rpth research & practice in thrombosis & haemostasis

ABSTRACTS

ARTERIAL THROMBOEMBOLISM

ACUTE CORONARY SYNDROMES

PB0001 | Clopidogrel Resistance and P2y12 Receptor Gene Polymorphisms in Patients with Non-ST Elevated Acute Coronary Syndrome

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Background: The prevalence of antiplatelet drug resistance during antiplatelet therapy varies from 20% to 45% for clopidogrel usage. The reasons and risk factors of this state are not completely known. As P2Y12 receptor plays key role in platelet activation and data on its role for clopidogrel resistance is inconsistent the study of this gene polymorphisms is actual and perspective.
Aims: The aim of this study was to investigate the association of P2Y12 polymorphisms and clopidogrel resistance due to the platelet aggregation at patients with non-ST elevated acute coronary syndrome.
Methods: 200 patients with non-ST elevated acute coronary syndrome from Bukovinian region (Ukraine) were genotyped in order to the H1(744T) and H2 (744C) haplotypes of the P2Y12 receptor gene. Aggregation studies with J.Born method. Decreasing of ADP-induced platelet aggregation < 10%, 10-29%, and ≥30% compared to the basal level considered as "clopidogrel resistance", "partial clopidogrel resistance" or "clopidogrel sensitiveness".
Results: In addition to specific genotype presentation (H1/H1; H1/H2; H2/H2) we have divided patients into the groups: homozygotes with H1/H1 (68 persons, 34.0%), homozygotes with H2/H2 mutation (18 persons, 9.0%) and heterozygotes H1/H2 (114 persons, 57%).
The spontaneous and ADP-induced aggregation of platelets after 7 days of dual antiplatelet therapy was significantly higher in H1/H2 and H2/H2 genotypes in compare to the H1/H1 genotype (p,p1< 0.05). The time of aggregation was shortest in mutant H2/H2 genotype (p< 0.05). The higher incidence of "clopidogrel resistance" and "partial clopidogrel resistance" patients was registered in H2/H2 genotype (odds ratio - 9.72), and, also, in H1/H2 genotype (odds ratio - 3.55), Mantel-Haenszel χ^2 - 20.62, p< 0.001. Generalized odds ratio (Agresti's alpha) was 3,746 [CI 95% 2,122-6,613].
Conclusions: This study supports the association of P2RY12 gene polymorphisms with platelet aggregation level, platelet dysfunction and higher incidence of "clopidogrel resistance" in genotypes H2/H2 and H1/H2 at patients with non-ST elevated acute coronary syndrome.

PB0002 | Improved Antithrombotic Activity and Diminished Bleeding Side Effect of a PEGylated αIIbβ3 Antagonist, Disintegrin

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Background: The applicability of protein drugs is confined by protein degradation and rapid elimination. PEGylation of polypeptides improves protein stability by sterically obstructing the degradation by serum proteases and reduces renal clearance by the increased mass.
Aims: To produce a pharmaceutically modified disintegrin derivative with improved physicochemical, pharmacokinetic, and antithrombotic properties.
Methods: We utilized NH_2-terminal-specific PEGylation technique to modify the disintegrin derivative KGDRR. We compared the antithrombotic activities of intact KGDRR (RR) and PEGylated KGDRR (P-RR) both *in vitro* and *in vivo* systems. In addition, the functional half-life in inhibiting platelet aggregation and the tendency in causing bleeding side effect were investigated.
Results: P-RR exhibited optimal potency in inhibiting platelet aggregation of human and mouse platelet-rich plasma induced by collagen or ADP *in vitro* with a lower IC_{50} than the intact derivative RR. In illumination-induced mesenteric venous thrombosis model, RR and P-RR efficaciously prevented occlusive thrombosis in dose-dependent manner. In rotational thromboelastometry assay, P-RR did not induce hypocoagulation in human whole blood even given at a higher concentration (30 μg/mL), while RR slightly prolonged clotting time. However, at equally efficacious antithrombotic dosages, both RR and

cohort and 5 (rate 1.3 x 100 patient-years) in DOAC cohort (Relative Risk 1.9; 95% CI 0.6-7.4; p=0.2).

The univariate logistic regression analysis including both cohorts showed that patients with recurrent ICH were more frequently males, hypertensive, with a history of previous Stroke/TIA and older than patients without recurrence. None of these differences reached statistical significance. VKA patients showed a higher (but not statistically significant) risk of recurrence with respect to DOAC patients (OR 1.9) (95% CI 0.7-6.7; p=0.2).

Conclusions: A trend toward fewer ICH recurrences was detected among patients who resumed DOACs after ICH in comparison to the previously reported rate of patients on warfarin.

PB2071 | More Precise Dosing of Acenocoumarol for Better Control in Patients Aged above 80 Years, a Randomized Controlled Pilot Study

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Background: Many elderly patients are confined to treatment with vitamin K antagonists (VKA) instead of direct oral anticoagulants (DOACs). However, quality of VKA treatment declines with age. At the same time, the average VKA dose requirement decreases with age. This increases the day-to-day variation in VKA dose.

Aims: To obtain information on the effect size for, and feasibility of a full scale trial to assess whether more precise dosing of acenocoumarol increases the quality of VKA treatment in elderly patients.

Methods: In this pilot study we randomized 80 patients aged 80 and above who used 0.5-2.0 mg acenocoumarol daily to either regular dosing in 1.0 mg acenocoumarol increments, or more precise dosing with 0.5 mg increments. We compared changes in time in therapeutic range (TTR) and International Normalised Ratio (INR) variability (VGR) between the two treatment groups, in the six month before and six months during study period. In addition changes in anticoagulation-related quality of life were assessed using PACT-Q.

Results: Patients were aged 84±3 years. Overall baseline TTR was 61% (± 19.2). TTR had improved in both groups, but somewhat more in the intervention group (3.4%, 9.0 vs 5.6; 95% CI -3.7 to 10.5). The INR variability also improved, slightly more in the 0.5 mg group. PACT-Q convenience remained constant in time and did not differ between groups. PACT-Q satisfaction decreased, almost equally, in both groups. Four dosing errors related to dose increments occurred, three in the intervention and one in the control group.

Conclusions: Although more precise dosing of acenocoumarol leads to a slightly better quality of anticoagulation, this effect is too small to convey a relevant clinical benefit. We will not proceed with a full scale RCT. Notably, the overall decrease in treatment satisfaction should be considered when performing future anticoagulation studies in this population.

PB2072 | Time in Therapeutic Range During Therapy with Vitamin K Antagonists Is Lower in Women than in Men and Is Not Explained by Differences in Age

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Background: Adherence and efficacy of anticoagulant therapy with vitamin K antagonists (VKA) is evaluated by Time in Therapeutic Range (TTR). Percentage TTR above 65% is considered appropriate. A few reports suggest that TTR in women might be lower than in men, and hypothesize that women on VKA, being usually older than men, are more sick and thus less adherent. Since not all patients are amenable to direct oral anticoagulants, persistence on VKA for these patients is a necessity for preventing embolism. Thus, understanding what affects TTR is relevant since it could promote preventive measures to ensure effective anticoagulation.

Aims: To ascertain whether women have a lower TTR than men and to study which factors affect TTR among patients with atrial fibrillation and mechanical valves undergoing chronic VKA therapy at a University Hospital Anticoagulant Clinic.

Methods: We retrospectively studied 2428 patients on VKA (1168 women and 1260 men). Differences were analyzed by ANOVA and t-test or non parametric tests, as appropriate. Influence of variables on TTR was evaluated by multiple regression analysis.

Results: The Table shows main characteristics of patients. Women were older than men (81±11.2 vs 78±12.3 years, p< 0.0001), had a lower TTR (65±20.3 vs 69±19.8%, p< 0.0001), but did not differ by extent of comorbidity (Charlson Comorbidity Index): median score was 5 in both groups. In multiple regression analysis, sex, type of VKA and indication for anticoagulation (atrial fibrillation or mechanical valves) weighted slightly on TTR in all patients, while duration of anticoagulation and age did not.

TABLE 1 Characteristics of patients on VKAs by sex

Sex	Number	TTR % Mean (SD)	Age Years Mean (SD)	CCI index Median (range)	Time on VKAs Days Mean (SD)	Type of VKAs % on warfarin	Indication for anticoagulation % atrial fibrillation
Men	1260	69 (19.8)	78 (12.3)	5 (0-14)	2676 (1888.9)	88	73
Women	1168	65 (20.3)	81 (11.2)	5 (0-10)	2792 (1948.5)	88	70

Conclusions: We confirm that women have lower TTR than men. Age did not concur to determine TTR values, nor did comorbidity. We could not identify a variable among those studied that could extensively explain the observed difference in TTR between men and women. Further studies should perhaps focus on dietary habits and/or genetics.

PB2073 | Towards Individualizing Apixaban Therapy in Elderly Patients Through Thrombin Generation

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Background: Apixaban treatment in elderly patients is challenging because health conditions and hypercoagulability status modify its safety profile. As monitoring apixaban levels could be insufficient, thrombin generation assay (TGA) might better predict the anticoagulant effect.

Aims: To determine correlation between apixaban plasma concentration (AXa) and TGA in two groups: under (*≤70y*) and over 70 years old (*>70y*), and estimate inter-individual variability (CVi) in patients *>70y*.

Methods: Patients with atrial fibrillation taking apixaban 2.5 or 5 mg BID were enrolled after obtaining ethical approval and informed consent. Blood was taken at peak and trough. AXa was determined with apixaban calibrated chromogenic anti-FXa assay. TGA parameters: peak height (PH), endogenous thrombin potential (ETP) were assessed by calibrated automated thrombogram activated with tissue factor 5 pM (Thrombinoscope). Statistics: Spearman's correlation, Shapiro Wilks, Levene, Wilcoxon, Student tests.

Results: 39 patients (27 *>70y*) received 2.5 mg and 42 patients (27 *>70y*) received 5 mg. Patients on 2.5 mg: *>70y* achieved higher AXa at trough and peak compared with *≤70y* ($p < 0.001$); ETP and PH were significantly lower in *>70y* compared with *≤70y*, at trough and peak. Patients on 5 mg: in *>70y* AXa was higher at trough and peak, compared with *≤70y* ($p < 0.002$). ETP and PH were lower in *>70y*, without significant difference, comparing with *≤70y*. In patients*>70y* CVi for AXa with 2.5 mg was higher than for 5 mg (peak 46/41%, trough 60/51%). CVi for ETP with 5 mg was lower than for 2.5 mg (peak 33/41%, trough 35/38%).

Conclusions: Elderly patients achieved higher apixaban levels and lower ETP, compared with the younger age group at both doses. Nevertheless, at 5 mg ETP showed no difference between age groups reaching similar values irrespective of apixaban's plasma level. TGA reflects the anticoagulant effect depending on each patient's coagulation status. It could help individualizing apixaban treatment with moderate inter-individual variation.

PB2074 | Anticoagulant Management Strategies in Cancer Patients with Atrial Fibrillation in Daily Clinical Practice

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Background: Few small studies have evaluated the optimal anticoagulant management of atrial fibrillation (AF) in patients with cancer and direct comparative studies between different oral

TABLE 1 Primary anticoagulant strategy of cancer patients with AF

		2012-2013	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	Total	No anticoagulants
Cohort 1 N=181	No anticoagulants	3	1	13	7	13	11	48	27%
	LMWH	0	0	4	3	6	6	19	
	VKA	3	11	21	24	13	12	84	
	DOAC	0	0	0	3	9	18	30	
Cohort 2 N=361	No anticoagulants	11	3	9	9	9	14	55	15%
	LMWH	1	0	3	1	4	1	10	
	VKA	27	36	53	44	50	58	268	
	DOAC	0	0	1	1	7	19	28	