therapeutic range (2.0–3.0 + 0.2), encompassing a period of at least 2 weeks and with a maximum difference between the mean daily dosages of 25%. The association between genotypes and time-to-achieve stability was evaluated using survival analysis techniques. A Cox proportional hazard model was used to assess the relative risk of achieving a first period of stability in the follow-up period.

Results: Results showed that time-to-achieve treatment stability with acenocoumarol is decreased significantly for carriers of ABCB1 c.3433TT genotype and extended in wild-type and heterozygous subjects (HR, 2.94 [IC 1.22–7.09]). Similarly, carriers of ABCB1 c.2677GT or TT genotypes reached more rapidly stability than wild-type subjects (HR, 2.15 [IC, 1.07–4.98] and HR, 3.00 [IC, 1.08–8.36], respectively). The other tested polymorphisms (CYP2C9, CYP2C19 and VKORC1) had no influence on the time-to-achieve stability.

Conclusion: Our results suggest for the first time that time-to-achieve stability with acenocoumarol is shorter to reach in carriers of ABCB1 c.3433TT and carriers of ABCB1 c.2677GT/TT combined. Further studies are required to assess whether the identification of ABCB1 genotypes before treatment with acenocoumarol may be useful for a safer and rapid anticoagulation stabilization.

Disclosure of Interest: None declared.

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, CYP4F2, OCT2, and POR (rs1057868 and rs2868177). Demographics (sex, age, body mass index [BMI], pathology, and concomitant drugs) and acenocoumarol stable dose, INR, and CYP2C9 (rs9923231), CYP4F2 (rs1799853 and *3 · rs1057910), CYP4F2 and APOE (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 prospective recruited. Blood samples were taken for genotyping genetic variants of VKORC1 (rs9923231, CYP2C9 (*2 · rs1799853 and *3 · 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, CYP2C9, 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 POR×CYP2C9 and POR×CYP4F2 interactions were introduced in the GLM. Also demographic and clinical information were added. Only CYP2C9 *1/*3×POR G/G (rs2868177) and CYP2C9*1/*2×POR 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 T/T and APOE T/T genotypes, 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.

Conclusion: 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: 34.5 L/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-