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 withacenocoumarol is decreased significantly for carriers of ABCC1 c.3433TT genotype and extended in wild-type and heterozygous subjects (HR, 2.94 [IC 1.22–7.09]). Similarly, carriers of ABCC1 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 withacenocoumarol is shorter to reach in carriers of ABCC1 c.3433TT andcarriers of ABCC1 c.2677GT/TT combined. Further studies are required to assess whether the identification of ABCC1 genotypes before treatment withacenocoumarol may be useful for a safer and rapid anticoagulation stabilization. **Disclosure of Interest:** None declared.

### PP130—EVALUATION OF THE INFLUENCE OF CYTOCHROME P450 2C9/3A5 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, and currently CYP4F2 and APOE genes (Borobia et al. PLoS One 7(7):e41360). POR is required for drug metabolism by all microsomalcytochrome P450 enzymes and has been arisen their influence in warfarin dose. Our objective is to investigate the influence of POR genetic variants onacenocoumarol 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 · rs1799853 and *3 · rs1057910), CYP4F2, and APOE genes. Fifty healthy volunteers genotyped for the c.808 G>T variant, and the increased clearance of metformin associated with OCT2 was studied. Patients (or Materials) and Methods: Fifty healthy volunteers genotyped for the c.808 G>T were enrolled in the study. 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, Lp = 0.004; Crenal: GG, TT: 21.4 L/h, 27.8 L/h and 37.6 L/h, P = 0.005. In 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; CLsec: 27.8 L/h 21.6 L/h, P = 0.022. **Conclusion:** Counteracting effects of the genetic variations OCT2 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-

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ute to the optimization of its dosing. The aim of this study was to evaluate the influence of genetic and clinical factors on TAC pharmacokinetic variability in stable pediatric renal transplant patients.

**Patients (or Materials) and Methods:** This study was nested in a previous Prograf® to Advagraf® conversion clinical trial in pediatric patients (Eudra CT: 2009-017600-90). Tacrolimus pharmacokinetic analysis was performed using a noncompartmental analysis. CYP3A5 (*3 rs776746 C>G), ABCB1 (rs1045642 C>T), POR (*28 rs1057868 C>T and rs2868177 A>G) genotypes were determined by RT-PCR using commercial Taqman® assays. The impact of individual genetic variants on TAC AUC~24 (adjusted by administered dose/kg) was evaluated and an additive unweighted genetic score was build. Multivariate linear regression was performed including genetic (genetic score), demographic, and clinical information as independent variables and TAC weight-adjusted apparent oral clearance as dependent variable.

**Results:** Twenty-one kidney transplant pediatric patients (aged between 4 and 17 years) on stable TAC dose were included (12 males and 9 females). Mean (SD) body weight was 42.85 (15.42) kg. Subjects homozygote for CYP3A5*3 and the carriers of rs1045642, rs1057868, or rs2868177 have higher exposure to TAC than noncarriers (P < 0.05). Genetic score groups was as follows: 0 (Group 1), 1 (Group 2), 2 (Group 3), 3 (Group 4), and 4 (Group 5) genetic variants in CYP3A5, ABCB1, and POR genes. There was an increase in TAC dose/kg adjusted AUC as the number of variants in genetic score increase (trendy P = 0.023) and its value is 288% higher in group 5 compared with group 1. Genetic score, BMI, and concomitant deflazacort use were the only covariates retained in the multivariate regression model that explained 64.4% of weight-adjusted apparent oral clearance total variability. Genetic score, the concomitant deflazacort use and BMI explained 33%, 18%, and 15.4% of the total variability, respectively. Mean absolute error (SD) of the predicted weight-adjusted apparent oral clearance was of 32.82% (23.36%).

**Conclusion:** Genetic score composed by variants in CYP3A5, ABCB1, and POR genes, along BMI and concomitant deflazacort use, explain a clinically significant amount of the variability in oral clearance of tacrolimus. Larger studies are needed to evaluate the potential utility of these variables in predictive TAC dosing algorithms.

**Disclosure of Interest:** None declared.

**PP133—PHARMACOGENETICS OF THE HUMAN SEROTONIN TRANSPORTER**

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**Introduction:** The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) 5-HT is actively cleared from synaptic spaces by SLC6A4, a high-affinity, Na+, and Cl−−dependent transporter localized in pre-synaptic neuronal membranes. This brain 5-HT transporter appears to be a principal site of action of many antidepressant drugs including those of the tricyclic, SSRIs, and SSNRIs class. Many patients with depression are drug resistant. We hypothesized that changes in the transporter protein due to coding single nucleotide polymorphisms (SNPs) in SLC6A4 may affect transporter–drug interactions and thus may contribute to the resistance to antidepressant drug treatment.

**Patients (or Materials) and Methods:** We screened SNP databases (dbSNP, 1000 Genomes, ESP) for SERT gene variants in the human SLC6A4 gene. We specifically focused on nonsynonymous SNPs (nsSNPs), that is, SNPs located in coding regions and resulting in amino acid variation in protein products of genes. The impact of amino acid substitutions caused by nsSNPs in SLC6A4 on the structure and function of SERT was investigated by using 6 different in silico prediction tools. Based on the crystal structure of the bacterial homologue LeuT, a homology model of SERT was performed, and the positions of the amino acid substitutions relative to the proposed substrate binding pocket were identified. A rating scale integrating results from in silico predictions and 3D modeling was applied to extract those nsSNPs with a potentially high impact on the structure and function of SERT.

**Results:** In future in vitro testing in transfected cells, these mutations were inserted in an expression vector by site-directed mutagenesis. For future in vitro testing in transfected cells, these mutations were inserted in an expression vector by site-directed mutagenesis. Results: We identified 6 nsSNPs within the SLC6A4 gene with potential effects on protein function. Two of them (H143Y and R144Q) reside nearby the cytoplasmic pore between helix 2 (H2) and H3, which is involved in substrate binding. In both cases, the mutation results in a charge change and most likely in an altered pore opening of SERT. The third SNP (isoleucine 179 to valine) protrudes into the predicted binding cavity of inhibitor and substrate and therefore may influence substrate–transporter interaction. Another SNP causes the expression of a polar threonine 270 instead of a hydrophobic iso-leucine also projecting into the cytoplasmic pore region. The P339L SNP is expected to destabilize H6, which is involved in substrate and inhibitor binding. The V488M SNP in H10 is close to the extracellular pore and may affect antidepressant binding.

**Conclusion:** By applying a comprehensive screening approach, we identified 6 naturally occurring nsSNPs that are expected to affect substrate (5-HT) and inhibitor (antidepressant drug) binding to SERT. We generated transiently transfected cell lines expressing the 6 variants. Future experiments will have to demonstrate the effects of these nsSNPs on SERT expression and transport function. Of particular interest is the impact of the variants on the inhibition of SERT by antidepressant drugs.

**Disclosure of Interest:** None declared.

**PP134—ESOMEPRAZOLE USED AS A BOOSTER IN A HIV ULTRARAPID CY2C19 METABOLIZER TREATED WITH VORICONAZOLE**

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**Introduction:** Voriconazole, an antifungal agent, is metabolized by CYP450 2C19 (CYP2C19). CYP2C19 activity is modulated by drug–drug interactions (DDI) and genetic polymorphisms. We report a case of therapeutic use of esomeprazole that “boosted” voriconazole plasma concentrations in a CYP2C19 ultrarapid metabolizer HIV patient treated with a CYP2C19 inducer among her antiretroviral treatment (HAART).

**Patients (or Materials) and Methods:** A 35-year-old African female was diagnosed with AIDS in May 2012. A duodenal histoplasmosis and cryptococcosis infections were treated from June 2012 with a 3-week regimen of amphotericin B–fluconazole then oral voriconazole 100 mg BID. HAART was initiated (emtricitabine, tenofovir, and raltegravir). Voriconazole doses were increased and given intravenously (4 mg/kg/12 h IV) as she developed a single large intracranial mass. Several voriconazole trough concentrations (C0) were measured below the therapeutic range (1.0–4.0 µg/mL). CYP2C19 genotype was tested and came heterozygous for the variant allele CYP2C19*17, which is associated with an ultrarapid phenotype. A treatment with esomeprazole 40 mg BID was started and titrated because of severe epigastralgia (hiostolpamocytosis). Subsequent voriconazole C0 were within the therapeutic range. After the proton pump inhibitor was switched to ranitidine, voriconazole C0 were again infratherapeutic despite an increase in voriconazole doses.