A comparison between Captopril, Valsartan, Carvedilol and Conventional therapy in the treatment of heart failure

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الخلاصة

أجريت هذه الدراسة لغرض المقارنة بين الكابتوبريل, الفالسارتان, الكارفيدولول والعلاج التقليدي من حيث مدى فعالية وخلو الأدوية من الآثار السلبية وتحسين وظيفة القلب ونوعية الفعاليات الحيوية اليومية وتقليل معدل الوفيات والدخول إلى المستشفى للمرضى المصابين بعجز القلب.

شملت هذه الدراسة (80) مريضاً تم تشخيص المرضى على انهم مصابين بعجز القلب (Class I-IV) من قبل طبيب اختصاصي في نفس المستشفى. وشملت أيضاً الدراسة (15) شخصاً من الأصحاء (الفريق المسيطر).

تم تقسيم المرضى إلى أربعة مجاميع, المجموعة الأولى أعطيت الكابتوبريل 25ملغم مرتين يومياً, المجموعة الثانية أعطيت فالسارتان 80ملغم مرة واحدة يومياً, أما المجموعة الثالثة فقد أعطيت كارفيدولول 12,5 ملغم مرتين يومياً. أما المجموعة الرابعة فقد أعطيت العلاج التقليدي.

أستمر المرضى بتلقي نفس العلاج والمراقبة لمدة شهرين متتاليين وأخذت القياسات التالية : ضغط الدم, قبل إعطاء العلاج (أي عند البداية) وبعد إعطاء العلاج شهرياً لمدة شهرين.

كان هناك نسبة عالية من التحسن في مرتبة الأداء الوظيفي المعتمدة في نيويورك (NYHA Fnctional Class) لمجموعة الفالسارتان بنسبة 80% والكارفيدولول بنسبة 70% ولم يكن هناك تدهور صحي أو حالة وفاة في كلا المجموعتين.

وكان هناك تدهور صحي في مجموعة الكابتوبريل بنسبة 10% (مع وفاة اثنان من المرضى). أما العلاج التقليدي فكان نسبة التدهور الصحي 20% (مع وفاة مريض واحد).

وانخفض عدد الدخول إلى المستشفى أثناء الدراسة بشكل واضح لمجموعتي الفالسارتان والكارفيدولول ولكن بشكل أقل في مجموعة الكابتوبريل بينما لم يحدث أي تغيير واضح في تقليل الدخول إلى المستشفى لمجموعة العلاج التقليدي أثناء الدراسة.

كان هناك إنخفاض واضح في ضغط الدم للمجاميع الأربعة, أما معدل سرعة القلب (HR) فكان هناك زيادة واضحة في كل من مجموعة الكابتوبريل والفالسارتان. بينما كان هناك تناقض واضح في معدل سرعة القلب لكل من الكارفيدولول والعلاج التقليدي.

نستنتج من هذه الدراسة أن الكارفيدولول أو الفالسارتان يؤدي إلى تحسين واضح في وظيفة عمل عضلة القلب مع تحسين في أداء الفعاليات اليومية وتقليل معدل الوفيات والدخول إلى المستشفى للمرضى المصابين بعجز القلب .

ABSTRACT

A comparison was done between captopril, valsartan, carvedilol & the conventional therapy in patients with heart failure. The difference was reflected on the survival rate and hospital admissions.

Eighty patients were enrolled in this study, all were diagnosed as having heart failure (Class I – IV). They were grouped into four groups each consisted of 20 patients.

group I were given captopril 25mg twice daily,

group II were given valsartan 80mg once daily,

group III had carvedilol 12.5mg twice daily, and group IV were given the conventional therapy (digoxin, diuretics, nitrates …. etc.).

Blood pressure and heart rate were checked at baseline (before treatment) & after one and two months after initiation therapy.

Data were compared to those of 15 healthy & subjects included in the study as well.

Results revealed that a significant ($p<0.05$) reduction in blood pressure was noticed for the four groups. The heart rate was increased significantly ($p<0.05$) in the captopril & valsartan groups after two months while decreased significantly following carvedilol & conventional treatment.

As a whole, a high percentage of improvement in the functional class of NYHA was found in the valsartan (80%) & the carvedilol (70%) groups, as no health deterioration was noticed in any of these two groups & no one died.

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While the improvement percentage was to a lesser extent among patients on captopril the conventional therapy (10% and 20% respectively) with reported deaths.
The number of hospitalization during the follow up period was reduced significantly ($p<0.001$) in the valsartan and carvedilol groups and to a lesser extent in the captopril group while there was no significant reduction in hospital admissions of patients on the conventional therapy.
According to this, carvedilol or valsartan improved cardiac function, quality of life, reduced mortality and morbidity in patients with heart failure leading to a better short & long term prognosis.

INTRODUCTION:

Heart failure is a clinical syndrome[1,2], characterized by the inability of the heart to pump sufficient blood to meet the needs of the body[3,4]. It's predominantly a disease of middle aged & elderly. With age, major cardiovascular disorder rise in incidence & prevalence[5,6], whereas heart failure is considered the most frequent cause of hospitalization for people at age 65 years & older, adding greatly to the coot of treatment[2,7]. The mortality & morbidity have become a major public health issue with the care of pts. with heart failure accounting for substantial use of health care resources.
The major objectives of treating H.F. are reducing mortality, improving the quality of life which include relief of symptoms, ansoidance of side effects of therapy & reduce hospitalization.
The therapeutic goal for CHF is to[8,9] cardiac output.
Three classes of drugs have been shown to be clinically effective in reducing symptoms & prolonging life[2,10,11,12]:
vasodilators that reduce the load on the myocardium.
diuretic agents that decrease extracellular fluid volume.
inotropic agents that increase the strength of contraction.
B – blockers.
Carvedilol is a non selective B – blocker with $\alpha 1$ adrenoreceptor antagonism activity. It was approved in the united states in September 1995 for the treatment of pts. with essential hypertension & in May 1997 to become the 1st. adrenoreceptor blocking agent for the treatment of symptomatic HF[13,14]. Most of vasodilator activity of carvedilol is due to its ability to block $\alpha 1$ receptor leads vasodilation & reducing preload & after load[15].
Valsartan is a specific angiotensin II antagonist acting on AT1 receptor[16,17]. Unlike ACEI, valsartan dose not interfere with kinase II an enzyme responsible for degradation of bradykinine which may be associated wilts the side effect of cough & angioneurotic edema[18,19].
Captopril is a specific competitive inhibitor of angiotensin I converting enzyme. It has been shown to improve left ventricular function, reduces the activation of renin – angiotensin aldosterone system, preload, preserve electrolyte level & improves the ejection fraction[20,21].
The aim of this study was to assess the efficacy & benefits of the newly introduced drugs in the treatment of heart failure, valsartan or carvedilol in improving cardiac function, quality of life, reducing mortality & morbidity & the side effects of the drugs.
In comparison with other agents captopril & conventional therapy.

SUBJECTS AND METHODS:

A total of 80 patients were enrolled in this study with symptomatic heart failure of age range 22 – 71 years. In addition to 15 healthy subjects considered as a control group with matching age as the patient group. Patients were in & out patients selected from Ibn Al-Nafis hospital for cardiovascular diseases & were diagnosed & followed up by a specialist cardiologist.
Patients were randomized into four groups each consisted of 20 individuals;
GroupI : received captopril (6.25mg twice/day for 3–7 days then the dose was increased to 12.5mg twice daily for another few days then 25mg twice daily).

Group II : received valsartan (80mg once daily).
Group III : given an initial dose of carvedilol (3.125mg twice daily for 1–2 weeks) followed by 6.25mg twice daily for another 1–2 weeks then a maintenance dose of 12.5mg twice daily.
Group IV : received standard therapy of heart failure only (but not valsartan, carvedilol, or captopril) as indicated according to the patient's requirement.
The blood pressure and heart rate for each patient was measured before initiation therapy then one & two months after initiation therapy.
Results were compared with the control group.
Improvement in symptomatology of heart failure described by NYHA class.
Data on death and number of hospital admissions were obtained.

Statistical analysis:

All values were expressed as the mean±SD or percentage. Statistical significance of results were determined by means of student "t" test for paired data and confirmed by analysis of Variance (ANOVA).
Z–test (test of proportion) used for the comparability of baseline characteristics in the two groups.

RESULTS:

Blood pressure:

The systolic blood pressure increased significantly ($p<0.05$) in all patients at base line, compared with control subjects (118.6±6.67mmHg) (table–1).

Table 1 . The changes in mean systolic Blood pressure (SBP mmHg standing position) at base line and after one, two months for the patients compared to control subjects.

Control N=15	**118.6±6.67**	**At base line.**	**After 1 month**	**After 2 months**	**M1**	**M2**	**M3**	**M4**
Captopril N=20		138.3±8.5	129.7±5.9	123±4.1	S	S	S	S
Valsartan N=20		128.5±11.7	124.5±7.5	121.25±2.2	S	S	NS	S
Carvedilol N=20		130.5±8.5	126.5±8.9	123.5±4.1	S	S	S	S
Conventional N=20		137.5±10.3	126.5±8.9	126±6.4	S	S	S	S
P value		S!	NS	NS				

Value are mean ± SD
S= significant P<0.05
NS= non significant p>0.05
M1= control with at base line, M2= control with at 1 month,
M3= control with at 2 months, M4= at base line with at 2 months.
! Except valsartan and carvedilol, captopril and conventional are non significant.

However, it was reduced significantly after two months treatment in all the four groups of patients. Captopril reduced blood pressure from 138.3±8.5mmHg to 123±4.1mmHg, Valsartan from 128.5±11.7mmHg to 121±2.2mmHg, Carvedilol from 130.5±8.5mmHg to 123.5±4.1 and the conventional therapy from 137.5±10.3mmHg to 126±6.4mmHg. The difference between captopril, valsartan, carvedilol and conventional drugs was statistically not significant in reducing the systolic blood pressure (table–1).
The diastolic blood pressure increased significantly ($p<0.05$) in all groups of patients, except for the captopril group, at base line when compared with the control subjects (86.6± 4.1mmHg) (table–2).

Table 2 . The changes in mean diastolic Blood pressure (DBP mmHg standing position) at base line and after one, two months for the patients compared to control subjects.

Control N=15	**86.6±4.1**	**At base line.**	**After 1 month**	**After 2 months**	**M1**	**M2**	**M3**	**M4**
Captopril N=20		88.75±5.8	86.25±6.1	82.9±6.1	NS	NS	S	S
Valsartan N=20		91.1±3.9	88.3±4.2	85.75±3.3	S	NS	NS	S
Carvedilol N=20		92.3±4.6	88.65±3.5	87.25±3.7	S	NS	NS	S
Conventional N=20		91.25±5.1	88.75±3.5	87.25±3.7	S	NS	NS	S
P value		NS	NS	NS				

Value are mean ± SD
S= significant P<0.05
NS= non significant p>0.05
M1= control with at base line, M2= control with at 1 month,
M3= control with at 2 month, M4= at base line with at 2 month.

After two months of initiation therapy, the diastolic blood pressure decreased significantly from baseline, with captopril from 88.75±5.8mmHg to 82.9±6.1mmHg, valsartan from 91.1±3.9mmHg to 85.75±3.3mmHg, carvedilol from 92.3±4.6mmHg to 87.25±3.7mmHg. and conventional therapy from 91.25±5.1mmHg to 87.25±3.7mmHg.
After two months of therapy the diastolic blood pressure was approximatly close to the control level and all the drug used had the same potency in reducing the diastolic blood pressure.

Heart rate:

As shown in table – 3, after two months of treatment there was significant ($p<0.05$) increase in the heart rate with captopril, and valsartan from 81.5±7.4 beat/min. to 88.9±5.1 beat/min. and from 80.25±12.7 beat/min. to 89±5.3 beat/min. respectively. While for carvedilol and the conventional therapy resulted in a significant decrease of heart rate from 86.9±10.4 beat/min. to 81.5±6.9 beat/min. and from 85.2±10.4 beat/min. to 81.7±6.5 beat/min. respectively, with levels non significantly different from the control (table – 3).

Table 3 . The changes in mean heart rate (beat/minute) at base line and after one, two months for the patients compared to control subjects.

Control N=15	78.5±4.2	At base line.	After 1 month	After 2 months	M1	M2	M3	M4
Captopril N=20		81.5±7.4	86.25±4.1	88.9±5.1	NS	S	S	S
Valsartan N=20		80.25±12.7	85.65±7.5	89.2±5.3	NS	S	S	S
Carvedilol N=20		86.9±10.4	84±7.7	81.5±6.9	S	S	NS	S
Conventional N=20		85.2±10.4	83.45±7.4	81.7±6.5	S	S	NS	S
P value		NS!	NS	NS!				

Value are mean ± SD
S= significant P<0.05
NS= non significant p>0.05
M1= control with at base line, M2= control with at 1 month,
M3= control with at 2 month, M4= at base line with at 2 month.
! Except valsartan and carvedilol, captopril and conventional are significant.

Functional class:

The functional class was considered to have improved if patients functional class status changed from higher class to lower class (i.e. change from class II to I) of the NYHA classification. It was considered to have deteriorated if the functional class changed from lower to higher class or if the patient died[22].

As shown in table – 4 and fig. – 1 that a certain percentage of patients on captopril and the conventional therapy showed improvement (45% and 25% respectively) in the functional class. However, 45% and 55% of patients condition remained unchanged. While 10% and 20% of the cases on captopril and the conventional therapy were deteriorated with two deaths in the captopril group and one death in the conventional therapy group.

Table 4 . Changes in functional class of heart failure from baseline to two months.

	Functional Class At base line				Functional Class After two months			
	I	II	III	IV	I	II	III	IV
Captopril	0	4	7	9	2	4	9	5
Valsartan	0	3	6	11	3	6	9	2
Carvedilol	0	9	8	3	5	12	3	0
Conventional	4	2	11	3	4	4	8	4

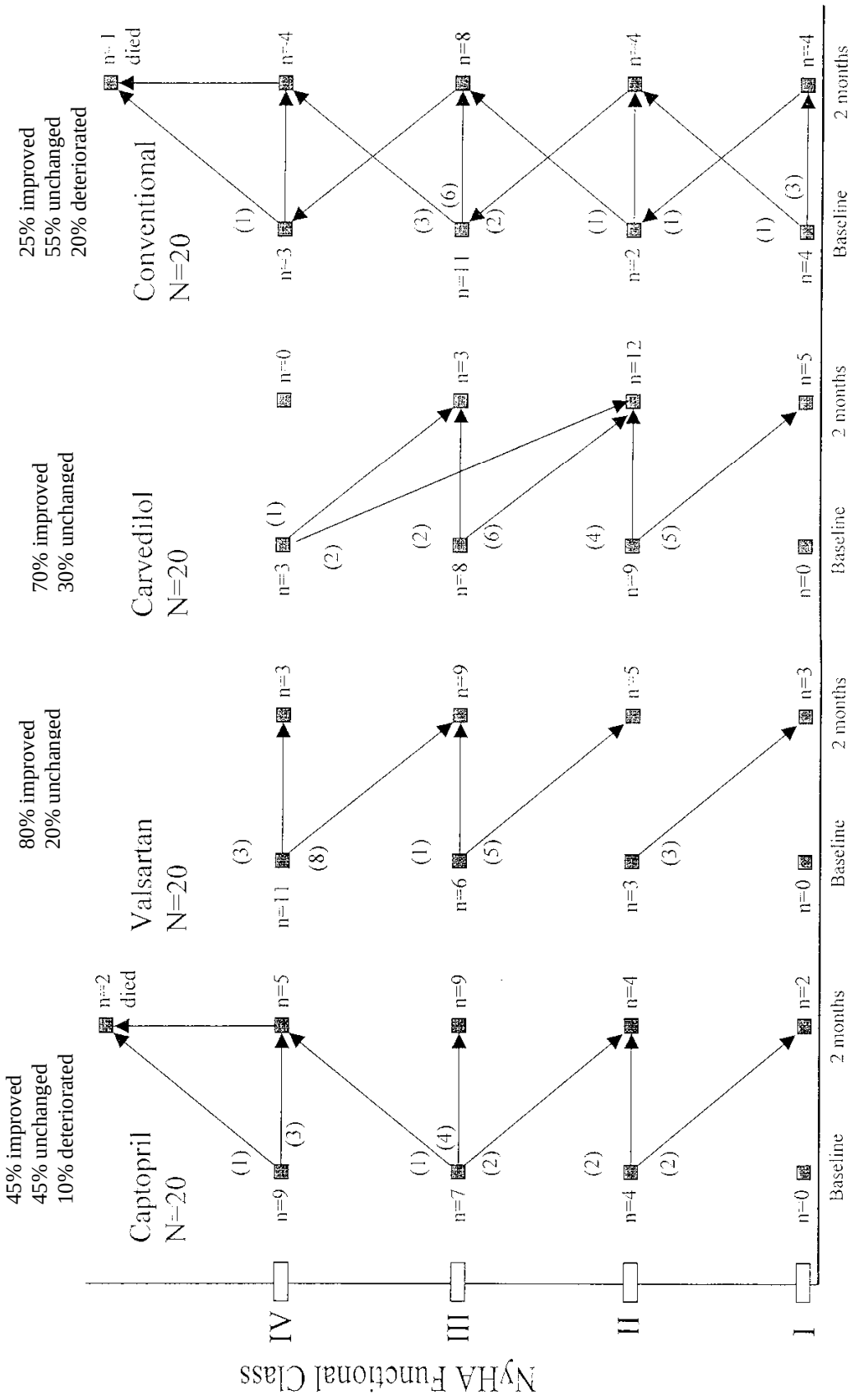

FIG 1 . CHANGES IN FUNCTIONAL CLASS FROM BASELINE TO 2 MONTHS FOR THE PATIENTS.

Patients on valsartan or carvedilol showed improvement (80% and 70% respectively) in the functional class, while valsartan and carvedilol remained unchanged (20% and 30% respectively). In comparison, valsartan and carvedilol versus captopril and conventional groups were significantly different ($p<0.05$).

Mortality rate:

Death occurred in two out of twenty patients (10%) in the captopril group and one out of twenty patients (5%) in the conventional group, while no one died among patients on valsartan or carvedilol.
The mortality rate was reduced significantly in valsartan and carvedilol versus captopril & conventional groups ($p<0.05$).

Reduction in hospital admission:

As shown in (table–5) before study period (i.e. previous admissions) there was no significant difference in hospital admission between all patients, but during study period (i.e. admission after initiation of therapy throughout study period) there was reduction in hospital admission with captopril from 32 (160%) to 12 (60%) ($p<0.05$), valsartan from 31 (155%) to 3 (15%) ($p<0.001$), carvedilol from 30 (150%) to 1 (5%) ($p<0.001$), while for the conventional group, there was no significant reduction in hospital admission, from 33 (165%) to 30 (150%) ($p>0.05$).

Table 5 . Hospitalization of patients before and during study.

	Captopril N=20	**Valsartan N=20**	**Carvedilol N=20**	**Conventional N=20**	**P value**
Before study	32 (160%)	31 (155%)	30 (150%)	33 (165%)	NS
During study	12 (60%)	3 (15%)	1 (5%)	30 (150%)	S
P value	S	HS	HS	NS	

S= significant P<0.05
NS= non significant p>0.05
HS= highly significant P<0.001

Adverse effects:

(Table–6) revealed that mayor common side effects encountered in patients after initiation of therapy, patients on captopril complained of cough (60%), G1 disorders (20%), vertigo (40%), hypotension (20%), headache (15%) and upper respiratory tract infection (5%).
Patients on valsartan complained of hypotension 25%, headache (20%), G1 disorder (10%), cough, vertigo, fatigue and sweating (5%) each.
Patients on carvedilol complained of hypotension (20%), G1 disorder (15%), fatigue and sweating (10%), cough, vertigo and headache (5%) each. While patients on conventional therapy complained of G1 disorder (45%), headache (30%), cough (25%), upper respiratory tract infection 20% and hypotension (10%).
Between groups comparisons are all significantly different, except for carvedilol and valsartan with respect to cough, G1 disorder, vertigo and hypotension in which there was no significant difference.

Table 6 . Percentage side effects of the drugs used in the study.

Side effects %	Captopril N=20	Valsartan N=20	Catvedilol N=20	Conventional N=20	P value
Cough	60	5	5	25	S!
G.I Disorder	25	10	15	45	S!
Vertigo	40	5	5	0	S!
Headache	15	20	5	30	S
Hypotension	20	25	20	10	NS!
U.R.T. Infection	5	0	0	20	S
Fatigue sweating	0	5	10	0	S

Values are percentages
S= significant P<0.05
NS= non significant p>0.05
! Except valsartan and carvedilol are non significant.
!! Except conventional is significant

DISCUSSION:

The primary objectives of treating heart failure are to improve clinical status, increase exercise tolerance, improve survival rate and reduce the frequency of hospitalization.
Previous studies have shown that captopril, valsartan and carvedilol each of them can improve cardiac function, reduce symptoms of heart failure, improve functional capacity and enhance exercise tolerance[23,24,25,26].
Regarding this work, a comparative study was done to evaluate the difference between captopril, valsartan, carvedilol and conventional therapy in patients with heart failure (functional class I to IV) considering the efficacy and safety of these drugs.
Hypertension is an important risk factor for developing heart failure. The systolic and diastolic blood pressure were significantly decreased from base line for all groups in our study.
The heart rate was found to increase significantly when captopril or valsartan were used. While the heart rate decreased significantly following the administration of carvedilol and conventional therapy (table–3).
Blocking the rennin angiotensin aldosterone system prevents or reserves cardiac remodeling and improves prognosis in cardiovascular disease beyond the effect on blood pressure.
Valsartan acts by selectively blocking angiotensin type I receptors and shows similar efficiency and improved tolerability compared with ACEI. This drug may provide additional benefits in controlling the cardiovascular complication of hypertension.
A previous report[27] compared the acute hemodynamic effects of metoprolol with those of carvedilol in patients with dilated cardiomyopathy both drugs significantly reduced heart rate, but carvedilol also reduced mean arterial pressure, systemic vascular resistance on left ventricular filling pressure. Also the antioxidant action of carvedilol was found to reduce the atherosclerotic process[28].
Valsartan capacity to lower blood pressure and effects on glomerular filtration rate, protein urea, and hyperkalemia are similar to those of ACEI, which makes valsartan an alternative to ACEI[29]. Another additional beneficial effect of carvedilol is that it produces renal and systemic vasodilation (not seen with other β - blockers) because of its α1- blocker, decreases the risk of fluid retention in heart failure[2].
Within two months of therapy, valsartan and carvedilol had improved the functional class (NYHA) by 80% and 70% respectively (table–4), adding to this, there was no mortality rate in these two groups.

Hospital admissions reduced (table–5), this is in agreement with previous reports[30,31] that valsartan and carvedilol demonstrated a significant reduction in morbidity and mortality.
So the present study suggested that both drugs are superior to captopril in improving survival in heart failure patients.
Adverse effects were reported, most of them disappeared spontaneously or after adjustment of concomitant medications which did not require the discontinuation of treatment (table–6). There was no difference in the adverse effects between valsartan and carvedilol with respect to cough, G1 disorders, vertigo, fatigue, sweating, and hypotension.
While the incidence of adverse effects was slightly higher in captopril and conventional groups. Indeed many of the side effects of captopril are related to suppression of angiotensin II formation and accumulation of bradykinin, Which is responsible for some of the adverse effects such as cough, angioedema, renal dysfunction and hypotension[32].

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