

narcotized animals (Kier LB et al., 1966). But the mechanism of their activity is not clarified. The goal of this research is to examine the ability of 3-(3-[1,2,4]triazolo)-oxatriazolium-5-olate (AS-6) to generate NO, to activate sGC, and to alter systemic arterial pressure at awake rats.

The ability of AS-6 to generate NO was estimated by its reaction with oxyhemoglobin in the presence and absence of glutathione. Also NO (nitrite) formation in the presence of AS-6 was measured by the Griess reaction. Activity of sGC was measured by using purified enzyme from porcine lung in the presence of 10-200 microM AS-6 with alpha-[³²P]GTP as a substrate. To examine hypotensive activity of AS-6 male Wistar rats (200-300 g weight) were catheterized and mean arterial pressure was measured. AS-6 was administrated at doses 0.012-120 mg/kg to rats of experimental group in two days. Control group were administrated with corresponding DMSO solutions.

We demonstrated that AS-6 doesn't generate detectable levels of NO both in the presence and absence of glutathione. AS-6 activated purified sGC in dose-dependent manner with 22-fold maximal activation. This activation could be potentiated by allosteric sGC activator YC-1 and completely blocked by heme-dependent sGC inhibitor ODO. In vivo AS-6 caused MAP decrease, 5.4 and 8.4 mm Hg, ($p < 0.05$) at doses 12 and 120 mg/kg, respectively. MAP was significantly decreased from 15th min and was stably reduced for 15 min.

Intravenous administration of AS-6 leads to prolonged arterial pressure decrease in awake rats. It seems to be that AS-6 activates sGC in heme-dependent NO-independent manner.

Key Words: NO/Cgmp-Dependent Vasodilation, Oxatriazolium-5-Olate Derivatives, Soluble Guanylate Cyclase

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AVOIDING ADVERSE CARDIOVASCULAR OUTCOMES WITH PROMPT BLOOD PRESSURE CONTROL: AN ECONOMIC ANALYSIS BASED ON THE VALSARTAN ANTIHYPERTENSIVE LONG-TERM USE EVALUATION (VALUE) TRIAL

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Improved outcomes in hypertensive patients are usually ascribed to the benefit of gradual blood pressure (BP) control over the long-term. There is a paucity of data on the effects of prompt BP lowering on cardiovascular (CV) outcomes over the short-term. Recent results from the VALUE trial demonstrate significant reductions in CV events in patients at high CV risk, associated with BP lowering over the first 3 months. This analysis therefore examines the cost-effectiveness of antihypertensive therapy, based on CV event rate reduction in the first 3 months of the VALUE trial.

An economic model was developed to determine costs per event avoided for stroke and all-cause mortality in the 0-3 month period of the VALUE trial (the only discrete outcomes showing significant differences between regimens in the early treatment period). Drug utilization was determined from the VALUE publication (Julius et al. Lancet, 2004; 363:2022); drug costs were taken from public sources reflecting retail pharmacy pricing. Stroke and all-cause mortality event rates were determined from the published paper using Kaplan-Meier graphs and reported odds ratios (OR) with 95% confidence intervals (CI), for valsartan vs amlodipine: stroke 1.94 (1.10-3.42); all-cause mortality 2.84 (1.51-5.34). Sensitivity analyses were conducted based on the upper and lower bounds of the CI for the OR and $\pm 20\%$ on event rates.

Over 3 months, amlodipine-based treatment reduced mean systolic BP by 3.8 mm Hg more than valsartan-based treatment, leading to reduction of 36 strokes and 53 fewer deaths per 15,000 patients. Associated drug cost is \$9.67 higher per patient with amlodipine vs. valsartan. Cost per stroke averted is \$4,003 and cost per all-cause death avoided is \$2,742. Sensitivity analyses demonstrated a range of \$2,282-\$26,698 per stroke averted and \$1,821-\$6,582 per all-cause death avoided.

All antihypertensive regimens may not be equally efficacious at rapidly reducing BP to goal. Among patients at relatively high risk for CV events, prompt BP reduction with amlodipine-based therapy as seen in VALUE, can reduce stroke and all-cause mortality within the first 3 months. These results reinforce the cost-effectiveness of optimal combination antihypertensive therapy for early and aggressive BP lowering to reduce CV events.

Key Words: Combination Therapy, Dihydropyridine Calcium Channel Blockers, Hypertension

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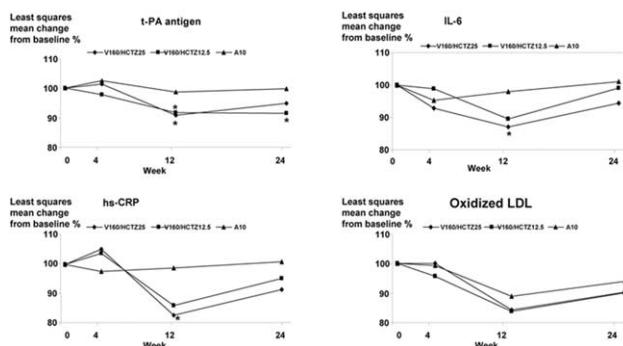
FIXED-DOSE VALSARTAN + HYDROCHLOROTHIAZIDE COMBINATION THERAPY COMPARED WITH AMLODIPINE MONOTHERAPY IN HYPERTENSIVE PATIENTS WITH ADDITIONAL CARDIOVASCULAR RISK FACTORS: THE VAST STUDY

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Objectives: To determine whether the combination of valsartan 160 mg and hydrochlorothiazide (HCTZ) 25 mg once-daily (od) is more effective than amlodipine 10 mg od in reducing systolic blood pressure (BP) in patients suffering from moderate hypertension combined with at least one other cardiovascular risk factor or concomitant condition. Further, to study the effects of treatment on vascular markers.

Methods: A multicenter, randomized, double-blind, active-controlled, three-arm study over 24 weeks. After a two-week single-blind placebo run-in period, 1088 stage-II hypertensive patients with additional risk factors were randomized to three groups, two receiving valsartan 160 mg od and one group receiving amlodipine 5 mg od. At Week 4, HCTZ 12.5 mg and 25 mg respectively, were added to the valsartan groups and the amlodipine dose was force-titrated to 10 mg od. Patients were followed-up for a total of 24 weeks.

Results: The combination of valsartan 160 mg + HCTZ 25 mg reduced systolic BP significantly ($p < 0.05$) more than amlodipine monotherapy (least-squares mean change from baseline 29.7 ± 0.7 mmHg and 27.6 ± 0.7 mmHg, respectively). For diastolic BP the values were 11.1 ± 0.4 mmHg and 10.8 ± 0.4 mmHg, respectively (differences not significant). Levels of IL-6, t-PA antigen and hs-CRP were reduced with both combination therapies at week 12 (figure). Significantly more patients discontinued because of adverse events in the amlodipine group (18.2%) than in the combination-therapy groups (4.2% and 3.5%) over the 6 months treatment period.



Conclusions: Valsartan 160 mg+HCTZ 25 mg is an effective and well-tolerated therapy in this patient population with possible beneficial effects on vascular markers.

Key Words: Combination Therapy, High-Risk Patients, Vascular Markers

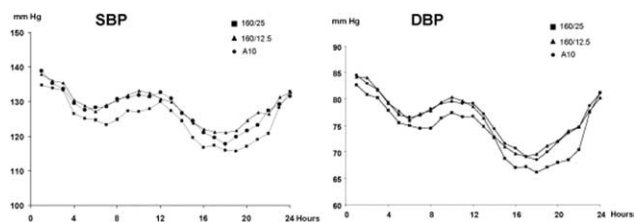
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24-HOUR AMBULATORY BLOOD-PRESSURE EFFECTS OF VALSARTAN + HYDROCHLOROTHIAZIDE COMBINATIONS COMPARED WITH AMLODIPINE IN HYPERTENSIVE PATIENTS AT INCREASED CARDIOVASCULAR RISK

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In a randomised, double-blind trial, the effects on 24-hr ABP of the combination valsartan 160 mg od and hydrochlorothiazide (HCTZ) 25 or 12.5 mg during 24 weeks of therapy were compared with the effects of amlodipine 10 mg monotherapy (group A10) in 474 stage-II hypertensive patients with additional cardiovascular risk factors. After a two-week single-blind placebo run-in period, patients were randomised to receive valsartan 160 mg od or amlodipine 5 mg od. At Week 4, HCTZ 12.5 mg (group V160/HCTZ12.5) and 25 mg (group V160/HCTZ25) were added to the valsartan groups and in the A10 patients the amlodipine dose was force-titrated to 10 mg od.

All treatments reduced BP as well as night-time and daytime BP levels from baseline. 24-hr SBP was reduced by 15.9 ± 1.0 mmHg (least-squares mean change \pm SE), 19.3 ± 1.0 mmHg and 16.1 ± 1.1 mmHg in the V160/HCTZ12.5, V160/HCTZ25 and A10 groups, respectively and 24-hr DBP was reduced by 9.3 ± 0.6 mmHg, 11.4 ± 0.6 mmHg and 9.6 ± 0.7 mmHg in the three groups. The differences between the V160/HCTZ25 group and the A10 group were significant ($p < 0.05$) for the changes in 24-hr systolic BP as well as for changes in daytime systolic BP and night-time diastolic BP. Control rates defined as ABPM $\leq 130/80$ mmHg were: 48.4%, 60.8% and 50.9% in the V160/HCTZ12.5, V160/25 and A10 groups, respectively; the differences between the V160/HCTZ25 group and the other two treatment groups were significant at $p < 0.05$.



In conclusion, the fixed-dose combination of valsartan 160 mg + HCTZ 25 mg od is an attractive therapeutic option measured on the effects on 24-hr ABPM, night-time and daytime BP reduction and control rates in hypertensive patients at additional cardiovascular risk.

Key Words: Blood-Pressure Load, Circadian Blood Pressure, Control Rates

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HOME VERSUS CLINIC BLOOD PRESSURE MONITORING IN THE ASSESSMENT OF THE ANTIHYPERTENSIVE EFFICACY OF COMBINATION PHARMACOTHERAPY

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Self-blood pressure monitoring at home (HBP) is regarded as an important adjunct to clinic measurements (CBP) in hypertensive patients. This study compared HBP with CBP measurements in the assessment of the additional antihypertensive effect of several drugs administered in patients uncontrolled on antihypertensive drug monotherapy.

Hypertensive patients uncontrolled on diltiazem monotherapy (240 mg o.d.) were randomized to receive add-on therapy with the thiazide diuretic (TZD) chlorthalidone (12.5 mg), the dihydropyridine calcium antagonist (DCA) felodipine (5 mg), the ACE inhibitor (ACEI) lisinopril (10 mg), or the angiotensin receptor blocker (ARB) valsartan (80 mg) for 8 weeks. Add-on treatment was doubled if CBP remained uncontrolled after 4 weeks of randomized combination pharmacotherapy. CBP (triplicate measurements) and HBP (3 days, duplicate morning and evening self-measurements) were measured before randomisation and after 4 and 8 weeks using validated automated oscillometric devices A&D 767.

A total of 185 completed the study (mean age 63.9 ± 10.6 years, 43% men). Before randomization average CBP ($158.6 \pm 13.1/86.1 \pm 9.4$ mmHg, systolic/diastolic) was higher than average HBP ($150.3 \pm 13.3/83.0 \pm 8.6$ mmHg) ($p < 0.001$). After 8 weeks of combination pharmacotherapy a significant decline in both CBP and HBP was observed with all drugs ($p < 0.001$, table).

Blood pressure decline achieved by each drug combination (SBP systolic; DBP diastolic; mmHg)

Added drug	N	Clinic SBP	Home SBP	Clinic DBP	Home DBP
TZD	51	22.8 ± 13.1	16.0 ± 10.8	8.5 ± 9.2	5.5 ± 7.6
DCA	36	26.6 ± 17.0	20.5 ± 14.0	9.2 ± 8.5	6.3 ± 6.2
ACEI	50	18.8 ± 15.7	16.6 ± 12.0	6.5 ± 10.6	6.5 ± 6.7
ARB	48	20.9 ± 13.8	15.2 ± 10.8	6.7 ± 9.2	4.5 ± 6.3

There was no statistically significant difference in the additive antihypertensive effects of the four drug classes assessed using either CBP or HBP measurements.

HBP monitoring is a useful alternative to CBP for the assessment of the additional antihypertensive effect of drugs administered in hypertensive patients uncontrolled on monotherapy.

Key Words: Combination Treatment, Diltiazem, Self-Home Blood Pressure Monitoring

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AN EFFICACY EVALUATION OF OLMESARTAN MEDOXOMIL/HYDROCHLOROTHIAZIDE (OM/HCT) AND AMLODIPINE BESYLATE/BENAZEPRIL HYDROCHLORIDE (AM/BN)

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Most hypertensive patients require more than one agent in order to achieve adequate blood pressure (BP) control. Fixed-dose combination antihypertensive treatments such as OM/HCT and AM/BN have advantages over monotherapy including increased efficacy, reduced side effects and lower costs. The aim of this review is to compare the efficacy of OM/HCT with AM/BN in similarly designed placebo-controlled factorial studies. MEDLINE, EMBASE and BIOSIS searches identified 4 randomized, double-blind, placebo-controlled, factorial-design efficacy studies. One study compared OM/HCT to OM or HCT monotherapy (Chrysant et al, *Am J Hypertens* 2004;17:252-9) and 3 studies compared