards to the decrease in DBP ($p=0.149$). No significant differences in the absolute mean reduction in blood pressure after three months were observed between patients with and without diabetes ($p=0.407$ for SBP and $p=0.558$ for DBP).

Two other significant changes were noted in our study population between baseline and three months. Mean heart rate decreased significantly from 82 ± 11.7 bpm at baseline to 78 ± 7.0 bpm at 3 months ($p < 0.001$). In addition, the mean weight of the patients decreased significantly from 81.9 ± 12 kg at baseline to 80.8 ± 11.3 kg after three months of treatment ($p < 0.001$).

Safety:-

Ramipril/HCTZ was well tolerated. Only six of the 472 patients enrolled (1.3%) experienced AEs. One patient each in the ramipril/HCTZ 10/12.5 mg subgroup (0.2%) experienced cough, a lower respiratory tract infection and arthralgia, while three patients in the ramipril/HCTZ 10/25 mg subgroup experienced cough (0.64%). The study drug was considered to be related to the AE in three (0.64%) events. All AEs were mild and no AE resulted in discontinuation of the patient from the study.

Adherence:-

Adherence to the study medication was good. Out of the 409 patients included in the efficacy population, 378 (92.4%) were compliant with the study medication. Adherence was significantly better with ramipril/HCTZ 10/12.5 mg than with 10/25 mg (96.3% vs. 77.6%; $p < 0.001$). All causes for non-compliance were related to the patients forgetting to take the study medication. The mean ($\pm$ SD) number of missed doses/week in non-compliant patients was 2.3 ± 1.2 (1.6 ± 1.2 with ramipril/HCTZ 10/12.5 mg vs. 2.8 ± 1.0 with ramipril/HCTZ 10/25 mg).

Table 1:- Demographic and clinical characteristics of the study population at inclusion

Age (years)	
Mean $\pm$ SD	44.9 $\pm$ 8.2
Median (range)	44 (25-67)
Sex, M/F	317/110 (74.2/25.8%)
Race/ethnicity	
Asian	272 (63.7%)
Arab	146 (34.3%)
Caucasian	9 (2.1%)
Physical examination	
Normal/abnormal	421/6 (98.6/1.4%)
Body mass index, kg/m ²	
Mean $\pm$ SD	28.4 $\pm$ 3.9
Median (range)	28.1 (18.5-44.3)
Pulse, bpm	
Mean $\pm$ SD	82.4 $\pm$ 11.7
Median (range)	80 (55-126)
SBP, mmHg	
Mean $\pm$ SD	157.3 $\pm$ 13.1
Median (range)	155 (125*-215)
DBP, mmHg	
Mean $\pm$ SD	98.5 $\pm$ 7.3
Median (range)	100 (69**-130)
Smoking history	
Current smoker†	83 (19.4%)
Previous smoker#	73 (17.1%)
Never smoked	271 (63.5%)
Concomitant medical and surgical illnesses, yes/no	226/201 (52.9/47.1%)
Types of concomitant illness (MedDRA coding)	
Metabolism and nutrition disorders	374 (87.6%)
Cardiac disorders	18 (4.2%)
Gastrointestinal disorders	16 (3.8%)
Respiratory, thoracic and mediastinal disorders	6 (1.4%)
Surgical and medical procedures	6 (1.4%)
Infections and infestations	6 (1.4%)
Musculoskeletal and connective tissue disorders	6 (1.2%)
Psychiatric disorders	2 (0.5%)
Other ^s	3 (0.6%)
Diabetes mellitus, yes/no	97/330 (22.7/77.3%)
Obesity, yes/no	51/376 (11.9/98.1%)
Family history of hypertension, yes/no	280/147 (65.6/34.4%)

Time since diagnosis of hypertension	
<1 year	139 (32.6%)
<5 years	196 (45.9%)
5- <10 years	50 (11.7%)
10- <15 years	28 (6.6%)
≥15 years	14 (3.3%)
Current antihypertensive monotherapy	
Calcium channel blockers	127 (29.7%)
Angiotensin II receptor blockers	108 (25.3%)
Angiotensin-converting enzyme inhibitors	95 (22.2%)
Beta blockers	88 (20.6%)
Alpha 2 agonists	4 (0.9%)
Thiazide-like diuretics	4 (0.9%)
Thiazide diuretics	1 (0.2%)
Duration of antihypertensive monotherapy (months)	
Mean ± SD	6.4 ± 3.0
Median (range)	6.1 (1.0-11.8)
Other concomitant medications, yes/no	191/236 (44.7/55.3%)
Types of concomitant therapy	
Lipid lowering drugs	154 (36.1%)
Antidiabetic drugs	146 (34.2%)
Anti-platelet agents	40 (9.4%)
Neurotonic agents	14 (3.3%)
Vasodilating drugs	4 (0.9%)
Other	43 (10.1%)
Antihypertensive combination given at baseline	
Ramipril/HCTZ - 10/12.5 mg/day	392 (91.8%)
Ramipril/HCTZ – 10/25 mg/day	35 (8.2%)

Values are presented as mean ± SD, median (range), or n (%) for the 427 eligible patients. SBP: systolic blood pressure; DBP: diastolic blood pressure. *DBP out of control, **SDP out of control, †At least one cigarette/day for the past 7 days, # stopped at least 8 days previously, §nervous system (n=1), reproductive system and breast (n=1) and general disorders (n=1).

Table 2:- Effectiveness of ramipril/HCTZ after three months as a function of dose and of diabetic comorbidity

	Ramipril/HCTZ 10 mg / 12.5 mg (N = 324)	Ramipril/HCTZ 10 mg / 25 mg (N = 85)	All doses (N = 409)
All patients (N = 409)	213/324 (65.7% [60.5%-70.9%])	47/85 (55.3% [44.5%-66.1%])	260/409 (63.6% [58.9%-68.3%])
Patients with diabetes (N = 94)	3/74 (4.1% [1.4%-11.3%])	1/20 (5.0% [0.9%-23.6%])	4/94 (4.3% [0.01%-8.4%])
Patients without diabetes (N = 315)	210/250 (84.0% [79.0%-88.0%])	46/65 (70.8% [58.8%-80.4%])	256/315 (81.3% [76.9%-85.6%])

Values are presented as n/N (% [95% confidence intervals]) for the 409 analysable patients.

Table 3:- Blood pressure measurements at baseline and after three months, and changes in blood pressure in different patient subgroups

Patient subgroup	Baseline		3 months		Absolute mean reduction		Mean % reduction		p value	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Ramipril/HCTZ 10/12.5 mg 10/25 mg	155 ±	98 ±	130 ±	82 ±	24.1 ±	15.8 ±	15.3 ±	15.8 ±	0.002	0.149
	10.8	6.8	7.2	4.6	11.0	7.3	6.3	6.6		
	167 ±	101 ±	134 ±	83 ±	32.0 ±	17.6 ±	18.6 ±	17.0 ±		
	15.8	8.3	5.9	4.1	16.3	8.5	7.5	7.0		

With diabetes	156 ± 13.0	98 ± 7.6	131 ± 6.2	83 ± 4.3	25.0 ± 12.1	15.5 ± 7.4	15.6 ± 6.1	15.4 ± 6.6	0.407	0.558
Without diabetes	157 ± 12.9	99 ± 7.1	131 ± 7.4	82 ± 4.6	26.0 ± 12.9	16.1 ± 7.6	16.1 ± 6.9	16.2 ± 6.8		

Values shown are presented as mean values ± SD. SBP: systolic blood pressure; DBP: diastolic blood pressure.

Figure 1:- Patient disposition at inclusion.

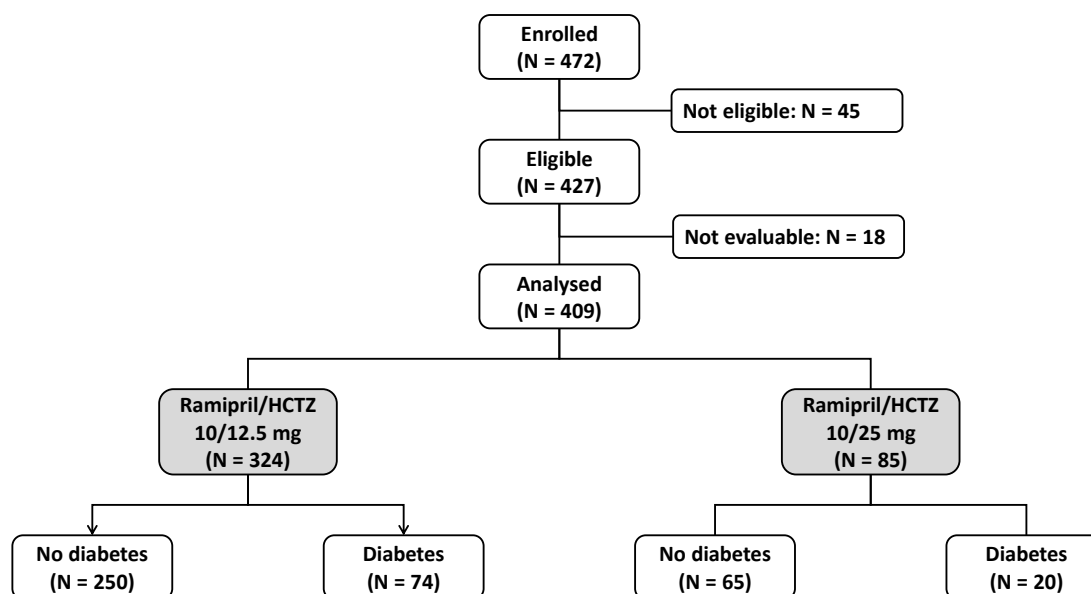
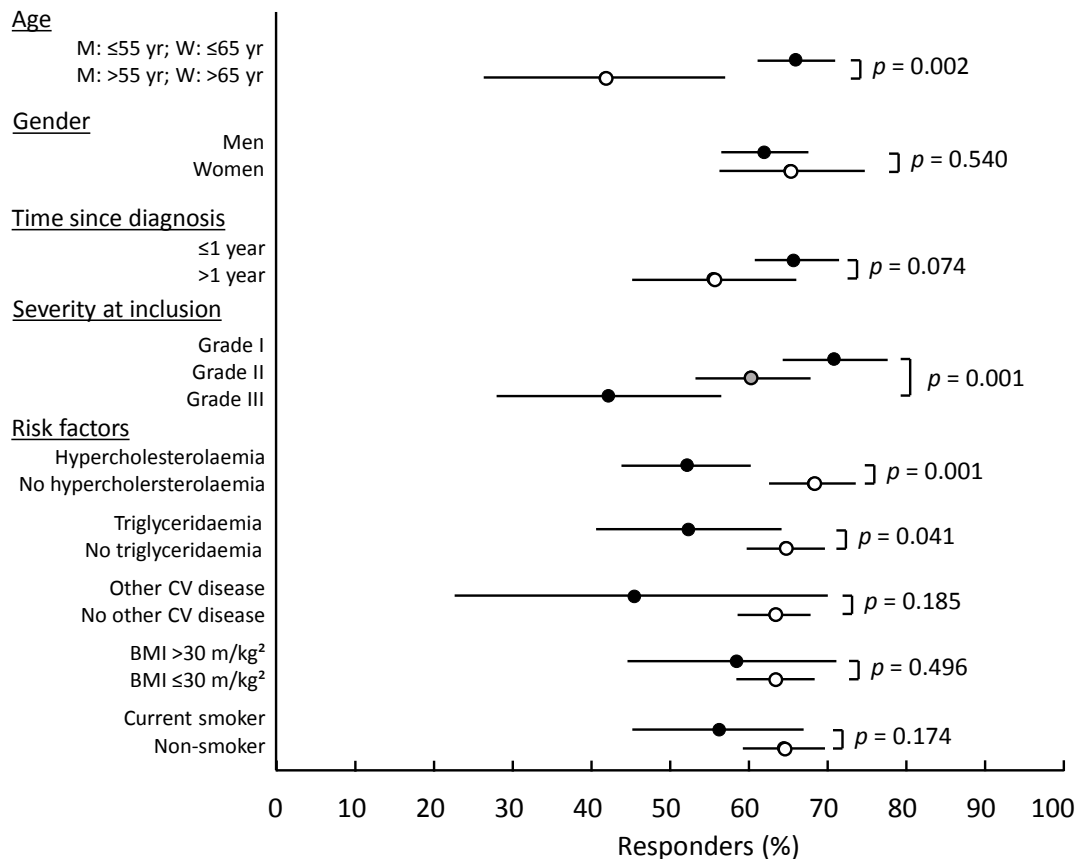


Figure 2:-Blood pressure control in patient subgroups.

Discussion:-

This multicentre, non-interventional, observational study, carried out in three countries in the Gulf region, shows that nearly two-thirds (63.6%) of previously treated patients with hypertension monotherapy achieved blood pressure targets according to 2007 ESH recommendations (Mancia et al., 2007) in the three months following a switch to FDC ramipril/HCTZ. The proportion of patients achieving the blood pressure target was numerically lower at the higher of the two doses evaluated (55.3% at 10/25 mg/day), than at the lower dose (65.7% at 10/12.5 mg), but this difference was not statistically significant ($p=0.075$). The lower response at the higher dose may be due to the higher percentage of patients with more difficult to treat grade III hypertension who received this dose.

The extent of blood pressure control was lower in patients with diabetes than in those without (4.3% vs 81.3%). This difference was observed both for ramipril/HCTZ 10/12.5 mg (4.1% vs 84%) and for ramipril/HCTZ 10/25 mg (5.0% vs 70.8%). At the time that the protocol for this study was prepared, the 2007 ESH guidelines for the treatment of hypertension in operation at the time recommended two distinct blood pressure targets, namely <140/90 mmHg in low- to moderate- risk individuals and <130/80 mmHg in high-risk patients including those with diabetes (Mancia et al., 2007). Since then, the results of extensive reviews of randomized controlled trials have shown that the recommendation to lower blood pressure to <130/80 mmHg in patients with diabetes, renal disease or with a history of cardiovascular disease is not supported by any real evidence (Zanchetti et al., 2009, Arguedas et al., 2013, Upadhyay et al., 2011) and the guidelines from the ESH, ASH (American Society of Hypertension), ISH (International Society of Hypertension), JNC (Joint National Committee) and NICE (National Institute for Health and Clinical Excellence) have recently been updated so that the target for patients with diabetes is now less strict (now <140/90 mmHg as for non-diabetic patients) (European Society of Cardiology, 2013, Weber et al., 2014, James et al., 2014, National clinical Guideline Centre, 2011). The use of the most recent guidelines for target blood pressure in our study would have resulted in more patients with diabetes achieving blood pressure control.

In our study, a significantly higher percentage of patients with Grade I hypertension achieved the blood pressure target compared to those with Grade II and Grade III hypertension (71.6% vs. 61% and 42.9%, respectively) ($p < 0.001$). Although patients with Grade III hypertension received the higher dose of ramipril/HCTZ 10/25 mg more frequently than those with less severe hypertension, they remained difficult to treat.

With respect to metabolic or cardiovascular risk factors for hypertension, fewer patients with hypercholesterolemia, hypertriglyceridemia or in the higher-risk age group (men >55 years and women >65 years) achieved target blood pressure control.

In contrast, obesity, smoking status, comorbid cardiovascular disorders, gender, BMI and hypertension duration were not associated with the extent of blood pressure control. Overall, 25 (58.1%) of patients in the high-risk age group failed to achieve their blood pressure target compared to 124 (33.9%) of those in the low-risk age group ($p = 0.002$).

The recent guidelines for the treatment of hypertension in elderly patients are inconsistent. The JNC 8 guidelines suggest that it might be sufficient to treat high blood pressure to a target of <150/90 mmHg or lower in patients >60 years of age (James et al., 2014), whereas other guidelines (Weber et al., 2014, Aronow et al., 2011), including the recent ESH 2013 recommendations (European Society of Cardiology, 2013), suggest a goal of <140/90 mmHg in persons ≤ 80 years-old and <150/90 mmHg only in frail persons aged ≥ 80 years. We used a target of <140 mmHg in this study, although our oldest patient was only 67-years-old and did not fall into the age group (≥ 80 years of age) where a less ambitious blood pressure target (SBP 140-145 mmHg) is considered sufficient (Weber et al., 2014, Aronow et al., 2011). Thus, the target blood pressure evaluated in the older patients in our study is consistent with current practice guidelines.

With respect to absolute blood pressure reduction, this was significant for both mean SBP and mean DBP after one month of ramipril/HCTZ FDC treatment, with an even greater reduction after 3 months of treatment. Patients who received ramipril/HCTZ 10/12.5 mg had a lower relative reduction in SPB than those who received ramipril/HCTZ 10/25 mg, with a similar relative change in DBP measurements. Ramipril/HCTZ FDC were well-tolerated with a low rate of mild AEs reported (1.3%) and adherence was good (92.4%) with a significantly higher compliance rate for ramipril/HCTZ 10/12.5 mg than for ramipril/HCTZ 10/25 mg.

The study is limited by the use of the 2007 ESH guidelines for blood pressure targets (Mancia et al., 2007). This was due to the timing of the study and data analysis, but the use of lower targets in diabetic patients as defined in recent guidelines would have increased rather than decreased the percentage of diabetic patients who achieved the blood pressure targets. In addition, the study population was not as large as originally intended. At the start of the study it was planned to enrol 750 patients. However, due to difficulties in recruitment only 472 patients were actually included. Nonetheless, for a sample size of 472 enrolled patients and with 63.6% achieving the target blood pressure at three months, the precision of the estimate (95%CI) was 4.34%, which is considered adequate and consistent with the pre-specified goal of the study. Finally, only a small proportion of the study population had diabetes (22.7%) which is a known risk group in which hypertension can be difficult to treat.

Although it is possible to achieve blood pressure targets in some patients through lifestyle interventions such as taking regular exercise, limiting salt intake to 5–6 g/day and lowering BMI to 25 kg/m² (Dickinson et al., 2006), or though antihypertensive monotherapy, the majority of patients (70%–80%) will require the use of two or more antihypertensive agents (Morgan et al., 2001). Every patient has specific genetic and acquired risk factors, baseline blood pressure, cardiovascular and other comorbidities and, for this reason, treatment should be individualized taking into account the preference of each patient in order to achieve the maximum therapeutic effect. Optimal initial therapy offered promptly after diagnosis can achieve early blood pressure control and thus encourage adherence.

Based on our results and those of others (Heidbreder et al., 1992, Oigman et al., 2003, Okpechi et al., 2011, Scholze et al., 1993), a large body of evidence suggests that combined therapy with ramipril/HCTZ is effective and well-tolerated in the management of hypertension in the real-world treatment setting. It is of particular interest in patients who are sub-optimally controlled by antihypertensive monotherapy, especially non-diabetic patients and those with grade I hypertension. Our data complement the limited available clinical data in Gulf countries on the number of patients achieving blood pressure control targets when treated with ramipril /HCTZ FDCs.

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