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Intra-patient variability of tacrolimus levels and cardiac allograft outcomes

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Introduction

- **Intra-patient variability (IPV) of Tacrolimus (TAC) levels is a risk factor for poor long-term outcomes after renal transplantation.**

  Borra et al. Nephrol. Dial. Transplant. 2010

- **Erratic TAC exposure as assessed by the standard deviation of TAC levels has been shown to predict chronic lung allograft dysfunction and survival**

  Gallager et al, JHLT 2015

- **Measuring the intrapatient variability of immunosuppression drug levels is a tool that can be utilised to measure adherence.**

Aim of the study

- **To investigate whether high IPV of TAC levels within the first year after heart transplantation was associated with poor outcomes.**

Methods

- **Retrospective analysis of heart transplants from August 2007 - April 2015, immunosuppression was induction with Rabbit Anti-Thymocyte Globulin, TAC, Mycophenolate and steroids. Steroids were weaned over 6-12 months and TAC dose was reduced, with target levels:**
  - **Months 1-3: 10-15ng/ml**
  - **Months 3-6: 8-11ng/ml**
  - **Months 6-12: 7-10ng/ml**
  - **Then reduced to 5-7ng/ml thereafter.**
- **Of the 147 transplanted, we excluded 65 patients who either died (n=32) or had TAC discontinued (n=34) within 1 year after transplantation.**
- **Coefficient of variance (COV) was defined as standard deviation / mean of TAC levels taken at monthly intervals for the 1st year after transplant. High variability (HV) was defined as a COV greater than the median.**
- **The proportion of time in therapeutic range was analysed**
- **Outcomes were treated Acute Rejection Episodes (ARE), Renal Impairment (RI) defined as eGFR <60ml/min/1.73m^2, Cardiac Allograft Vasculopathy (CAV) detected by angiography or CT, Donor Specific Antibodies (DSA) and death. Also a composite end-point of medium-long-term outcomes.**

Results

TABLE 1: PATIENTS' DEMOGRAPHICS

	High Variability N - 50	Low Variability N - 31	p
COV (mean ± sd)	0.32±0.07	0.19±0.03	<0.005
Age (years)	42±14	44.7±13	ns
Follow up (months, median, range)	42.8 (13.7-104.8)	47.8 (11.7-105.6)	ns
Gender			
Female	15	6	ns
Male	36	25	
Diagnosis			
Dilated cardiomyopathy	28	19	ns
Ischemic cardiomyopathy	8	3	
Other	14	9	

FIG 1: PERCENTAGE TIME IN THERAPEUTIC TAC RANGE

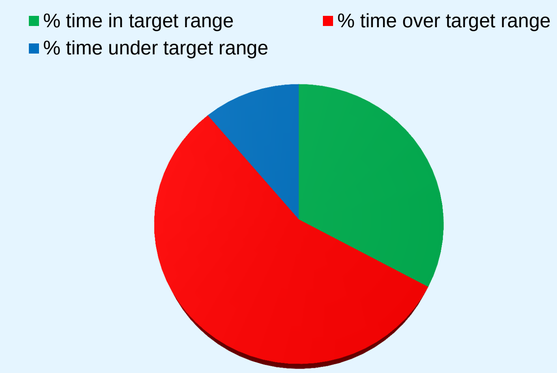
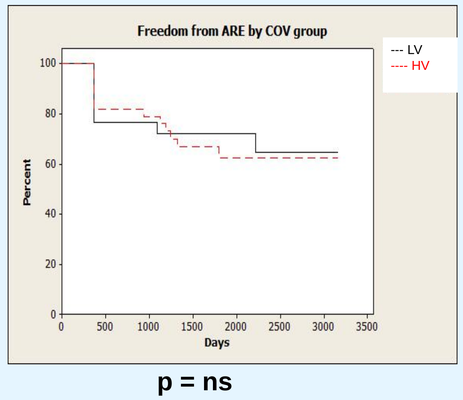


TABLE 2: OUTCOMES IN THE TWO GROUPS

	ARE	CAV	DSA	Death	Renal impairment (RI, eGFR<60 ml/min/1.73m^2)	Composite end point (incidence of RI, CAV, DSA or death)
HV (n= 50)	**15**	9	13	5	29	39
LV (n= 31)	**9**	4	4	1	16	18
P value	ns	ns	ns	ns	ns	0.056

- **The median COV of tacrolimus levels was 0.255**
- **Patients spent 55.9% of the time above the range and 11.2% below range (see fig) suggesting a bias in physician prescribing relative to theprotocol. There was no significant difference between the 2 groups.**
- **There was no significant difference between the HV and non-HV groups in the incidence of poor outcomes (see table 2) but there was a strong trend towards a worse composite outcome.**



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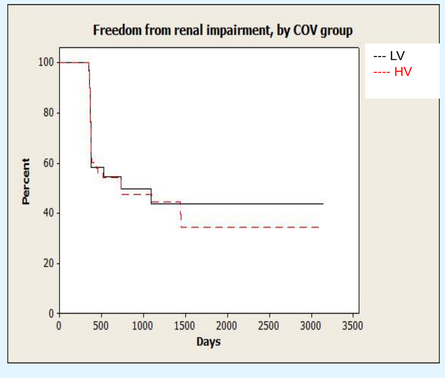

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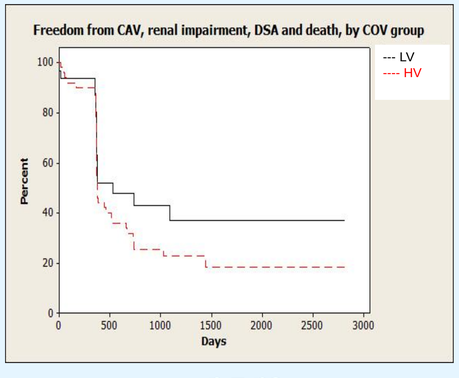

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Conclusions

While not statistically significant there was a trend towards more adverse events for patients with high TAC variability in the composite analysis.