Medical Journal of the
Islamic Republic of Iran

Volume 9
Number 4
Winter 1374
February 1996

THE COMPARATIVE STUDY OF ANTI-HYPERTENSIVE TREATMENTS (CSAT): BACKGROUNDS, METHODS, AND THE PRELIMINARY RESULTS (INTERIM REPORT)

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ABSTRACT

The "Comparative Study of Antihypertensive Treatments"–CSAT is a placebo-controlled, randomized, double-blind clinical trial, with the primary objective of comparing the efficacy of different pharmacological treatments of hypertension. Drug side-effects, patient compliance, and alterations in the patients' quality of life are also compared. Subjects with mild to moderate diastolic hypertension aged above 30 are randomized into either of 5 groups receiving methyldopa, atenolol, nifedipine, triamterene-H, or placebo. After a dose titration phase, the minimum drug dose required to achieve a therapeutic goal of less than 91 mmHg for diastolic blood pressure (DBP) is determined, and the patient then enters a maintenance phase of 6 months.

This report presents the preliminary results of drug efficacy in 136 subjects who have completed the dose titration phase. Age, sex, baseline systolic blood pressure (SBP) and baseline DBP were all well balanced across placebo and drug groups: mean age ± SD = 51.9 ± 9.2 years; sex distribution: 56.6% males: mean DBP ± SD = 98.5 ± 5.4 mmHg; mean SBP ± SD = 152.1 ± 14.4 mmHg; (SD = standard deviation, SBP and DBP values were measured in the sitting position). SBP and DBP reduction in the active treatment groups (mean ± SE: 17.8 ± 1.4 mmHg for SBP, 12.4 ± 0.7 mmHg for DBP) were significantly greater than in the placebo group (mean ± SE: 7.9 ± 1.6 mmHg for SBP, 7.23 ± 0.9 mmHg forDBP) at the end of the dose titration phase ($P < 0.00001$). There was greater SBP reduction with atenolol 23.9 ± 3.2 mmHg) than with either nifedipine (12.5 ± 2.3 mmHg) or triamterene-H (16.2 ± 2.7 mmHg), $P<0.05$. This difference was not observed in patients aged above 50, but was significant in the below 50 age group. Pharmacological treatment was more efficacious in SBP reduction in women than in men (22 ± 2.1 mmHg in women versus 14.0 ± 1.7 mmHg in men, $P<0.01$). No similar difference between the two sexes was detected in the placebo group. This

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interim report of the CSAT emphasizes the importance of pharmacological therapy, and depicts significant differences in the antihypertensive efficacy of various drug groups. Establishing new research centers and reaching desired sample sizes are currently being undertaken.
MJIRI, Vol. 9, No. 4, 285-293, 1996.

INTRODUCTION

Prior to the advent of antihypertensive drug therapy in the 1950s, hypertension was considered an incurable and potentially lethal condition. The gradual elucidation of the dangerous complications of hypertension, along with the availability of effective antihypertensive drugs, led to increasing utilization of these drugs.

Shortly after the introduction of antihypertensive drug therapy, epidemiologic studies and clinical trials showed that while stroke risk has been considerably lowered (≅40%), the reduction in coronary artery disease has been far less than predicted (14% reduction observed versus 25% expected)[2]. Can the biochemical alterations induced by drugs account for the difference?, and more important, to what extent can the more recently available drugs affect further decrements in the cardiovascular complications of hypertension?

Considering the fact that hypertension generally requires long-term, usually life-long treatment, the choice of treatment must be directed to effectively controlling hypertension, with minimum overt or covert side-effects and minimum adverse effects on the patient's life quality and life style. This will ensure the patient's maximum compliance over time. What can actually minimize the mortality of hypertension, is the selection of the proper treatment for each patient individually. In a study performed by the Cardiovascular Research Center of the Tehran University of Medical Sciences on 10,180 subjects aged over 15 in the city of Tehran, 12% of the subjects had "hypertensive" DBP readings on a single measurement. Only 47% of these people were aware of their hypertension, and only 31% were receiving antihypertensives[3].

This clearly illustrates the necessity of a comprehensive clinical study, aimed at helping the health care providers choose appropriate antihypertensive therapies. The "Comparative Study of Antihypertensive Treatments" (CSAT) was designed to respond to this demand. Thus, it compares four classes of antihypertensive drugs commonly used in Iran in a prospective, controlled fashion.

This article reviews the CSAT objectives and methods and presents an interim report of the data concerning the efficacy and side-effects of the drugs eight months after the onset of the study.

The main objective of this study was to compare four classes of antihypertensives, considering efficacy and the ability to keep BP controlled over time. Besides this, overt and covert side-effects (such as alterations in biochemical or hematologic parameters), halting or reversal of the complications (left ventricular hypertrophy, retinal vascular changes), alterations in the patients' quality of life, and the patients' compliance were also compared among the groups.

PATIENTS AND METHODS

Study design

The CSAT is a randomized, placebo-controlled, double-blind clinical trial. A total of 1200 males and females aged over 30 with mild to moderate diastolic hypertension who are taking no or only one drug were admitted and randomized into different therapeutic groups (Table I). Prior to admission, the patients were screened for the presence of exclusion criteria (Table II). These criteria include factors increasing the risk of hypertensive complications, definitive proof of end-organ damage, contraindications to any of the studied antihypertensives, and failure of the patient to comply with the medical advice given by the clinic. In the first visit, the patients were classified into stratum 1 (those who have never used an antihypertensive on a regular basis) or stratum 2 (those who have regularly used an antihypertensive agent). The antihypertensive agent of stratum 2 patients was gradually tapered, providing they do not meet the criteria for exclusion (Table II). BP measurements were obtained two weeks after complete cessation of the antihypertensive drug (the wash-out phase), and the patients were admitted using the same inclusion criteria as stratum 1 patients. The patients' BPs were measured two more times, and those wth a baseline DBP of 91-114 mmHg (calculated as the average of three readings) who were free of the exclusion criteria were admitted to the study. A written informed consent was then obtained, and the patients were subsequently randomized into one of the following groups: 1- triamterene-H 2- atenolol 3- methyldopa 4- nifedipine 5- placebo. Nifedipine was started with its minimum therapeutic dose. The initial

Table I. Study criteria.

Design of the Comparative Study of Antihypertensive Treatments, 1200 samples
Randomized, double-blind, placebo-controlled
Men and women over 30 years of age
No clinical, pharmacological or Biochemical exclusion criteria
Mild to moderately severe hypertension (*DBP = 91-114mmHg)
Five groups:
Placebo group (600 people)
Diuretic (150 people)
Beta blocker (150 people)
Central alpha agonist (150 people)
Calcium channel blocker (150 people)

* DBP = diastolic blood pressure

Table II. Exclusion criteria.

Exclusion Criteria of CSAT
Blood Pressure: Stratum One: DBP**<91 or DBP >114 or SBP*>200 mmHg
Stratum Two: DBP>99 or SBP >170 mmHg (in the first visit)
Current consumption of two or more antihypertensives.
Clinical Exclusion Criteria:
History of other cardiovascular disease, diabetes mellitus, asthma, gout, pregnancy, collagen vascular disease,...
Pharmacological contraindications, drug interactions.
Evidence of poor compliance.
Biochemical Exclusion Criteria:
Hyperglycemia, disturbed LFT***, disturbed RFT†, hyperuricemia, hyperlipidemia, neutropenia, coagulopathies, hematuria, proteinuria.

* SBP = systolic blood pressure; **DBP = diastolic blood pressure; ***LFT = liver function tests;
† RFT = renal function tests

dose of the other three agents was twice the minimum therapeutic dose. Dosing intervals differ for different drugs (Table III). In order to prevent this from being a potential source of bias, and to keep both the patient and the examiner blind to whether the patient is receiving drug or placebo, there is one placebo group for each drug group, with exactly identical dosing intervals and drug forms.

Patients were assigned to different groups by systematic randomization with stratification based on age and sex. Randomization was performed by people who were by no means involved in the measurements. Instructions on how to use the drugs were orally explained to the patients, with the aid of prepared brochures which were specific to each therapeutic group (consisting of an active drug group and the corresponding placebo groups). All patients received brief written instructions on improving their life style and the importance of compliance with the instructions. These included lowering sodium intake, regular exercise, using a high calcium diet, and weight reduction for obese patients.

Drug therapy, dose titration and maintenance phase

After randomization, the patients entered the dose titration phase. During this phase BP measurements in standing and sitting positions were obtained every two weeks, and the appropriate dose of the drug was determined considering DBP and patient compliance (in all steps of the study, BP was considered as the average of the readings obtained at the last two clinic visits). If the patient failed to reach a therapeutic goal of DBP<90 mmHg after two consecutive visits, a second dose of the same drug, twice the first dose, was started and if this second dose failed to achieve the therapeutic goal after two consecutive visits, the patients in the active drug groups would enter the second therapeutic step. This step constituted the addition of atenolol for

Table III. Drug groups and dosages.

CSAT Drug Groups and Dosages*								
	Placebo				Drug			
Step 1	**Triamt.-H****	**Atenolol**	**Methyldopa**	**Nifedipine**	**Triamt.-H (mg)**	**Atenolol (mg)**	**Methyldopa (mg)**	**Nifedipine (mg)**
Dose 1	1	1	1	1	25	50	250	10
Dose 2	2	2	2	2	50	100	500	20
Pills per day	1	1	2	3	1	1	2	3
Step 2	–	–	–	–	**Atenolol**	**Triamt.-H**	**Triamt.-H**	**Triamt.-H**
Dose 1	–	–	–	–	50	25	25	25
Dose 2	–	–	–	–	100	50	50	50

*All drugs and placebos have been provided as tablets.

**Triamterene-H, Dose 1: 25mg Hydrochlorothiazide + 50mg Triamterene.

the triamterene-H group, and the addition of triamterene-H for all other groups. The patients in the placebo groups would enter the maintenance phase even if their DBP remained uncontrolled after the administration of the second dose.

Patients who had achieved the therapeutic goal in two consecutive visits during the dose titration phase would enter a maintenance phase of six months. BP readings were obtained on a monthly basis during this phase, and the study was considered completed for any individual patient if his/her DBP remained <90 mmHg throughout the maintenance phase. If DBP readings above 90 mmHg were detected in two consecutive visits during the maintenance phase, the patient re-entered the dose titration phase.

"Therapeutic response" was evaluated based on the ability of the drug in reaching the therapeutic goal and maintaining that throughout the study. A patient was considered a "non-responder" if he/she entered the second therapeutic step at any time during the study (for drug groups) or failed to achieve the therapeutic goal (for placebo groups).

Table IV. Data collection and measurements.

Data Collection and Measurements
Blood pressure
Weight
Height
Pulse rate
Arm circumference
Waist to hip ratio
Questionnaires
Health condition
Dietary habits and frequencies
Side-effects
Exit
Medical history
Compliance (pill count, interview)
Fundoscopic examination
Standard 12 lead ECG
Biochemical, hematological and urinary tests

Measurements

All information and measurements were obtained by specially trained medical students. A "Board of Education and Quality Control" undertook the training of these students, and controlled and ensured the validity of the information obtained by them.

At each visit, the BP was measured with the patient seated and rested for five minutes, in the right arm, with the arm at rest and at heart level. Two measurements, two minutes apart, were taken at each visit. Sphygmomanometers with conventional-sized cuffs (12×23 cm) and mercury manometers were used. The pressure recorded for a visit was the average of two BP readings which were at most 10 mmHg different, after correction for arm circumference.[1,4] Systolic and diastolic blood pressures were determined according to the first and the fifth Korotkoff phases, respectively. The baseline blood pressure was calculated as the average of DBP readings obtained in the sitting position

Table V. Causes of exit and sample attrition.

Causes of Exit and Sample Attrition
A- Exit:
Sitting systolic BP > 200 mmHg.
Sitting diastolic BP < 70 mmHg in dose level 1
Sitting diastolic BP > 124 mmHg.
Standing Systolic BP < 100 mmHg.
Pulse rate < 45
Serious side-effects
Poor compliance (at least in two consecutive visits).
B - Sample Attrition:
Random events.
Systematic.

at the 2nd and 3rd eligibility visits (the last two visits before randomization). These readings were obtained in the morning and afternoon respectively, and at least one week apart. The patient was instructed to rest in the sitting position for 5 minutes, and the blood pressure was measured immediately and 2 minutes after standing. After admission, sitting and standing blood pressures were recorded at each visit (afternoon). Compliance was assessed using a questionnaire and a count of pills at each visit. Measurements at each visit were considered valuable only if compliance had been desirable (80-120%). The patients were screened for overt side-effects at the beginning and upon completion of the study by means of a questionnaire consisting of 57 questions which directly or indirectly addressed all known side-effects of the drugs. To quantify the severity of side-effects, a 4-point scale (free of side-effects, mild, moderate, severe) was introduced, depicting the impact of the side-effect on the patient's daily activities.[5]

Body mass indices and waist/hip ratios were determined for all patients. Patients were weighed without shoes and with reasonable clothing, using conventional weighing machines, which were readjusted every week with standard 20 kg weights. A standard 12-lead electrocardiogram was obtained at the beginning and upon completion of the study, and was searched for exclusion criteria (Table II) and/or left ventricular hypertrophy (according to Bonner's criteria[6]).

Direct fundoscopy was performed by ophthalmology residents. Laboratory tests on blood and urine were performed before admission, and were repeated at the third and sixth months of the maintenance phase (Table II). All laboratory tests were performed and checked in the Research Laboratory of the Cardiovascular Research Center, Tehran University of Medical Sciences. Total cholesterol, triglyceride, and HDL cholesterol levels were measured directly. VLDL cholesterol was calculated by dividing the triglyceride level by 5, and LDL cholesterol was calculated by subtracting HDL cholesterol and VLDL cholesterol from the total cholesterol level.

To monitor changes in the quality of life, the questionnaire used in the Rand study was adopted.[7,8] This includes 57 items by which 9 dimensions (physical well-being, energy, mental well-being, functioning, physical ability perceptions, social relations, social associations, sleep disturbances, job satisfaction) were assessed at the beginning and end of the study.

To assess sodium intake, dietary habits and dietary frequencies were studied semiquantitatively at the beginning and end of the study. Physical activity was also assessed in the beginning and end by recording type, frequency, and duration of activity.

Sample size calculation and sample attrition

Sample size has been calculated using the results of the interim analysis of therapeutic efficacy (at which the study is primarily aimed), and corrected according to the formula of Fleiss et al.[9]

In order to detect a difference of 15% with a type I error of 0.05 and a statistical power of 80%, 150 patients were required in each group.[10]

Considering the undesirable effect of sample attrition on comparing drug efficacies and its potential to lead to bias while analyzing the data, necessary measures have been taken to maximize compliance. Besides this, different reasons for loss to follow-up were sought by a special questionnaire. These reasons fell into two categories: 1-development of some side-effect in the patient after admission, and 2- refusal to attend the clinic or failure to comply with the therapeutic instructions for any other reasons. All lost-to-follow-up cases belonging to the second category were studied using a special self-administrative questionnaire and, based on the answers, somebody who was unaware of the patient's group would decide whether the reason had been medical (of significance to the study) or non-medical (by chance) (Table V).

Data analyses

Data was analyzed using the SPSS/PC+ statistical package. Analyses of variance were employed to detect therapeutic differences for measurable variables, and relevant adjustments were performed (stratified analyses of variance were employed to detect therapeutic differences for measurable variables). Categorical variables (such as side-effects) were analyzed by means of chi-square and Fischer exact

Table VI. Comparison of basic characteristics.

Group	No.	Age (Yr) mean ± SD*	Men (%)	SBP** (mmHg) mean ± SD	DBP*** (mmHg) mean ± SD
Atenolol	21	49.25 ± 7.75	66.7	157.04 ± 14.37	99.8 ± 4.92
Methyldopa	18	50.94 ± 9.02	61.1	151.33 ± 12.3	99.27 ± 5.8
Nifedipine	18	52.16 ± 7.7	61.1	147.33 ± 16.46	96.83 ± 6.1
Triamterene-H	19	53.22 ± 8.9	52.6	155.63 ± 15.37	100.78 ± 5.48
Overall	76	51.33 ± 8.36	60.5	153.3 ± 14.91	99.07 ± 5.63
Placebo	60	52.48 ± 9.82	52.4	151.08 ± 13.79	97.75 ± 5.06

*SD=standard deviation; **SBP=systolic blood pressure; ***DBP = diastolic blood pressure

Table VII. Systolic and diastolic BP of patients at the end of the dose titration phase.

	Mean BP ± SD ; No. of cases					
	Atenolol	Methyldopa	Nifedipine	Triamterene-H	Overall	Placebo
Systolic BP after dose titration phase (mmHg)	133.09±14.3;20	134.84±8.9;17	134.77±9.6;18	139.36±13.2;18	135.47±11.9;76	143.78±13.9;60
Diastolic BP after dose titration phase (mmHg)	85.19±4.8;20	87.83±6.4;14	85.22±5.4;18	85.52±4.5;18	86.65±5.4±76	90.55±8.5;60

tests. To analyze alterations in quality of life, each patient's responses for each quality of life index were first ranked, then the sum of the ranks for all indices for each patient was compared by analysis of variance. For comparison of quantitative variables across the therapeutic groups, possible significant differences among placebo groups were sought by an analysis of variance. If this indicated no significant difference, the placebo groups were combined into one placebo group. Two-tailed tests at the 0.05 level of significance were used to assess differences between drug groups and the placebo group. To compare drug groups with one another, pairwise comparisons were performed by the "least significant difference method". To study the efficacy of drug therapy in general, a comparison was performed between all drug groups combined and the placebo group.[11,12]

RESULTS

Over 2700 patients were visited at our clinic in Dr. Shariati Hospital, Tehran during the eight months from the beginning of the study. Only 223 of these were eligible for the study (baseline DBP of 91-114 mmHg, baseline SBP<200 mmHg, absence of the exclusion criteria). These patients were randomized into different drug or placebo groups. To date, 136 patients have completed the dose titration phase, and this report presents the analyses of data of these patients.

All different therapeutic groups had a well-balanced distribution of baseline characteristics (age, sex, baseline DBP, baseline SBP) at the time of randomization and there were no significant differences among the groups. Mean age was 51.3 in drug groups and 52.5 in placebo groups, there were 60.5% males in drug groups and 53.4% males in placebo groups, baseline SBP was 153.3 mmHg and 151.1 mmHg and baseline DBP 99.1 mmHg and 97.8 mmHg for drug and placebo groups, respectively (Table VI).

At the completion of the dose titration phase (which took 43.2 days on average) there was a significant reduction in SBP and DBP in all therapeutic groups (as compared with the baseline values). SBP decreased to

Table VIII. Mean blood pressure reduction after completion of the dose titration phase

	Mean BP reduction ± SE * ; No. of cases		
	Total drug groups	Placebo	P
Systolic BP reduction (mmHg)	17.8 ± 1.3; 76	7.96 ± 1.5; 60	0.00001
Diastolic BP reduction (mmHg)	12.42 ± 0.7; 76	7.32 ± 0.8; 60	0.00001

* SE = standard error of mean

Table IX. Mean blood pressure reduction after completion of the dose titration phase.

	Mean BP reduction ± SE ; No. of cases				
	Atenolol	Methyldopa	Nifedipine	Triamterene-H	Placebo
Systolic BP (mmHg)					
All cases	23.9 ± 3.2; 20	17.4 ± 1.9; 15	12.5 ± 2.3: 18	16.2 ± 2.7; 18	7.9 ± 1.5; 60
< 50 years old	23.7 ± 3.3; 14	15.5 ± 2.7; 8	9.3 ± 2.8; 9	10.4 ± 2.8; 7	4.4 ± 1.6; 25
> 50 years old	19.6 ± 6.7; 6	19.2 ± 2.7; 9	15.7 ± 3.7; 9	20.2 ± 4.0; 11	10.8 ± 2.5; 30
Diastolic BP (mmHg)					
All cases	12.4 ± 3.0; 20	11.4 ± 1.2; 15	11.6 ± 1.6; 18	12.2 ± 1.6; 18	7.32 ± 0.89; 60
< 50 years old	14.3 ± 1.3; 14	12.0 ± 2.2; 8	9.0 ± 2.2; 9	10.8 ± 2.3; 7	7.2 ± 0.9; 25
> 50 years old	11.3 ± 2.4; 6	11.0 ± 1.4; 9	14.2 ± 2.2; 9	14.0 ± 1.9; 11	7.4 ± 1.5; 30

135.5 in drug and placebo groups respectively, and DBP to 86.7 and 90.6, respectively (Table VII).

Comparing drug treatment with placebo indicates significantly greater SBP and DBP reductions with drug than with placebo (P<0.00001) (Table VIII). For the drug group, the reduction in blood pressure (mean±SE) was 17.8±1.39 mmHg for SBP and 12.42±0.71 mmHg for DBP. Corresponding figures for the placebo group were 7.96±1.53 mmHg and 7.32±0.89 mmHg, respectively. This did not apply to all individual drug groups: SBP reduction in the nifedipine group was not significantly greater than placebo (P=0.14). Nevertheless, all drugs caused significantly greater DBP reductions as compared to placebo (P<0.03) (Table IX).

Atenolol was shown to have more efficacy in reducing SBP than nifedipine or triamterene-H (SBP reduction in mmHg, mean±SE: 23.9±3.2 for atenolol, 16.2±2.7 for triamterene-H, 12.5±2.3 for nifedipine; P<0.05). Atenolol had also induced a greater decrease in DBP than other drugs, but this difference was not statistically significant (P=0.52) (Table IX).

The patients had a mean age of 51.8 years, and the median of their age distribution curve was approximately 50 years, therefore it seems reasonable to divide the patients into over 50 and below 50 age groups. In the below 50 age group, it was more clearly demonstrable that atenolol is more efficacious in reducing SBP than nifedipine or triamterene-H (Table IX). In contrast, in the over 50 age group, triamterene-H decreased SBP slightly more than the other drugs; the difference was not significant, however (P=0.8) (Table IX). There was no significant difference in the efficacy of the drugs to reduce DBP in either of the age groups.

Drug therapy in general was much more efficacious in reducing SBP in women (SBP reduction in mmHg, mean±SE:14.5±1.6 in men, 22.2±2.1 in women; P=0.009). This was not true with placebo (i.e., there was no significant difference in SBP reduction between men and women who were receiving placebo), nor was there any significant difference in compliance between the two sexes (87% in males vs. 85% in females).

DISCUSSION

The CSAT is the first study to compare common antihypertensive drugs in Iran, and in addition to its predetermined aims and the usefulness of its results in guiding Iranian physicians in the selection of antihypertensives, it can pave the way for further research.

This study has a favorable subject encompassment, owing to participation of patients of both sexes and an eligibility age of above 30 years. The large sample size of 150 subjects in each therapeutic group provides the study with a desirable statistical power to detect therapeutic differences among groups. The design of the study offers the opportunity of comparing active drug therapy with placebo and thus supports the clinical significance of the results, especially by obviating the negative effect of placebo on patient compliance. Few studies have so far attempted to compare more than two classes of drugs simultaneously with consideration to their efficacy in reducing DBP. In the randomized, placebo-controlled TOMHS (Treatment of Mild Hypertension Study)[11], five classes of antihypertensives (diuretic, beta-blocker, alpha-blocker, calcium channel blocker, and angiotensin converting enzyme inhibitor) and placebo were compared. All patients were given special diets to reduce weight and restrict sodium intake, and a program to increase physical activity was supplied to all patients. The study was aimed at comparing the mentioned groups with regard to efficacy, side-effects and quality of life changes in short term, and the evolution of coronary disease in long term. No significant difference was found between the drug groups regarding the short term objectives, but it must be noted that only 45-69 year old men had been admitted to the TOMHS, and therefore our report of greater efficacy of atenolol in younger patients does not contradict the results of the TOMHS. Saunders et al.[11] have compared atenolol, captopril and verapamil in black patients, and have reported significant BP reductions in short term. In another study performed by the Department of Veterans Affairs Cooperative Study Groups,[13] six antihypertensives (hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem and prazosin) have been compared, but the participants were exclusively males, mostly aged blacks. Firm data concerning possible sex differences in the response to antihypertensives are lacking, nevertheless the results of this study could not be extrapolated to women. The subject encompassment of our study has been lowered by the exclusion of patients who had some contraindication to the studied drugs (Table II).

In our study, the opportunity to compare drugs with different dosing intervals was provided for the first time by having one placebo group for each drug group. This is essential for comparing efficacy and compliance.

This report presents the analyses performed on the preliminary data of only a small portion of the patients, and the effects of drug therapy on the quality of life, left ventricular hypertrophy, fundoscopic changes, and laboratory measurements are still awaited. The reported results indicate that drug therapy significantly decreases SBP and DBP in hypertensive patients. The greater efficacy of atenolol (as compared with nifedipine or triamterene-H) in reducing SBP in patients below 50 years of age can support theories that attribute essential hypertension in younger patients to an overactivity of the cardiovascular system. Along with the JNC-V recommendations[1] –which are based on long term studies–our results propose atenolol as the first line of therapy for essential hypertension in relatively young patients in whom this drug is not contraindicated.

Considering the fact that no difference existed between men and women in the efficacy of placebo or compliance, the observed difference in response to drug therapy (greater SBP reduction in women) deserves more attention to find possible effective factors and to elucidate the role of sex. This difference can also encourage drug therapy in hypertensive females by demonstrating its greater effectiveness. It must be mentioned again that appropriate comparisons between drug groups can not yet be made due to the currently small sample size, and we are still on the way to reach the determined sample size and final results.

Once more we emphasize an individualized approach to the treatment of hypertension. Small differences in efficacy among various drugs may be overshadowed by changes in the patients' quality of life.[14] We hope the final results of the CSAT can guide physicians in selecting the most appropriate antihypertensive therapy with regard to the patients' personal characteristics such as age, sex, life-style, physical and mental characteristics, and also considering the unique traits of the Iranian society. Studies with long term design are required to assess differences in the effect of various therapies on cardiovascular-related mortality.

ACKNOWLEDGEMENTS

The CSAT is financially supported by the Cardiovascular Research Center of Tehran University of Medical Sciences. We wish to acknowledge the cooperation of Dr. Farshid Alaeddiny, drug supply manager of the Cardiovascular Research Center, and the following pharmaceutical companies: Tolid Daru (atenolol, nifedipine), Sobhan (triamterene-H), and

Daru-Pakhsh (methyldopa) and members of the CSAT group.

The CSAT is supervised by Seyyed Hassan Arefi, MD, Associate Professor of Tehran University of Medical Sciences, and Morteza Naghavi, MD, Chairman of the Cardiovascular Reseach Center.

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