Efficacy, safety and Cardiovascular Disease Risk Lowering Ability of ACE Inhibitors, β-Blockers and Combination Antihypertensive Drug Regimes in Iraq

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Abstract

Hypertension is a major health problem throughout the world because of its high prevalence and its association with increased risk of cardiovascular diseases. It is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. The aim of this study was to compare the efficacy, safety and cardiovascular disease risk lowering ability, of three antihypertensive drug regimens.

A retrospective study was carried out on 66 hypertensive patients, divided in to three groups based on their antihypertensive drug regimens (ACE inhibitors, β-blockers treated and combination antihypertensive therapy, the combination therapy consist of two or more of the following antihypertensive drugs ACE inhibitor diuretic, CCBs β-blockers), the study also included 22 healthy individuals. Duration of treatment was 2-10 years. Blood pressure and pulse rate were measured and blood sample was collected, and the serum processed for the measurement of lipid profiles, fasting blood glucose, liver function test, kidney function test, electrolytes, and C-reactive protein. Cardiovascular disease risk lowering ability have been assessed by cardiovascular risk assessor computer program.

The results shows that systolic and diastolic blood pressure in the three antihypertensive drug regimens treated group, were significantly higher than systolic and diastolic blood pressure in control healthy individuals indicating that these antihypertensive drug regimens were unable to reach hypertension treatment target, although ACE inhibitors and combination antihypertensive drugs reach minimal hypertension treatment target.

ACE inhibitors regimen did not show any significant adverse effects on lipid profiles and blood glucose, while β-blockers regimen adversely affected it. Most predominant adverse effects that appear, in ACE inhibitors treated group were dry cough and taste disturbances, in β-blockers treated group were bradycardia and sleep disturbances while in combination therapy treated group were according to the combination used. In combination containing thiazide diuretics, disturbed lipid profiles and hyperurecemia were predominant and in combination containing calcium channel blockers constipation and peripheral edema were predominant.

Coronary heart disease and stroke risk percentage in all three antihypertensive drug regimens were significantly higher compared to control healthy individuals group, and all three antihypertensive drugs regimens have the same cardiovascular risk lowering ability.

In conclusion the results indicated that all three antihypertensive drug regimens used were not efficient enough to reach hypertension treatment target, the combination therapy and ACE inhibitors regimens were only capable to reach minimal hypertension treatment target which is ≤150/90 mm Hg.

Key words: ACE inhibitors, B blockers, Hypertension.

مقارنة فعالية ثلاثة نظم دوائية تستخدم لمعالجة فرط ضغط الدم ومقارنة سلامة هذه النظم الدوائية وقدرتها على تقليل خطر الاصابة بالأمراض القلبية والوعائية

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الخلاصة

فرط ضغط الدم هي مشكلة صحية رئيسية في جميع انحاء العالم بسبب انتشارها الكبير وارتباطها مع زيادة خطر الاصابة بالامراض القلبية الوعائية . ويعرف بضغط الدم الانقباضي ≤ 140 ملم زئبقي او ضغط الدم الانبساطي ≤ 90 ملم زئبقي . الهدف الاساسي لمعالجة مريض فرط ضغط الدم هو تحقيق الحد الاقصى من تقليل خطر الاصابة بالأمراض القلبية الوعائية والوفيات على المدى الطويل .

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والهدف من هذه الدراسة هو مقارنة فعالية ثلاثة نظم دوائية تستخدم لمعالجة فرط ضغط الدم ومقارنة سلامة هذه النظم الدوائية وقدرتها على تقليل خطر الاصابة بالأمراض القلبية والوعائية . اجريت هذه الدراسة على 66 مريض مصاب بفرط الدم خضعوا للمعالجة الدوائية المضادة لفرط ضغط الدم لمدة تتراوح بين سنتين الى عشر سنوات ، 22 منهم تمت معالجتهم بواسطة مثبطات الانزيم المحول للأنجيوتنسين و 22 مريض بواسطة مثبطات مستقبلات البيتا و 22 مريض بواسطة نوعين من الادوية المضادة لفرط ضغط الدم وايضا 22 من الافراد الاصحاء شاركوا في الدراسة .

وقد تم قياس ضغط الدم ومعدل النبض وجمعت عينات من الدم ، وتمت معالجة المصل لقياس مستوى الدهون في الدم (الكوليسترول ، الدهون الثلاثية وبروتين شحمي مرتفع الكثافة) ، قياس مستوى السكر الصيامي في الدم ، اختبار وظيفة الكبد (AST,ALT,ALP and GGT) اختبار وظيفة الكلى (حامض اليوريك ، اليوريا ، الكرياتينين) ، قياس مستوى الايونات (Na,Ca,Mg,Cl) وقياس القيمة النوعية لبروتين C التفاعلي . وقد تم تقييم مدى قابلية هذه النظم الدوائية على تقليل خطر الاصابة بالأمراض القلبية الوعائية بواسطة برنامج حاسوبي لتقييم خطر الاصابة بالأمراض القلبية الوعائية .

النتائج تبين ان ضغط الدم الانقباضي والانبساطي في المجموعات الثلاث التي استخدمت نظم مختلفة لمعالجة فرط ضغط الدم كان اعلى بكثير من ضغط الدم الانقباضي والانبساطي عند الاشخاص الاصحاء ، وهذا يبين ان هذه النظم الدوائية الثلاث المستخدمة لمعالجة فرط ضغط الدم لم تسطع الوصول الى هدف معالجة فرط ضغط الدم الى ان المعالجة بالادوية المثبطة للانزيم المحول للأنجيوتنسين والنظام المكون من نوعين من مضادات فرط ضغط الدم بلغت الحد الادنى من هدف معالجة فرط ضغط الدم .

نظام الادوية المثبطة للأنزيم المحول للأنجيوتنسين لم يظهر اية تأثيرات عكسية كبيرة على مستوى الدهون والسكر في الدم في حين ان مثبطات مستقبلات البيتا اثرت عكسيا عليها . التأثيرات العكسية السائدة التي ظهرت في المجموعة التي استخدمت مثبطات الانزيم المحول للأنجيوتنسين كانت السعال الجاف واضطرابات المذاق ، اما في المجموعة التي استخدمت نوعين من الادوية المضادة لفرط ضغط الدم فكانت التأثيرات العكسية بحسب التركيبة المستخدمة ، ففي المجموعة التي استخدمت التركيبة المحتوية على مدرات الول الثيازيدية كان ه ناك تأثير سلبي على مستوى الدهون في الدم وارتفاع مستوى حامض اليوريك في الدم اما في المجموعة التي استخدمت التركيبة المحتوية على مثبطات قنوات الكالسيوم فكان التأثير العكسي الظاهر هو الامساك والوذمة الطرفية . نسبة خطر الاصابة بمرض الشريان التاجي والسكتة الدماغية في المجموعات الثلاث التي استخدمت نظم مختلفة لمعالجة فرط ضغط الدم كانت اعلى بكثير مقارنة مع مجموعة الافراد الاصحاء ، وقابلية النظم الدوائية الثلاث المستخدمة لمعالجة فرط ضغط الدم على تقليل نسبة خطر الاصابة بمرض الشريان التاجي والسكتة الدماغي ة كانت متشابهة .

نستنتج من النتائج ان النظم الدوائية الثلاث الم ستخدمة لمعالجة فرط الدم المستخدمة لمعالجة فرط الدم لم تكن فعالة بدرجة كافية للوصول الى هدف معالجة فرط ضغط الدم وان المعالجة بالأدوية المثبطة للأنزيم المحول للآنجيوتنسين والنظام المكون من نوعين من مضادات فرط ضغط الدم بلغت الحد الادنى من ه دف معالجة ضغط الدم ≥ 90 / 150 ملم زئبقي .

الكلمات المفتاحية : مثبطات الانزيم المحول للأنجيوتنسين ، مثبطات مستقبلات البيتا ، فرط ضغط الدم .

Introduction

Hypertension is defined as systolic blood pressure (SBP) ≥ 140 mmHg and /or diastolic blood pressure (DBP) ≥ 90 mmHg and /or the use of antihypertensive medication[1]. Although hypertension may occur secondary to other disease processes, primary or essential hypertension is more common occurring in 90-95 % of the hypertension population[2], a disorder of unknown origin affecting the blood pressure regulating mechanism [3].

The primary goal of treatment of the hypertensive patient is to achieve the maximum reduction in the long-term total risk of cardiovascular morbidity and mortality, as well as treatment of the raised BP [4].

Blood pressure goal recommendations are based on results from randomized, controlled studies and recommendations from guidelines committees (Table 1) [5].

Table 1: Recommended Target BP Goals

Guideline	Uncomplicated	Not TOD or Clinical CVD; at Least 1 CV Risk Factor Excluding Diabetes	Diabetes *
JNC VI	<140/90		<130/85 mm Hg
NKF	mm Hg	<140/90 mm Hg	≤130/80 mm Hg
ADA			≤130/80 mm Hg

NKF indicates National Kidney Foundation; ADA, American Diabetes Association. TOD, target organ damage; JNC, Joint National Committee; CVD, Cardiovascular disease.

*JNC VI BP goal also recommended for those with TOD or clinical CVD.

Treatment involves non-pharmacological measures, followed by the staged introduction of drugs, starting with those of proven benefit and least likely to produce side effects [6]. Essential hypertension is a very heterogeneous disease and different pressor mechanisms might interact to increase BP, therefore it is not surprising that antihypertensive drugs, given as monotherapy, normalize BP in only a fraction of hypertensive patients [7].

The JNC 6 recommendations acknowledge evidence from clinical trials, demonstrate that most patients with hypertension require at least 2 antihypertensive drugs to reach target BP levels. The addition of a second antihypertensive agent with a different mechanism of action should be initiated when adequate doses of an initial agent fail to achieve target BP goals [8].Furthermore, combination therapy should be considered as initial therapy for patients who are more than 20 mmHg above their SBP target and more than 10 mmHg above their DBP target; one agent should be a thiazide-type diuretic unless otherwise indicated [9].

British Hypertension Society (BHS) guidelines recommend ACE inhibitors as first-line agents for younger, non-black patients [10], and recommended to start treatment with either an ACE inhibitors or an angiotensin receptor blockers (ARB) in patients who are likely to have normal or raised plasma renin (i.e. younger white people), and with either a thiazide diuretics or a calcium channel blockers (CCB) in older people and people of African origin (who are more likely to have low plasma renin). If the target BP is not achieved but the drug is well tolerated, then a drug of the other group is added, it is best not to increase the dose of any drug excessively, as this often causes adverse effects [6].

National Institute for Health and Clinical Excellence (NICE) stated that the decision not to recommend β-blockers for first line therapy is based on the evidence suggests that they perform less well than other antihypertensive drugs, particularly in the elderly, and the increasing evidence that the most frequently used β-blockers at usual doses carries an unacceptable risk of provoking type 2 diabetes. Recent clinical studies have suggested that antihypertensive agents that inhibit the renin angiotensin system (RAS) may reduce risk for new-onset type 2 diabetes [11].

The exclusion criteria included patients with:

The aim of the study was to compare the effectiveness of three antihypertensive drug regimens used to treat hypertension in Dohok city in northern Iraq, to compare the adverse effects of these drugs, and the extent to which each regimen have the ability to decrease the cardiovascular disease risk.

Patients and Methods

The study was carried out in Duhok Governorate from 15th of December 2010 to the end of June 2011. Sixty six hypertensive patients, 20 males and 46 females, with an age range from 29-75 years, the mean age was 51.88 years, they were divided into three groups each group included 22 patients according to their antihypertensive drug regimen.

Group one:

This group included 22 hypertensive patients, 6 males and 16 females, with an age range from 29-75 years, the mean age was 54.77 years, 8 of them in addition to ACE inhibitors were treated with 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors for dyslipidemia and 9 patients were diadetic hypertensive.

Group two:

This group included 22 hypertensive patients, 6 males and 16 females with an age range from 42-74 years, the mean age was 55.04 years, 8 of them in addition to β-blockers, were treated with HMG-CoA reductase inhibitors for dyslipidemia and 5 patients were diabetic hypertensive.

Group three:

This group included 22 hypertensive patients, 8 males and 14 females with an age range from 34-70 years, the mean age was 54.27 years, 9 of them in addition to combination antihypertensive therapy were treated with HMG-CoA reductase inhibitors for dyslipidemia and 7 patients were diabetic hypertensive,(the combination therapy consist of two or more of the following antihypertensive drugs, ACE inhibitor, diuretics, CCBs, β-blockers).

Control group: The control group included 22 healthy subjects, free from hypertension, lipid disorders, diabetes mellitus, CVD and renal disease, 8 males and 14 females and their ages ranged from 31-57 years, the mean age was 43.45 years.

Inclusion criteria include:

1. Essential hypertensive patients.
2. Age range between 25-80 years old
1. cardiovascular disease.

2. renal disease.
3. liver disease.
4. smokers.
5. Pregnant women.

Patients have been informed about the aims of the study and the parameters that will be taken to assess the efficacy and safety of the treatment. Each patient have been asked to attend the hospital or the health center at three months interval for follow-up.

Systolic and diastolic BP were the primary efficacy parameters, they were measured by electronic BP measuring device and cuff appropriate for arm size, the same device was used to measure pulse rate, BP measurements were taken during first and second study visit, after participant had been seated for at least 5 minutes.

Safety was evaluated by asking patients about possible adverse effects, recorded during first and second study visit, and laboratory biochemical analysis of lipid profiles (TC, TG, HDL, LDL and VLDL), fasting serum glucose, liver function test (aspartate aminotransferase, AST, alanine aminotransferase, ALT, alkaline phosphatase, ALP and GGT), kidney function test (uric acid, urea and creatinine), electrolytes (Ca, Mg, K, Na and Cl).

Cardiovascular risk lowering ability have been assessed by cardiovascular risk assessor computer program, the program compute coronary heart disease (CHD) and stroke as the percentage likelihood of an event over a period of 10 years for e.g. a risk of 30% means that there is a 30 in 100 chance of an event in the next 10 years, and laboratory biochemical assessment of C-reactive protein (qualitative) , and pulse rate measurement.

All data were analyzed using the statistical package for social science (SPSS) version 14; using one way analysis of variance (ANOVA), the comparison among groups were done using least significant difference test (LSD). All the results were expressed as mean ± standard error (SE) of mean. The level of significance was set at $p \leq 0.05$.

Results

Results are shown in the following tables:

Table 2: SBP and DBP in control healthy individuals and hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

* $P \leq 0.05$ significant difference from the control.

Group	N	SBP (mmHg)	DBP (mmHg)
Control	22	121.27 ± 2	78.81 ± 1
ACE inhibitors	22	146.18 ± 3 *	90.27 ± 2 *
β-blockers	22	151.13 ± 3 *	89.31 ± 2 *
Combination therapy	22	144.54 ± 3 *	88.40 ± 2 *

Table 3: Lipid profiles (TC, TG, HDL, LDL and VLDL) in control healthy individuals and hypertensive patients treated with different antihypertensive drug regimens and HMG-CoA reductase inhibitors. Each value represents mean± standard error of mean.

Group	N	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL(mg/dl)
Control	22	179.36 ± 6	102.45 ± 7	49.36 ± 1	96.04 ± 3	22.59 ± 2
ACE inhibitors	8	188.50 ± 5	140.25 ± 22	42.75 ± 1	101.87 ± 3	25.12 ± 3
β-blockers	8	195.87 ± 12	173.00 ± 17*	43.00 ± 2	106.37 ± 6	32.62 ± 2 *
Combination therapy	9	188.77 ± 14	184.33 ± 18 *a	43.66 ± 2	99.88 ± 6	37.22 ± 4 *a

* $P \leq 0.05$ significant difference from the control.

[a] $P \leq 0.05$ significant difference from ACE inhibitors treated group.

Table 4: Lipid profiles (TC, TG, HDL, LDL and VLDL) in control healthy individuals and hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

Group	N	TC (mg/dl)	TG (mg/dl)	HD(mg/dl)	LDL(mg/dl)	VLDL(mg/dl)
Control	22	179.36 ± 6	102.45 ± 7	49.36 ± 1	96.04 ± 3	22.59 ± 2
ACE inhibitors	14	182.07 ± 4	152.25 ± 14	43.21 ± 2 *	110.71 ± 5	33.14 ± 4
β-blockers	14	200.71 ± 9 *	208.35 ± 27 *	37.00 ± 1 *[a]	122.50 ± 8 *	37.35 ± 4 *
Combination therapy	13	189.69 ± 9	192.38 ± 29 *	41.69 ± 2 *	111.30 ± 10	34.00 ± 4 *

* $P \leq 0.05$ significant difference from the control.
[a] $P \leq 0.05$ significant difference from ACE inhibitors treated group.

Table 5: Fasting serum glucose in control healthy individuals and non diabetic hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

Group	N	Pulse rate (beat/min)
Control	22	79.72 ± 1
ACE inhibitors	22	81.36 ± 1
β-blockers	22	70.31 ± 1 *[ab]
Combination therapy	22	76.04 ± 2 [a]

Table 6: Serum AST, ALT, ALP and GGT in control healthy individuals and hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

Group	N	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)
Control	22	30.31 ± 1	24.86 ± 1	233.90 ± 7	25.81 ± 1
ACE-I	22	29.37 ± 2	23.07 ± 1	251.18 ± 15	25.13 ± 1
β-blockers	22	30.50 ± 1	26.27 ± 2	236.86 ± 7	27.59 ± 1
Combination therapy	22	27.49 ± 1	24.34 ± 1	248.63 ± 14	29.77 ± 3

Table 7: Serum uric acid, serum urea and serum creatinine in control healthy individuals and retrospective hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

Group	N	Serum uric acid (mg/dl)	Serum urea (mg/dl)	Serum creatinine (mg/dl)
Control	22	3.72 ± 0.2	27.13 ± 1	0.84 ± 0.1
ACE inhibitors	22	4.21 ± 0.2	27.90 ± 1	0.83 ± 0.02
β-blockers	22	4.57 ± 0.3 *	29.23 ± 1	0.82 ± 0.03
Combination therapy	22	4.60 ± 0.2 *	29.21 ± 1	0.85 ± 0.21

* $P \leq 0.05$ significant difference from the control.

Table 8: Serum electrolytes (Ca^{+2}, Mg^{+2}, $K^{+,}$ Na^{+}, Cl^{-}) in control healthy individuals and hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

Group	N	Ca (mg/dl)	Mg(mg/dl)	K(mmol/L)	Na (mmol/L)	Cl (mmol/L)
Control	22	9.25 ± 0.15	1.77 ± 0.02	4.27 ± 0.10	141.81 ± 0.94	100.09 ± 0.66
ACE inhibitors	22	8.99 ± 0.11	1.79 ± 0.03	4.13 ± 0.08	139.04* ± 0.52	100.31 ± 0.69
β-blockers	22	9.11 ± 0.12	1.82 ± 0.02	4.18 ± 0.12	140.95 ± 0.71	101.31 ± 0.49
Combination therapy	22	9.01 ± 0.14	1.83 ± 0.03	4.15 ± 0.08	140.50 ± 0.81	100.04 ± 0.53

* $P \leq 0.05$ significant difference from the control.

Table 9: C-reactive protein qualitative value in control healthy individuals and hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

Group	N	Negative	%	Positive	%
Control	22	22	100%	0	0.00%
ACE inhibitors	22	16	72.72%	6	27.27%
β-blockers	22	15	68.18%	7	31.81%
Combination therapy	22	15	68.18%	7	31.81%

Table 10: Pulse rate in control healthy individuals and hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

Group	N	Pulse rate (beat/min)
Control	22	79.72 ± 1
ACE inhibitors	22	81.36 ± 1
β-blockers	22	70.31 ± 1 *ab
Combination therapy	22	76.04 ± 2 a

* $P \leq 0.05$ significant difference from the control.
[a] $P \leq 0.05$ significant difference from the ACE inhibitors treated group.
[b] $P \leq 0.05$ significant difference from the Combination therapy treated group.

Table 11: CHD risk % and stroke % based on SBP in control healthy individuals and non diabetic hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

Group	N	CHD risk %	Stroke risk %
Control	22	2.72 ± 0.5	0.52 ± 0.08
ACE inhibitors	13	11.25 ± 2 *	3.56 ± 1 *
B-blockers	17	11.55 ± 1 *	3.07 ± 0.5 *
Combination therapy	15	8.92 ± 1 *	2.32 ± 0.3 *

* $P \leq 0.05$ significant difference from the control.

Table 12: CHD risk % and stroke % based on SBP in control healthy individuals and retrospective diabetic hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

Group	N	CHD risk %	Stroke risk %
Control	22	2.72 ± 0.5	0.52 ± 0.08
ACE inhibitors	9	14.13 ± 2 *	4.77 ± 1 *
B-blockers	5	16.02 ± 3 *	4.34 ± 1 *
Combination therapy	7	14.27 ± 1 *	4.60 ± 0.7 *

* $P \leq 0.05$ significant difference from the control.

Table 13: CHD risk % and stroke % based on DBP in control healthy individuals and non-diabetic hypertensive patients treated with different antihypertensive drug regimens. Each value represents mean± standard error of mean.

Group	N	CHD risk %	Stroke risk %
Control	22	2.83 ± 0.6	0.54 ± 0.1
ACE inhibitors	13	11.01 ± 2 *	2.92 ± 1 *
β-blockers	17	10.56 ± 1 *	2.29 ± 0.4 *
Combination therapy	15	9.04 ± 1 *	2.28 ± 0.4 *

* $P \leq 0.05$ significant difference from the control.

Table 14: CHD risk % and stroke % based on DBP in control healthy individuals and retrospective diabetic hypertensive patients treated with different antihypertensive drugs. Each value represents mean± standard error of mean.

Group	N	CHD risk %	Stroke risk %
Control	22	2.83 ± 0.6	0.54 ± 0.1
ACE inhibitors	9	15.62 ± 3 *	5.27 ± 1 *
B-blockers	5	16.90 ± 3 *	3.76 ± 0.9 *
Combination therapy	7	13.82 ± 2 *	3.77 ± 0.5 *

* $P \leq 0.05$ significant difference from the control.

Discussion

The study compared the efficacy and safety of three antihypertensive drug regimens used to treat high BP in Duhok City, and the extent to which each regimen have the ability to decrease the CVD risk.

The efficacy of antihypertensive group of drug regimens

As shown in table (2) mean systolic and diastolic BP in control healthy individuals group were normal according to the BHS's classification of blood pressure [12]. Mean SBP and DBP in ACE inhibitors treated group were significantly higher than mean systolic and diastolic BP in control healthy individuals, which might indicate that we could not reach the normal systolic and diastolic BP in this group of patients. Similar results were reported by Heran etal, 2009, evaluating the BP lowering ability of 14 different ACE inhibitors in 12,954 participants. The study followed participants for approximately 6 weeks, the BP lowering effect was modest, and most of the BP lowering effect (about 70%) achieved with the lowest recommended dose of the ACE inhibitor drugs [13] [14].

Mean systolic and diastolic BP in β-blockers treated group were significantly higher than SBP and DBP in control healthy individuals group. This could indicate low effect of β-blockers when used as mono-therapy, similar results have been found in 10 randomized controlled studies in 16,164 patients, who were treated with either a diuretic or a β-blocker (Atenolol), BP was normalized in two-thirds of diuretic-treated patients but only one-third of patients treated with Atenolol as mono-therapy, diuretic therapy was superior with regard to all end points, and β-blockers were found to be ineffective except in reducing cerebrovascular events [15].

Mean systolic and diastolic BP in group treated with either two or three antihypertensive drugs i.e combination therapy were significantly higher than SBP and DBP in control healthy individuals group, but on the basis of on-treatment analysis patients whose BP below 150/90 mmHg were also not bad [16]. In similar combination study, the addition of hydrochlorothiazide (or bisoprolol) to therapy with bisoprolol (or hydrochlorothiazide) produced an incremental reduction in BP, dosages of hydrochlorothiazide as low as 6.25 mg/d contributed a significant antihypertensive effect [17].

The effect of antihypertensive group of drug regimens on lipid profiles

In present study, as shown in table (3) lipid profiles in ACE inhibitors treated group were not significantly different from mean of the same profiles in control healthy individuals group. In this group of patients we cannot indicate the effect of ACE inhibitors on lipid profiles because this group of patients also treated with HMG-CoA reductase inhibitors.

Mean lipid profiles in β-blockers treated group (TC, HDL and LDL), were within normal range and not significantly different from mean of the same profiles in control healthy individuals group and other treated groups (ACE inhibitors and combination therapy)**;** however this did not indicate that β-blockers had no effect on TC, LDL and HDL, but we could not observe these effects because of the action of HMG-CoA reductase inhibitors. Mean TG and VLDL were higher than normal and significantly higher than mean TG and VLDL in control healthy individuals group. This could indicate the bad effect of β-blockers on TG and VLDL in spite of the use of HMG-CoA reductase inhibitors. Similar results were reported in a study compared the effects of propranolol, pindolol, and atenolol given as a single daily dose for the control of hypertension, they observed small but significant increase in fasting plasma TG levels after 4 weeks of treatment.

These rises were not accompanied by changes in plasma cholesterol [18].

Mean lipid profiles in combination therapy treated group TC, HDL and LDL were not significantly different from healthy individuals group and other treated groups (ACE inhibitors and β-blockers). Again this did not indicate that combination therapy have no effect on TC, LDL and HDL, but HMG-CoA reductase inhibitors could normalize antihypertensive effects on these parameters. Regarding mean TG and VLDL, they were significantly higher than mean TG and VLDL in control healthy individuals group, which could indicate the bad effect of β-blockers and thiazide diuretics included in combination therapy on TG and VLDL, in spite of the use of HMG-CoA reductase inhibitors.

Table (4) showed lipid profiles in ACE inhibitors treated group TC, LDL, VLDL and TG were within normal range and did not significantly differ from the mean of the same profiles in control healthy individuals group. This could indicate that ACE inhibitors had no effect on lipid profiles. Similar study indicated that the ACE inhibitors appear to have no important effect on plasma lipids [19], however another study have been concluded that Fosinopril therapy for 6 months resulted in a reduction in lipid profiles [20]. Regarding HDL it was significantly lower than HDL of healthy individuals

Mean lipid profiles in β-blockers treated group were significantly different from lipid profiles in control healthy individuals group. This could indicate that β-blockers increased TC, LDL, VLDL and TG levels; and decreased HDL. Level of HDL was also significantly lower than HDL in ACE inhibitors group. This could give an indication that ACE inhibitors are better than β-blockers for decreasing the risk of CVD by keeping lipid profiles normal. In one study they have been found that antihypertensive treatment with β-blockers decreases HDL parameters, whereas treatment with ACE inhibitors appears to decrease TC and LDL-related parameters [21].

β-blockers have little effect on cholesterol levels but lead to an approximate 10% fall in cardioprotective HDL cholesterol and a 20 to 40 % rise in TG [22]. A study evaluated 45 patients with non-insulin-dependent diabetes mellitus and hypertension who were randomized to therapy with β-blockers, associated with a 5% reduction in HDL and a 12 % elevation in TG [19].

Mean lipid profiles in combination therapy treated group TC and LDL were not significantly different compared to control healthy individuals group and other treated groups. This could indicate that combination therapy have no effect on TC and LDL. The effect of combination therapy in most cases appears to reflect the sum of the effect of the individual drugs. A recent meta-analysis of over 450 published studies found that thiazide therapy raised the plasma cholesterol concentration by about 5 mg/dL (0.13 mmol/L) [23].

Mean TG was significantly higher in the combination therapy treated group than mean TG in control healthy individuals group. HDL was significantly lower than HDL in control healthy individuals group and VLDL was higher than VLDL in control healthy individuals group. This could indicate the increased effects of β-blockers, thizide diuretics and other antihypertensive drugs contained in combination therapy on TG and VLDL and decreased effect on HDL. Antihypertensive treatment with hydrochlorothiazide alone, or in combination with a β-blockers, was associated with increased TG and decreased HDL; this was not so for patients treated with an ARB alone or in combination a CCB [(24)].

The effect of three antihypertensive drug regimens on fasting serum glucose

Table 5 showed fasting serum glucose levels in non-diabetic hypertensive patients. Mean fasting serum glucose in 13 ACE inhibitors treated patients was not significantly different from mean fasting serum glucose in control healthy individuals group. This could give an indication that treating hypertensive patients with ACE inhibitors for long period did not affect blood glucose level. In contrast to our finding one study showed that captopril increased the insulin-mediated disposal of glucose, as compared with placebo, it had no effect on the basal insulin concentration, but it decreased the late (30- to 90-minute) insulin response to glucose and increased the early (2- to 6-minute) insulin peak this finding may be explained by an increase in insulin sensitivity with captopril [(25)]. Mean fasting serum glucose in 17 β-blockers treated group was significantly higher than fasting serum glucose in healthy individuals group and also significantly higher than fasting serum glucose in ACE inhibitors treated group. This could indicate that β-blockers increase serum glucose level and that ACE inhibitors are better for treating hypertension and not adversely affect serum glucose level. The diuretics and β-adrenoreceptor antagonists further decrease insulin sensitivity. The mechanisms by which β-blockers treatment exert its disadvantageous effects on serum glucose are not fully understood but several possibilities exist, alterations in insulin clearance and insulin secretion [(26)]. Long term use of metoprolol and atenolol causes metabolic abnormalities that may be related to the increased incidence of diabetes in patients with hypertension who are treated pharmacologically. These results may help to explain why the two drugs (metoprolol and atenolol) have failed consistently to reduce the incidence of CHD in several large scale studies [(27)].

In combination therapy treated group (15pateints), fasting serum glucose was significantly higher than fasting serum glucose level in healthy individual. This could indicate the effects of β- blockers and thiazide diuretics in increasing serum glucose, about 6 patients out of 15 their combination therapy contain β-blockers and about 10 patients out of 15 their combination therapy contain thiazide diuretics. These results could indicate that β-blockers and thiazide diuretics have increasing effect on serum glucose level and that ACE inhibitors are better in keeping serum glucose normal. Hydrochlorothiazide decreased the insulin-mediated disposal of glucose, as compared with placebo. It increased the basal insulin concentration and the late insulin response to glucose this may be explained by a decrease in insulin sensitivity with hydrochloro-thiazide [(25)].

Cardiovascular risk lowering ability of antihypertensive group of drugs regimens

Table 9 showed qualitative estimation of CRP in hypertensive patients, CRP are predictors of CVD [(28)], the risk of IHD and cerebrovascular disease was increased in persons who had CRP levels above 3 mg per liter, as compared with persons who had CRP levels below 1 mg per liter [(29)].

In ACE inhibitors treated group 6 out of 22 patients showed positive CRP value, while in β-blockers and combination therapy treated groups 7 out of 22 patients showed positive value. This could give an indication that ACE inhibitors are probably better in lowering cardiovascular risk in hypertensive patients. In one study ACE inhibitor treatment was associated with lower 2.6 fold median CRP levels and with a reduced 2 year cardiovascular risk compared with a different BP lowering regimen [(30)].

Table 10 showed pulse rate, in ACE inhibitors treated group was not significantly different from mean pulse rate in healthy individual. This could indicate that ACE inhibitors have no effect on pulse rate, however it was significantly higher than mean pulse rate in β-blockers treated groups and combination therapy treated group this is because of β-blocking activity of β-blockers in both β-blockers treated group and in combination therapy treated group which also contain β-blockers. Mean pulse rate in β-blocker treated group was significantly lower than mean pulse rate in healthy individual, and in ACE inhibitors

treated group and combination therapy treated group, this indicate the β-blocking effect of these drugs and could indicate the cardiovascular risk lowering effect of β-blockers, because the reduction of pulse rate by β-blockers is accompanied by a decrease in peripheral BP with consequently reduced cardiac oxygen consumption and a longer diastolic filling time allowing for increased coronary perfusion. β-blockers have consistently been shown to reduce cardiovascular mortality, sudden cardiac death, and reinfarction in patients recovering from previous infarction [(31)].

table 11 and 13 showed CHD risk % and stroke % based on SBP and DBP, respectively in non diabetic hypertensive patients treated with different antihypertensive drugs. CHD risk % and stroke risk % based on SBP and DBP in all three treated groups of patients showed higher risk % compared to control healthy individual group. This could indicate that antihypertensive drugs used were not efficient enough to decrease the % of CHD risk and stroke risk percentage. This may be explained by the inability of these drugs to reach the normal BP and adverse effect of some drugs cause increase TC and decrease HDL values.

The causal role of an elevated serum cholesterol level in the genesis of atherosclerosis and its clinical sequelae, particularly IHD, is now well established. The recognition of this role has been the impetus for numerous studies designed to test the hypothesis that a reduction in the cholesterol level will lead to a reduction in morbidity and mortality from CVD. Most of these studies have indeed demonstrated a reduction in the incidence of ischemic cardiac events, and some have also shown a reduction in mortality from CVD [(32)].

Randomized controlled studies indicates that an average reduction of 12-13 mmHg in SBP over 4 years of follow-up is associated with a 21% reduction in CHD, a 37% reduction in stroke risk, a 25% reduction in total cardiovascular mortality, and a 13% reduction in all-cause mortality [(33)]. A 5 mmHg lower DBP is associated with about a one-third lower risk of stroke whereas a 10 mmHg lower DBP is associated with more than a one-half lower risk of stroke. The strength of these associations was not clearly different in men and in women [(34)].

Table 12 and 14 showed CHD risk % and stroke % based on SBP and DBP, respectively in diabetic hypertensive patients treated with different antihypertensive drugs. CHD risk % and stroke risk % in all three treated groups of patients showed higher % risk compared to control healthy individual group and to non diabetic patient group. This could indicate that antihypertensive group of drugs used were not efficient enough to decrease the % of CHD risk and stroke risk percentage. This may be explained by the inability of these drugs to reach the normal BP and adverse effect of some drugs caused increase TC and decrease HDL values and high blood glucose level.

However inability of the antihypertensive drugs used in our study to decrease CHD risk% and stroke risk% was incompatible with the overview of placebo-controlled studies of ACE-inhibitors that revealed reductions in stroke (30%) CHD, (20%), and major cardiovascular events (21%). Also the overview of placebo-controlled studies in which CCBs showed reductions in stroke (39%) and major cardiovascular events (28%) [(35)].

There was no significant difference in CHD risk % and stroke risk % between different antihypertensive group of drug regimens used, similar result have been found in placebo-controlled study, no significant differences in total major cardiovascular events between regimens based on ACE inhibitors, CCB, or diuretics or β blockers, although ACE inhibitor-based regimens reduced BP less [(36)].

Conclusions

1. The study indicated that the antihypertensive regimens used were not able to reduce BP to the target level, but the combination therapy and ACE inhibitors regimens were only capable to reach minimal BP target which is ≤150/90 mm Hg.
2. In view of the results of this study ACE inhibitors are better than β-blockers and combination therapy containing both β-blockers and/or thiazid diuretics, they did not adversely affect lipid profiles and blood glucose.
3. The study indicated that all three antihypertensive drug regimens have the same cardiovascular risk lowering ability, more specific evaluation is required by excluding other cardiovascular risk factors.
4. The study suggested that ACE inhibitors may act to decrease the C-reactive protein level and as a consequence lowering cardiovascular disease risk, but to indicate this, more specific quantitative evaluation is required.

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