(age, BMI and presence of amiodarone or metabolic inducers) and genetic variables (genetic variants in CYP2C9, VKORC1, CYP4F2 and APOE genes). Our objective was to test the performance of the EU-PACT algorithm in our cohort of patients. Assess the influence of factors included in our algorithm but not considered in the EU-PACT algorithm, specifically CYP4F2 and APOE variants, and concomitant use of metabolic inducers.

Patients (or Materials) and Methods: We evaluated the performance of the EU-PACT algorithm in our cohort (HULP) using coefficient of determination ($R^2$). To investigate the contribution of variants in CYP4F2 and APOE, and concomitant metabolic inducers, we compared the real acenocoumarol doses of patients with these variables and those doses predicted by both models. A third model was built using as independent variables the dose predicted using EU-PACT algorithm in our cohort, APOE and CYP4F2 variants, and concomitant metabolic inducers. Paired McNemar’s test was used to compare both $R^2$.

Results: Variability explained by the EU-PACT’s algorithm when applied to our (HULP) cohort was 44.4%. The real mean dose in patients with at least 1 of the evaluated variables (CYP4F2, APOE variants or metabolic inducers) was 19.3 (8.1) mg/week while the dose calculated by the HULP-algorithm was almost the same (19.0 [5.4] mg/week) and the EU-PACT’s model underestimates almost 3 mg (16.0 [6.2] mg/week), $P < 0.001$. The third model, evaluating the contribution of CYP4F2 and APOE variants and concomitant metabolic inducers, is able to increase the $R^2$ from a 44.4% observed with the EU-PACT algorithm to 47.5% ($P < 0.05$).

Conclusion: EU-PACT shows a reasonable performance in an independent cohort with VTD. Inclusion of other known genes involved in high dose requirements as CYP4F2 and ApoE and enzyme inducer drugs, all included in HULP algorithm, seems to improve prediction of acenocoumarol dosing.

Disclosure of Interest: None declared.

PP128—IMPACT OF VARIABILITY IN THE BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) GENE IN EATING DISORDER PATIENTS

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Introduction: Eating behavior has been shown to be affected by the brain-derived neurotrophic factor (BDNF). In the present work, we have aimed to investigate whether BDNF genetic variability may influence physiological and psychopathological features in patients with eating disorders (ED) and/or modulate the risk for the disorder.

Patients (or Materials) and Methods: One hundred twenty unrelated female patients with anorexia or bulimia nervosa (AN, BN) and 125 healthy controls were genotyped for BDNF single nucleotide polymorphisms (SNPs). Associated psychopathological characteristics were assessed by the EDI-2 and SCL-90R inventories.

Results: With regard to physiological parameters, the rs16917237 TT genotype was associated with increased minimum weight (60.6 [19.3] vs 50.4 [11.9] kg; $P < 0.05$) and BMI (23.3 [7.9] vs 19.3 [4.1]; $P < 0.05$) in the whole population of patients with ED. The risk study showed that only the rs11030119 AA genotype increased the risk for AN (OR = 5.23 [1.32–20.98], $P = 0.02$), although the association lost significance after Bonferroni correction. AN patients who harbored the -270CC genotype scored higher than CT carriers in the Interpersonal Distrust scale of the EDI-2 questionnaire (6.9 [4.4] vs 2.9 [3.6]; Bonferroni $P < 0.05$). In the same manner, carriers of rs10835210 CC wildtype genotype showed higher scores for the Drive for Thinness scale (13.5 [5.0] vs 9.6 [6.0] for patients with the variant allele; Bonferroni $P < 0.05$). Finally, the haplotype study showed that 2 combinations (haplotypes *4 and *7) showed significantly higher scores in several scales of the EDI-2 and SCL-90R inventories than with those most common haplotype *1.

Conclusion: Variability in the BDNF gene locus may contribute to psychopathological features that are commonly found in ED patients.

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Disclosure of Interest: None declared.

PP129—TIME-TO-ACHIEVE STABILITY OF ANTICOAGULATION IS DECREASED IN ABCB1 MUTATED PATIENTS TREATED WITH ACENOCOUMAROL

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Introduction: Acenocoumarol is an oral anticoagulant of the coumarin type. These anticoagulants have a narrow therapeutic index and are characterized by a large interpatient variability that can be explained by numerous factors, including genetic factors. Dose variability due to polymorphisms in the VKORC1 and the CYP2C9 genes has been well characterized. The aim of our study was to investigate the potential association between ABCB1 polymorphisms and the time-to-achieve stability during acenocoumarol treatment.

Patients (or Materials) and Methods: We conducted a prospective observational study on 115 hospitalized patients, aged 18 years and over and starting acenocoumarol. Collected data included sex, age, anticoagulant indication, INR measurements, acenocoumarol doses, comorbidities, comediations, and genotype (ABCB1 c.3435C>T and c.2677G>T/A). Patients were followed from the date of the first acenocoumarol administration until time-to-achieve stability or the end of the observation period of 35 days. Time-to-achieve stability was defined as the first 3 consecutive INR measurements within the
PP130—EVALUATION OF THE INFLUENCE OF CYTOCHROME P450 OXIDOREDUCTASE (POR) IN THE STABLE DOSE OF ACENOCOUMAROL

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Introduction: Several pharmacogenetic algorithms have been developed to achieve the desired acenocoumarol therapeutic range as soon as possible to reduce the risk of hemorrhagic events or progression of the thrombotic disease. The main SNPs recognized to influence the adequate acenocoumarol dosing are located in CYP2C9, VKORC1, the thrombotic disease. The main SNPs recognized to influence the adequate acenocoumarol dosing are located in CYP2C9, VKORC1, CYP4F2 and APOE genes (Borobia et al. PLoS One 7(7):e41360). POR is required for drug metabolism by all microsomal cytochrome P450 enzymes and has been arisen their influence in warfarin dose. Our objective is to investigate the influence of POR genetic variants on acenocoumarol dosing.

Patients (or Materials) and Methods: Patients with thromboembolic disease, atrial fibrillation, and heart valve replacement were prospectively recruited. Blood samples were taken for genotyping genetic variants of VKORC1 (rs9923231), CYP2C9 (*2, *3, *2/*3), CYP4F2 (rs1057910), CYP4F2 (rs2108622), APOE (rs7412), and POR (rs1057868 and rs2868177). Demographics (sex, age, body weight, and height) as well as acenocoumarol stable dose, INR, and concurrent medications were also recorded. The influence of POR genetic variants on acenocoumarol stable dose was ascertained using a generalized linear model (GLM). In a baseline GML model an algorithm for dosing was developed including clinical factors (age, body mass index [BMI], pathology, and concomitant drugs) and VKORC1, CYP4F2, and APOE genetic variations. A second algorithm was developed adding to the baseline GML POR SNPs as independent factors including significant interactions with other genetic variants. Paired McNemar’s test was used to compare the R² of both models to evaluate POR SNPs contribution.

Results: A total of 282 Caucasian patients were included (147 with thromboembolic disease, 68 with atrial fibrillation, and 67 with heart valve replacement). Genetic information, including PORxCYP2C9 and PORxCYP4F2 interactions were introduced in the GML. Also demographic and clinical information were added. Only CYP2C9 *1/*1x3POR G/G (rs2868177) and CYP2C9*1/*2xPOR G/G (rs2868177) interactions reached the statistically significance (P = 0.04 and 0.018, respectively). Adding these interaction to the algorithm including age, BMI, pathology, enzyme inducers, amiodarone treatment, CYP2C9 *1/*3, CYP2C9 mut/mut (*2/*2, *2/*3 and *3/*3), VKORC1 A/G, VKORC1 A/A, CYP4F2 TT and APOE T/T genotype, R4* increased from 53.6% to 56.3%. This difference in R² do not reached statistical significance (P = 0.50).

Conclusion: POR (rs2868177) modulate the influence of CYP2C9 genetic variants on acenocoumarol doses, but its global influence appears to be low.

Disclosure of Interest: None declared.

PP131—INTERACTION BETWEEN POLYMORPHISMS IN OCT2 AND MATE1 AND METFORMIN RENAL CLEARANCE

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Introduction: The objective of the study was to determine the renal clearance of metformin in healthy Caucasian volunteers with and without the polymorphism c.808G>T (rs316019) in OCT2 and the relevance of gene–gene interactions between c.808 (G>T) and the promoter SNP g.-66T>C (rs2252281) in MATE1 and between c.808 (G>T) and the OCT1 reduced-function diplotypes.

Patients (or Materials) and Methods: Fifty healthy volunteers genotyped for the c.808 G>T were enrolled in the study. Thus, there were 25 GG, 20 GT, and 5 TT. The pharmacokinetics of a 500-mg single oral dose of metformin was studied.

Results: The renal and secretory clearance of metformin was increased for the volunteers with minor alleles in c.808 (G>T) who also were homozygous for the reference in the promoter variant g.-66 T>C in MATE1: Crenal: GG, GT, TT: 28.1 L/h, 34.5 L/h, and 44.8 L/h, P = 0.004; Csec: GG, GT, TT: 21.4 L/h, 27.8 L/h and 37.6 L/h, P = 0.005. Individuals heterozygous for both c.808 (G>T) and g.-66 T>C variants metformin renal and secretory clearance was reduced compared with reference individuals with the g.-66 T>C genotype: Crenal: 34.5L/h, 28.3 L/h, P = 0.022; Csec: 27.8 L/h 21.6 L/h, P = 0.022.

Conclusion: Counteracting effects of the genetic variations OCT2 c.808 (G>T) and MATE1 g.-66 T>C on the renal elimination of metformin has been demonstrated. The results suggested that OCT2 c.808 (G>T) has a dominant geno- to pheno-type correlation. But also that the genetic variation in MATE1 g.-66 T>C can counteract the increased clearance of metformin associated with OCT2 c.808 (G>T).

Disclosure of Interest: None declared.

PP132—CONTRIBUTION OF GENETIC (CYP3A5, ABCB1 AND POR) AND NON-GENETIC VARIABLES TO THE ORAL TACROLIMUS CLEARANCE IN CHILDREN’S WITH STABLE KIDNEY TRANSPLANT, DURING ADVAGRAF® TREATMENT

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Introduction: There is a large interindividual variation in tacrolimus (TAC) disposition. Genetic information (mainly CYP3A5) has been shown to influence TAC pharmacokinetics and potentially contrib-