



9A.04 CAN MOUNTAIN SICKNESS SYMPTOMS BE PREDICTED ON THE BASIS OF BLOOD COAGULATION PARAMETERS?

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Objective: The present study was performed to investigate the possible occurrence of global changes of blood coagulation (thromboelastometry) during exposure to high altitude hypoxia, and their relation with the occurrence of mountain sickness symptoms (quantified by the Lake Louise Score, LLS), in the frame of the HIGH altitude Cardiovascular Research(HIGHCARE) project at Everest base camp (BC,5400 m).

Design and Method: All participants (n=47;40±9 yrs) to HIGHCARE expedition underwent baseline clinical and instrumental evaluation at sea level(baseline), the day after reaching 3400 m by helicopter (Namche), after acute (BC1) and prolonged (2 weeks,BC2) exposure at 5400 m. Thromboelastometry (ROTEM Pentapharm, Munich, Germany), was performed on simple recalcified citrated plasma (spontaneous contact activation,NATEM) and upon addition of ellagic acid (intrinsic pathway,INTEM). All clinical and instrumental parameters were then entered in stepwise multivariate regression analysis to select independent predictors of LLS, which was determined in each study conditions.

Results: At Namche 23 out of 47 subjects had no symptoms of high altitude sickness (LLS=0) with LLS>3 in 2 subjects. At BC1 40 subjects had symptoms, 14 reporting a LLS >3 (0 in only 7 subjects). After chronic adaptation(BC2), only 17 had symptoms (LLS >3 in 1 subject). Oxygen saturation (beta =-0.859;p<0.0001), haematocrit (beta=0.228;p<0.004), expedition day (-0.263;p<0.006) and maximum velocity of clot formation at INTEM assay (beta=0.176;p<0.013) were identified as independent predictor of LLS at stepwise regression analysis. A score index, calculated on the basis of the four predictors corrected for regression coefficients, was then retrospectively used to stratify subjects in three classes of mountain sickness risk, according to data measured at Namche (acute hypoxia exposure).One out of 12 subjects in the first tertile versus 12 out of the remaining 35 subjects had LLS>3 at BC1(p<0.001).

Conclusions: INTEM assay revealed a reduced activity of coagulation intrinsic pathway at altitude. However the maximum velocity of clot formation at INTEM assay was selected as a positive independent predictor of LLS, indicating a link between rheological changes and adaptation to altitude.

9A.05 PROGNOSTIC VALUE OF BLOOD PRESSURE IN PATIENTS WITH CORONARY ARTERY DISEASE: EVIDENCE FROM THE ACTION TRIAL DATABASE

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The placebo-controlled ACTION trial examined the effects of added treatment with Nifedipine GITS on clinical outcomes in patients with stable symptomatic coronary artery disease (CAD). A retrospective further analysis of the database from ACTION has now evaluated the inter-relationships between a number of blood pressure (BP) parameters and subsequent cardiovascular outcomes.

Analyses were performed using multivariate Cox proportional hazard models to test the relationships between quintiles/quartiles of baseline BP and achieved BP after 6 weeks of the trial (by which time titration of both placebo and nifedipine GITS was complete).

A statistically significant (p<0.001) and consistent trend between baseline systolic BP and risk was shown for all the major endpoints pre-specified in the trial design (with the exception of coronary angiography). Thus, the lowest risk for myocardial infarction (MI) was apparent in those patients with baseline systolic BP <120mmHg. A similar (more pronounced) trend was shown for stroke: the respective hazard ratios in the lowest quintile of systolic BP compared to the referent highest quintile (SBP>150mmHg) were 0.45 (0.28,0.72) for stroke and 0.79 (0.60,1.02) for MI. Adjusting the model for treatment and for the use of antihypertensive therapy at baseline did not modify the outcomes in any statistical or meaningful fashion. Comparable results were obtained for the analysis of the data using the on-treatment BP levels at 6 weeks.

Similar results were obtained for pulse pressure (PP) with consistent trends for all major endpoints across the quintiles of PP. The hazard ratios in the lowest quintile of PP (<45 mmHg) were 0.58 (0.35,0.94) and 0.70 (0.53,0.94) for stroke and MI respectively.

For diastolic BP the results were less clear with a significant and consistent trend only observed for debilitating stroke.

Because of the retrospective nature of these analyses, the findings must be interpreted cautiously. However, there was no evidence to suggest that treatment in patients with baseline systolic BP <120mmHg was associated with a significant increase in cardiovascular risk.

9A.06 FIRST-LINE TREATMENT WITH ALISKIREN/AMLODIPINE COMBINATION PROVIDES ROBUST BLOOD PRESSURE REDUCTIONS IN PATIENTS WITH SEVERE HYPERTENSION

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Objective: To assess the effectiveness of initiating therapy with aliskiren/amlodipine (ALI/AML) compared to AML alone in reducing blood pressure (BP) in the subgroups of patients with severe (baseline msSBP: ≥180 to <200) and moderate BP (baseline msSBP ≥160 to <180 mmHg). **Methods:** This was an 8-wk, multicenter, randomized, double-blind study. After a 1 - 4-wk washout period, all eligible patients (msSBP ≥160 to <200 mmHg) were randomized (1:1) to receive a once-daily dose of ALI/AML 150/5 mg or AML 5 mg for 1 wk followed by double the initial dose (ALI/AML 300/10 mg or AML 10 mg) for 7 wks. Summary statistics for blood pressure reductions were produced and treatment comparisons were made using ANCOVA with treatment and region as factors, and corresponding baseline BP as a covariate. **Results:** Mean baseline BP was 187.1/97.1 and 167.7/94.2 mmHg for patients in the severe and moderate subgroups. Baseline BP levels were similar for both treatment groups. At Wk 8 endpoint, mean BP reductions from baseline were -49.2/-18.1 and -35.6/-15.4 mmHg with ALI/AML combination and -39.7/-13.6 and -29.5/-12.3 mmHg with AML alone in patients for the severe and moderate subgroups, respectively. Differences in least-square mean reductions in BP for ALI/AML vs. AML were significant for both subgroups (Table; p<0.01 from ANCOVA). The percentage of patients achieving BP control at Wk 8 was also significantly greater with ALI/AML vs. AML alone for both subgroups (Table; p<0.05). The overall incidence of AEs was similar between ALI/AML and AML groups. Peripheral edema was the most commonly reported AE, with lower incidence in ALI/AML (14.4%) than AML (18.3%). **Conclusion:** In patients with severe or moderate BP, first-line use of ALI/AML provided greater BP reductions and higher rates of BP control compared to AML alone. ALI/AML combination represents an important potential first-line treatment option for patients with moderate to severe hypertension.

	Severe hypertension (baseline SBP ≥ 180 to <200 mmHg) n=92		Moderate hypertension (baseline SBP ≥ 160 to <180 mmHg) n=371	
	ALI/AML n=45	AML n=47	ALI/AML n=188	AML n=183
LSM change in msSBP, mmHg \pm SE	-47.45 \pm 2.264**	-37.36 \pm 2.103	-35.30 \pm 1.043***	-28.83 \pm 1.062
LSM change in msDBP, mmHg \pm SE	-18.57 \pm 1.390**	-14.02 \pm 1.291	-15.66 \pm 0.616***	-11.95 \pm 0.626
BP control, n (%)	25 (55.6)*	16 (34.0)	131 (69.7)**	97 (53.0)

SE, standard error; LSM, least squares mean.
 * $p < 0.05$ vs. AML; ** $p < 0.01$ vs. AML; *** $p < 0.0001$ vs. AML.
 BP changes were analyzed by an ANCOVA model with treatment and region as factors, and the respective baseline BP as a covariate. BP control was analyzed using a logistic regression model with treatment and region as factors and baseline msSBP as a covariate.

9A.07 THE USE OF COMBINATION THERAPY BENEFITS ALL HYPERTENSIVE PATIENTS (POOR AND EXCELLENT RESPONDERS TO MONOTHERAPY) WHOSE BP WAS UNCONTROLLED

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Objective: Patients with a poor antihypertensive response to a given drug therapy are either switched to another agent or have a second agent added. We evaluated the response to continued mono- or add-on therapy in poor, good or excellent responders to valsartan (VAL) monotherapy (mono).

Design and Method: The data from two large hypertensive studies in patients whose blood pressure (BP) was uncontrolled (diastolic (DBP) > 90 mmHg) after 4 weeks on VAL mono (160–320 mg) was evaluated as to whether adding hydrochlorothiazide (HCTZ) to VAL (160–320 mg) results in greater reductions in BP than simply maintaining the patient on mono. A total of 4,567 (age = 54.8 ± 11 yrs; BP = $160.1 \pm 12/100.9 \pm 4$ mmHg; BMI = 29.4 ± 5 kg/m²) patients qualified after the single-blind run-in period and were subsequently randomized (double-blind) to continued VAL mono (160–320 mg), VAL (160–320 mg)/HCTZ (12.5 mg) low or VAL (160–

320 mg)/HCTZ (25 mg) high dose combination therapy for 8 additional weeks. At the end of the single blind run-in period patients were classified as either poor (systolic BP > 0 mmHg from baseline, n = 25%), good (SBP < 0 to -10 mmHg from baseline, n = 34%) or excellent initial responders (SBP > -10 mmHg from baseline, n = 41%) to VAL monotherapy.

Results: Initial poor-responders had the largest reductions in SBP on VAL mono (-13.7 mmHg); Val/HCTZ low (-19.3 mmHg) and Val/HCTZ high (-22.7 mmHg) doses with absolute BP levels at study end being similar to the initial good and excellent responder patients (Figure). Initial excellent responders to VAL monotherapy had only small additional reductions in SBP to continued VAL mono (-2.3 mmHg), patients randomized to Val/HCTZ low (-9.2 mmHg) and Val/HCTZ high (-10.8 mmHg) demonstrated additional reductions in BP. All 3 BP responder categories benefited from add-on HCTZ in a dose-related manner.

Conclusions: Classifying hypertensive patients as either poor, good or excellent responders to VAL monotherapy had little predictive value in determining which patients benefited from adding HCTZ to VAL mono.

