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RESEARCH ARTICLE

EFFICACY OF IRBESARTAN/HYDROCHLOROTHIAZIDE COMBINATION REGIMEN IN THE MANAGEMENT OF ESSENTIAL HYPERTENSION IN GULF COUNTRIES.

Nooshin Bazargani[1], Atef Shenouda[2], Mohammed Ismail[3], Nand Kishore[4], Rajeev Chathanath[5] and Rajendra Babu[6].

1. Dubai Hospital, Dubai, Uae.
2. Al Dallal Medical Complex, Bahrain.
3. Medical And Regulatory Affairs Department, Sanofi, UAE.
4. Riva Laser Medical Center, Dubai, UAE.
5. Atlas Star Medical Center, Muscat, Oman.
6. Apollo Clinic, Doha, Qatar.

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Abstract

Hypertension, a common risk factor for cardiovascular disease, is highly prevalent among the Gulf population. International guidelines recommend, in some cases, therapy for the treatment of hypertensive patients.

Aims: Our study aimed to evaluate the antihypertensive efficacy and safety of irbesartan/hydrochlorothiazide (IRBE/HCTZ) combination in patients from the Gulf region according to 2007 European Society of Hypertension guidelines.

Methods and Material: Our study registry was a multicentre, prospective, single-arm, observational study conducted in five Gulf countries between November 2011 and April 2014 (IRBEH_L_05891). Eligible patients with essential hypertension were treated with IRBE/HCTZ and followed for a period of three months. Data were collected at month 1 (optional) and month 3 (study conclusion). Measurement of systolic and diastolic blood pressure and percentage of patients who achieved blood pressure target were calculated at baseline and after three months of treatment.

Results: Overall, 1918 patients with essential hypertension were included in the efficacy population. Half of the patients (50.6%) achieved the required blood pressure control after three months of treatment. A significant reduction in both systolic and diastolic blood pressure was observed throughout the study (from 157/97 mmHg at baseline to 131/82 mmHg after three months; $P < 0.001$). Moreover, treatment was well tolerated.

Conclusion: The study suggests that the IRBE/HCTZ combination treatment is an efficient option in the treatment of hypertensive patients from the Gulf region in a real-life setting.

Corresponding Author:-Nooshin Bazargani.
Address:- Dubai Hospital, Dubai, UAE.

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Introduction:-

Hypertension is the principal risk factor for cardiovascular disease with a worldwide prevalence of 26.4% in 2000 and is expected to increase to 29.2% by 2025.[1,2] These very high numbers justify the need for appropriate management of hypertension especially with the impact that it can have on morbidity and mortality.[3]

Combining two classes of antihypertensive drugs might lower blood pressure (BP) to achieve target levels.[4] Many guidelines recommend the combined use of angiotensin II receptor blockers and diuretics, such as irbesartan (IRBE) and hydrochlorothiazide (HCTZ).[5-7] The present study evaluated the efficacy and safety of the IRBE/HCTZ combination in Gulf countries.

Subjects and Methods:-

Study Design and Patient Selection

Our current study was a multicentre, prospective, single-arm, observational registry study conducted at 80 active sites in five Gulf countries (United Arab Emirates [UAE], Kuwait, Oman, Bahrain and Qatar) between November 2011 and April 2014 (IRBEH_L_05891). The registry was approved by each site's independent ethics committee or institutional review board when required, and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000 including all subsequent amendments and with Good Epidemiology Practice guidelines. All patients provided written informed consent.

Participating physicians were randomly selected from a regional list of investigators experienced in the management of hypertension in hospitals or office-based practices in the Gulf.

Eligible patients were consecutively recruited and included men and women ≥ 18 years of age with essential hypertension, who had been previously treated with monotherapy for less than 12 months and were not controlled according to the 2007 European Society of Hypertension (ESH) – European Society of Cardiology (ESC) guidelines [5] and for whom IRBE/HCTZ combination was prescribed as per the sole discretion of the treating physician.

Patients with secondary hypertension or with significant chronic renal impairment and pregnant or breastfeeding women were excluded from the study. Also excluded were patients hypersensitive to IRBE, HCTZ, or other thiazide diuretics or having any contraindication for the use of IRBE/HCTZ according to the product labeling.

Patients meeting eligible criteria entered an average of three-month treatment period, which included three visits: at baseline, after one month (optional visit) and three months of follow-up. At baseline visit, all patients gave a detailed medical history and underwent a physical examination. Demographics, current treatment for hypertension and concomitant medications were also reported. Both systolic and diastolic BP (SBP and DBP, respectively) were also measured and the arm with the highest mean DBP was used for subsequent measurements (month 1 and month 3 visits). Patients who were prescribed IRBE/HCTZ combination as an antihypertensive treatment from baseline upon the physician sole decision were followed-up. At month 1 visit, the dose of IRBE/HCTZ was adjusted if the patient target SBP and DBP had not been achieved. The investigator adjusted the dose within the approved range for usage. Patients were informed to report any adverse events (AE) from the time they have signed the informed consent.
Site quality control was performed at minimum 10% of randomly selected centers in each participating country by qualified designated personnel. If specific issues were identified, the percentage of quality control in the concerned site/country was appropriately increased and corrective actions were implemented. Management of registry data was performed according to the following procedures: independent double data entry using DATACLIN CDMS software and modifications in the database were traced using an audit trail.

The primary endpoint was to determine the proportion of patients who achieved the target BP according to the 2007 ESH-ESC recommendations, i.e. < 130/80 mmHg for diabetic patients and < 140/90 mmHg for non-diabetic patients in the overall population and in the different study subgroups. Secondary endpoints included the proportion of patients receiving different daily dosage at baseline in the different study subgroups and the overall safety of IRBE/HCTZ.

Statistical Analyses:-

A sample of 1915 patients was calculated by assuming a dropout rate of 30%, a rate of BP control of 60% on IRBE/HCTZ combination and an estimated precision of ± 2.5% with a 95% confidence interval (CI).

Three populations were defined in this study: the safety, the eligible and the efficacy populations. The safety population consisted of all patients included in the study. The eligible population consisted of all patients who satisfied the eligibility criteria. The efficacy population consisted of all patients who satisfied the inclusion and exclusion criteria without major protocol violation and having evaluable primary endpoint (BP measurement) after baseline visit. Major protocol violations were considered when the primary endpoint was not available (BP not available at baseline and/or three months) and for patients not receiving IRBE/HCTZ combination during the three months. Continuous data were summarized using the number of non-missing data, mean, standard deviation (SD) and 95% CI. Number and percentage (95% CI) of patients who achieved target BP after three months of IRBE/HCTZ combination therapy were calculated and compared between subgroups using Chi-square test. Subgroups were considered depending on diabetic status (diabetic and non-diabetic), on hypertension grade at baseline ([Grade I, mild ≥ 140/90 mmHg], [Grade II, moderate ≥ 160/100 mmHg] and [Grade III, severe ≥ 180/110 mmHg]), on gender of the patients (men and women) and on IRBE/HCTZ daily dose (150/12.5, 300/12.5 and 300/25 mg/day). Mean changes in BP were tested using a Wilcoxon signed-rank test between baseline, month 1 and month 3. Subgroups statistical analyses of secondary endpoints were performed using Chi-square test and significance level was set as $P < 0.05$. All statistical analyses were generated using SPSS version 17.

Results:-

Physicians

A total of 80 clinically experienced physicians in the management of hypertension (cardiologists, primary care physicians, internists and general practitioners) participated in the study: 33 physicians from the UAE, 15 physicians from Kuwait, seven physicians from Bahrain, 16 physicians from Oman and nine physicians from Qatar.

Patients

Overall, 2020 patients were included in the safety population. Patient flow chart is provided in Figure 1. Eighty-one (4.0%) patients did not satisfy the inclusion/exclusion criteria and therefore 1939 patients were included in the descriptive (eligible) population. Of the 1939 patients, 21 (1.1%) patients were excluded from the analysis population due to loss to follow-up (14 patients), AEs (four patients), consent withdrawal (one patient), missing data from the primary study endpoint (one patient) and protocol deviation (one patient). AEs leading to exclusion were insomnia, pain in extremity, erectile dysfunction, polydipsia and gastritis, with the latter two AEs experienced by the same patient. Overall, the 1918 patients who completed the study were included in the efficacy population (Figure 1).

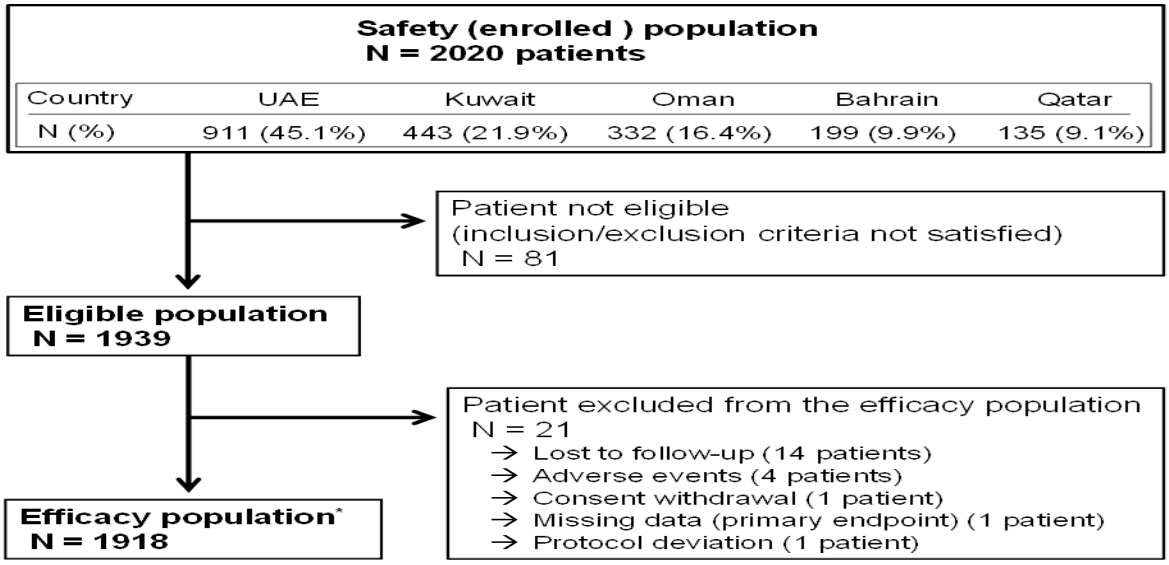

Figure 1:-Patient flow chart

UAE: United Arab Emirates.
*Patients included in the efficacy population were eligible patients who completed the study with blood pressure measurement available at the month 3 visit (90 ± 30 days).

Demographic Characteristics
Baseline demographics and baseline hypertension characteristics of eligible patients are shown in Table 1 and Table 2, respectively. Eligible patients had a mean age of 47.1 ± 8.8 years with a body mass index of 29.4 ± 4.3 kg/m² and the majority were men (71.3%). At baseline, mean SBP was 156.6 ± 12.1 mmHg and mean DBP was 97.0 ± 8.1 mmHg. Overall, 389 (20.1%) patients had dyslipidemia and 698 (36.0%) had diabetes mellitus (Table 1). The mean duration of hypertension was 19.2 ± 4.8 months. Of the 1939 eligible patients, 773 (39.9%), 949 (48.9%) and 217 (11.2%) patients suffered from mild (grade I), moderate (grade II) and severe (grade III) hypertension, respectively. Results revealed that 155 (8.1%) patients were suffering from hypertension complications at baseline. The most commonly reported ones were cardiovascular disorders in 76 (3.9%) patients and renal disease in 47 (2.4%) patients. Furthermore, 541 patients (27.9%) were administered angiotensin II receptor blockers before switching to IRBE/HCTZ. Finally, 1271 patients, making up around two thirds of the population (65.5%), were prescribed IRBE/HCTZ as 150/12.5 mg/day (Table 2).

Table 1:-Demography and baseline characteristics of the patients included in the analysis population (N = 1939)

	N	**Mean ± SD**
Age (years)	1939	47.1 ± 8.8
Height (cm)	1925	168.9 ± 7.8
Weight (Kg)	1929	83.9 ± 12.9
Body mass index (Kg/m^2)	1921	29.4 ± 4.3
Systolic blood pressure (mmHg)	1939	156.6 ± 12.1
Diastolic blood pressure (mmHg)	1939	97.0 ± 8.1
Pulse rate (beats/min)	1928	79.5 ± 8.7
	N	**n (%)**
Gender	1939	
Men		1382 (71.3)
Women		557 (28.7)
Diabetic patients	1939	698 (36.0)
Previous or concomitant disease*	1939	571 (29.4)
Dyslipidemia		389 (20.1)
Hyperuricemia		46 (2.4)
Hypothyroidism		32 (1.7)
Concomitant medications†	1939	702 (36.2)
Metformin		364 (18.8)
Atorvastatin		182 (9.4)

SD: standard deviation.
*Concomitant diseases in this table are those reported by > 30 patients.
†Concomitant medications in this table are those taken by > 90 patients.

Table 2:-Hypertension baseline characteristics of the patients included in the analysis population (N = 1939)

	N	**Mean ± SD**
Duration of hypertension (months)	1939	19.2 ± 4.8
	N	**n (%)**
Hypertension grade at baseline	1939	
Grade I hypertension "Mild"		773 (39.9)
Grade II hypertension "Moderate"		949 (48.9)
Grade III hypertension "Severe"		217 (11.2)
Reported hypertension complications*	1920	155 (8.1%)
Cardiovascular disorders		76 (3.9)

Renal disease		47 (2.4)
Impaired vision		26 (1.3)
Cerebrovascular disease		12 (0.6)
Other		14 (0.7)
Previous antihypertensive monotherapy†	1939	
Angiotensin II receptor blockers		541 (27.9)
Angiotensin-converting enzyme inhibitors		481 (24.8)
Calcium channel blockers		475 (24.5)
β-blockers		357 (18.4)
IRBE/HCTZ prescription (mg/day)	1939	
150/12.5		1271 (65.5)
300/12.5		587 (30.3)
300/25		81 (4.2)
IRBE/HCTZ: Irbesartan/hydrochlorothiazide; SD: Standard Deviation. *Each patient may have more than one complication. †Each patient may report more than one antihypertensive medication.		

Primary Endpoint: Antihypertensive Efficacy

After three months of treatment, 970 (50.6%; 95% CI: 48.3%-52.8%) patients in the efficacy population reached the BP target according to 2007 ESH-ESC recommendations. Even after only one month of treatment, 384 (20.0%; 95% CI: 18.2%-21.8%) patients had already achieved target BP, while 517 (27.0%) patients have not attended this optional visit. SBP and DBP decreased significantly throughout the study (Figure 2). Mean SBP for the efficacy population was 157.0 ± 12.1 mmHg at baseline, 138.0 ± 10.9 mmHg after one month and 131.0 ± 8.9 mmHg after three months. Significant reductions in mean SBP were noted after one month (18.6 mmHg, 95% CI: 18.0-19.2) and three months (25.3 mmHg, 95% CI: 24.7-25.8) of treatment ($P < 0.001$; Wilcoxon signed-rank test).

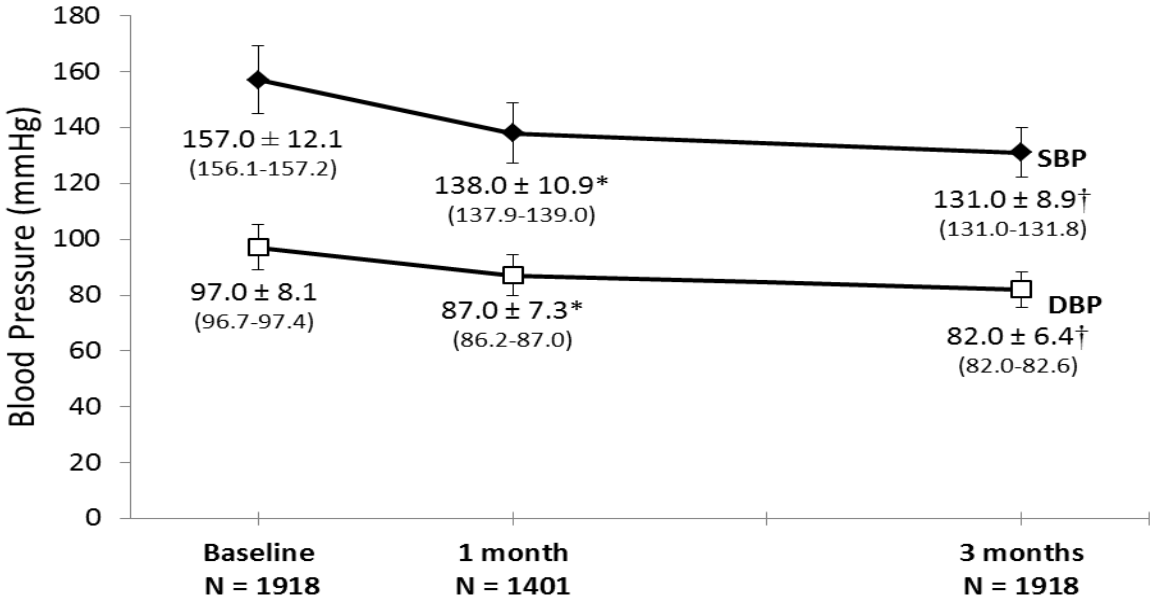

Figure 2:-Systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels at baseline and after one and three months of treatment with IRBE/HCTZ.

IRBE/HCTZ: Irbesartan/hydrochlorothiazide.

Values are mean ± standard deviation and their 95% confidence intervals (between parentheses).

*Wilcoxon signed-rank tests between baseline and visit 1: $P < 0.001$

†Wilcoxon signed-rank tests between baseline and visit 3: $P < 0.001$

At baseline, the mean DBP value was 97.0 ± 8.1 mmHg and reached 87.0 ± 7.3 mmHg after one month of treatment with a mean reduction of 10.7 mmHg (95% CI: 10.3-11.1; $P < 0.001$, Wilcoxon signed-rank test). A higher reduction was observed after three months of treatment (14.7 mmHg, 95% CI: 14.4-15.1; $P < 0.001$, Wilcoxon signed-rank test), mean DBP reaching value of 82.0 ± 6.4 mmHg.

Analyses of the antihypertensive responses according to hypertension grade, diabetic status, gender and daily doses were performed (Table 3). A statistically significant difference ($P < 0.001$; Chi-square test) was found between the three hypertension grades regarding achievement of BP target. After three months of treatment, the highest percentage of target achievement was found in patients with mild hypertension (58.8% [446/759]) followed by those with moderate (50.0% [473/946]) and severe hypertension (23.9% [51/213]) ($P < 0.001$; Chi-square test). BP target was more difficult to attain in diabetic hypertensive patients: Compared with non-diabetic patients, a significantly lower proportion of diabetic patients had achieved the goal BP after three months of IRBE/HCTZ treatment (71.5% [876/1226] versus 13.6% [94/692], $P < 0.001$; Chi-square test). A statistically significant difference ($P < 0.001$; Chi-square test) was found between the three treatment doses regarding achievement of BP target. After three months, more patients taking IRBE/HCTZ 150/12.5 mg/day achieved BP control (54.4% [683/1256]) compared to IRBE/HCTZ 300/12.5 mg/day (45.5% [265/582]) and IRBE/HCTZ 300/25 mg/day (27.5% [22/80]). After three months, a similar proportion of men and women achieved the goal BP ($P = 0.534$; Chi-square test).

Table 3:-Percentage of patients who achieved the goal blood pressure after 3 months of IRBE/HCTZ treatment in different sub-groups of the efficacy population (N = 1918)

	N	**Yes n (%)**	**No n (%)**	***P*-value***
Hypertension Grade	1918			
Grade I hypertension "Mild"	759	446 (58.8)	313 (41.2)	$P < 0.001$
Grade II hypertension "Moderate"	946	473 (50.0)	473 (50.0)	
Grade III hypertension "Severe"	213	51 (23.9)	162 (76.1)	
Diabetic status	1918			
Diabetic	692	94 (13.6)	598 (86.4)	$P < 0.001$
Non-diabetic	1226	876 (71.5)	350 (28.5)	
Gender	1918			
Men	1364	696 (51.0)	668 (49.0)	$P = 0.534$
Women	554	274 (49.5)	280 (50.5)	
IRBE/HCTZ prescribed daily doses (mg/day)	1918			
150/12.5	1256	683 (54.4)	573 (45.6)	$P < 0.001$
300/12.5	582	265 (45.5)	317 (54.5)	
300/25	80	22 (27.5)	58 (72.5)	

IRBE/HCTZ: Irbesartan/hydrochlorothiazide.
*Statistical analysis was performed using Chi-square test, significance level was set as $P< 0.05$

Secondary Endpoints: Subgroup Analyses

IRBE/HCTZ Daily Doses

Analyses of IRBE/HCTZ prescribed daily doses at baseline according to hypertension grade, diabetic status and gender were performed. Analyses of IRBE/HCTZ prescribed daily doses at baseline revealed a statistically significant difference with the grade of hypertension ($P < 0.001$; Chi-square test). A higher proportion of patients with grade III hypertension were prescribed IRBE/HCTZ 300/25 mg/day (9.9% [21/213]) compared to patients with grade I hypertension (4.1% [31/759]). Opposite trends were observed for the low dose regimen (150/12.5 mg/day), which was prescribed in 126 (59.1%) and 514 (67.7%) grade III and grade I patients, respectively. Moreover, prescribed daily doses at baseline differed significantly according to diabetic status ($P < 0.001$; Chi-square test). A higher proportion of diabetic patients (40.2% [278/692]) were prescribed IRBE/HCTZ 300/12.5 mg/day compared to non-diabetics (24.8% [304/1226]), whereas a higher proportion of non-diabetics (71.5% [877/1226]) were administered IRBE/HCTZ 150/12.5 mg/day compared to diabetics (54.8% [379/692]). No significant difference was found between men and women regarding prescribed daily dose of IRBE/HCTZ at baseline ($P = 0.711$; Chi-square test) (Table 4).

Table 4:-IRBE/HCTZ prescribed daily dose

IRBE/HCTZ (mg/day)	N	150/12.5 n (%)	300/12.5 n (%)	300/25 n (%)	*P*-value*
Hypertension grade	1918				
Grade I hypertension "Mild"	759	514 (67.7)	214 (28.2)	31 (4.1)	$P < 0.001$
Grade II hypertension "Moderate"	946	616 (65.1)	302 (31.9)	28 (3.0)	
Grade III hypertension "Severe"	213	126 (59.1)	66 (31.0)	21 (9.9)	
Diabetic status	1918				
Diabetic	692	379 (54.8)	278 (40.2)	35 (5.0)	$P < 0.001$
Non-diabetic	1226	877 (71.5)	304 (24.8)	45 (3.7)	
Gender	1918				
Men	1364	901 (66.1)	407 (29.8)	56 (4.1)	$P = 0.711$
Women	554	355 (64.1)	175 (31.6)	24 (4.3)	

IRBE/HCTZ: Irbesartan/hydrochlorothiazide.
*Statistical analysis was performed using Chi-square test, significance level was set as $P<0.05$

Safety Assessments

All 2020 enrolled patients were evaluated for safety. IRBE/HCTZ combination was well tolerated. A total of 59 AEs was reported, the majority of them being of mild (25/59) or moderate (33/59) severity. None of the reported events were considered as serious. The most frequently reported events were dizziness and orthostatic hypotension (6/59 for each), followed by nausea (5/59) and headache (4/59) (Table 5). According to physicians' assessment, it was considered to be a definite study drug relationship in ten events, probable relationship in 28 events, and possible relationship in eight events. On the other hand, 13 events were judged unrelated to IRBE/HCTZ.

Table 5:-Adverse events in the safety population (N = 2020)

Adverse Event (AE)	Count of AEs	Occurrence of AEs n (%)
Total	59	
Severity		
Mild	25	25 (1.24)
Moderate	33	33 (1.63)
Severe	1	1 (0.05)
Study drug relationship		
Definite	10	10 (0.50)
Probable	28	28 (1.39)
Possible	8	8 (0.40)
Not related	13	13 (0.64)
Reported AEs*		
Dizziness	6	6 (0.30)
Orthostatic hypotension	6	6 (0.30)
Nausea	5	5 (0.25)
Headache	4	4 (0.20)
Muscle spasms	3	3 (0.15)
Tinnitus	2	2 (0.10)
Diarrhea	2	2 (0.10)
Gout	2	2 (0.10)
Myalgia	2	2 (0.10)
Libido decreased	2	2 (0.10)
Erectile dysfunction	2	2 (0.10)

*The AEs reported in this table are those with an incidence in > 1 patient.

Discussion:-

Many patients suffering from hypertension are not adequately controlled when treated with monotherapy. A combination of two antihypertensive drugs has been shown to be effective in lowering BP to normal range.[3-5] The

purpose of the present study was to assess the antihypertensive efficacy of IRBE/HCTZ combination in Gulf countries by determining the number of patients who achieved the required BP control according to 2007 ESH-ESC recommendations. These guidelines set BP goals of < 140/90 mmHg for the general population with hypertension and < 130/80 mmHg for hypertensive patients with type-2 diabetes. [5]

Our results revealed that half of the patients achieved the required BP control after three months of treatment. A significant reduction in BP was observed throughout the study. Wilcoxon signed-rank tests showed a significant reduction ($P < 0.001$) in SBP and DBP values from baseline to month 1 and a further decrease from month 1 to month 3. The highest percentage of target achievement was found in patients with mild hypertension followed by those with moderate and severe hypertension. A better achievement of BP control was found in non-diabetic patients compared to diabetics. On the other hand, BP control was irrespective of the patient's gender.

The current study enrolled a large population of patients in the Gulf countries under real-life clinical practice. The demographic characteristics of the study participants were representative of the general population with hypertension and included patients, mostly men, overweight, diabetic and/or dyslipidemic which are in accordance with a previous work showing a comparable population.[8] Prior to enrolment, half of the study population was treated by monotherapy with angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors showing the relatively poor control rates achieved with monotherapy in the general population. [9]

Our study showed that a combination of IRBE/HCTZ therapy was associated with an improved control of SBP and DBP to a level below 140/90 mmHg in about half of study patients. After three months of therapy, 50.6% of patients had achieved the BP target and after only one month of treatment, 20.0% of patients had already achieved this target. The observed reduction of SBP and DBP from baseline to the third month is of great importance as it falls in the ranges that have been associated with a lower risk of coronary heart disease, stroke, and death. [10] Our findings are in line with the results of the INCLUSIVE (IRBE/HCTZ Blood Pressure Reductions in Diverse Patient Populations) trial that evaluated the efficacy of this combination in a broad range of patients. This study found that 69.0% of patients achieved their BP control with IRBE/HCTZ. The percentage of patients achieving BP target is higher than that observed in our study (50.6%). This may be attributable to the short (12 weeks) treatment period in MAGNIFICENT compared to 18 weeks in INCLUSIVE and to the fact that the latter study only included patients with mild hypertension who might be prone to reach BP goals easier. [11] On the other hand, only 13.6% of diabetic patients achieved target BP (< 130/80 mmHg) in our study compared to 40.0% in the INCLUSIVE study. These discrepancies could also be due to the length of the active treatment period as diabetic patients might need more time to attain BP goals than the general population. Nevertheless, the length of our study could also justify the fact that a lower proportion of patients with IRBE/HCTZ achieved the goal BP than previously reported. [11,12]

Our results also indicated that IRBE/HCTZ 150/12.5 mg/day achieved higher BP control rates compared to IRBE/HCTZ 300/12.5 mg/day and IRBE/HCTZ 300/25 mg/day. Given the importance of achieving BP control to reduce cardiovascular risk, our results suggest that IRBE/HCTZ 150/12.5 mg/day may offer advantages over the higher doses especially in patients with mild hypertension and in non-diabetic ones.

IRBE/HCTZ treatment was well tolerated with most AEs being of mild or moderate severity. These results are in accordance with many papers showing that angiotensin II receptor blockers such as IRBE have an acceptable safety profile when taken as monotherapy or in combination with HCTZ. [11-13]

One limitation of the current registry is the prospective study design in which the same patients are followed sequentially over time and therefore other possible factors might be responsible for reducing BP such as weight loss, the influence of concomitant medications and diabetes control. Moreover, the BP reached in this study population might be higher than the BP that can be achieved in the general population because even though the centers were randomly selected, the process followed may have increased awareness regarding the management of hypertensive patients.

Conclusion:-

This observational study conducted in UAE, Bahrain, Oman, Kuwait, and Qatar showed that the association of IRBE/HCTZ was effective in achieving BP target control in 50% of patients overall. BP control was observed for over 50% of grade I and grade II hypertension cases and for over 50% of patients receiving a low dose of

IRBE/HCTZ irrespectively of the hypertension grade. It is worthy to mention that 20.0% of patients reached their target after only one month of therapy. IRBE/HCTZ was well tolerated in the overall population.

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