ARE ANTIAGGREGANT AND ORAL ANTICOAGULANT THERAPIES ASSOCIATED WITH BLEEDING AND VASCULAR COMPLICATIONS IN THE FIRST THREE MONTHS AFTER KIDNEY TRANSPLANT?

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BACKGROUND and AIM

Early cardiovascular (CVE) and hemorrhagic events (HE) are a relatively rare, but serious complication of kidney transplantation (KTx), accounting for most deaths and graft failures in the first post-Ktx months.

Nowadays patients on dialysis are proposed for KTx even if they have a high comorbidity burden: they are commonly on antiaggregant (AAT) or oral anticoagulant therapy with vitamin K antagonists (VKA).

Actually KTR represent a very peculiar population in which baseline thrombotic and hemorrhagic risk are both elevated if compared with the general population.

In KTx surgery only few studies are available and report conflicting results on AAT and VKA management in the peri-transplant period.

Moreover patients on a dual antiplatelet therapy are not routinely transplanted in every transplant center and data on this population are lacking.

We performed a retrospective analysis on 911 consecutive KTx in order to analyze the impact of antiplatelet (AAT) and/or oral anticoagulation therapy (VKA) on hemorrhagic and thrombotic - which might be related to their withdrawal- and to identify the main risk factors for early hemorrhagic and thrombotic events.

PATIENTS and METHODS

Included patients

911 adult KTR (51.2 ± 12.5 years, 62.8% males), including deceased donor (95.7%) and living donor (4.3%) KTx. Patients on single antiplatelet therapy, double antiplatelet therapy (two different antiaggregants) and VKA were allowed to KTx.

Antiaggregant and anticoagulant management strategies.

Patients on VKA underwent surgery when PT-INR < 1.5 (FFP and vitamin K). After surgery, if the indication to anticoagulation persisted (ie: mechanical valve), they started enoxaparin (anti-factor Xa target of 0.5 – 0.9 IU/mL). Patients on AAT stopped it on the day of surgery and resumed it after 1-2 months; meanwhile they received enoxaparin (anti-Xa 0.3 – 0.5 IU/mL). All patients received a standard DVT prophylaxis (stockings or enoxaparin). Before 2004, enoxaparin was used at a dosage of 2000-4000 IU qd for DVT prophylaxis and 4000-6000 IU bid for anticoagulation (ie: mech. valve).

Endpoint

Only early HE and CVE were considered as outcomes, being defined as occurring within 90 days after transplantation.

Major HE included death or allograft loss due to major bleeding, need for surgical revision and transfusion of more than 10 blood units.

Major CVE included death for cardiovascular causes, allograft loss for thrombosis, renal arterial or vein thrombosis, AMI, stroke/TIA and deep vein thrombosis with or without pulmonary embolism .

RESULTS - 1

AAT and VKA use at Transplant					Endpoints	
Drug	Prevalence	Prim. Proph.	Sec. Proph.	Vasc. Access	HE (n=21)	CVE (n=32)
Single drug AAT	326 (39,5%)	192 (58,9%)	79 (24,2%)	55 (16,9%)	9 (2,76%)	15 (4,60%)
Aspirin	*266 (81,6%)*	*157 (59,0%)*	*67 (25,2%)*	*42 (15,8%)*	*8 (3,01%)*	*13 (4,89%)*
Ticlopid.	*40 (12,3%)*	*18 (45%)*	*12 (30%)*	*10 (25%)*	*1 (2,50%)*	*2 (5,00%)*
Dipiridam.	*19 (5,8%)*	*16 (84,2%)*	-	*3 (15,8%)*	*0*	*0*
Clopidog.	*1 (0,3%)*	*1 (100%)*	-	-	*0*	*0*
Aspirin+Ticlop.	12 (1,5%)	-	8 (67%)	4 (33%)	0	0
Any VKA	37 (4,5%)	-	29 (78,4%)	8 (21,6%)	4 (10,8%)*	5 (13,5%)*

HE occurred in 21/911 patients (2.3%), including 13 allograft bleeding (4 graft losses) and 1 fatal event.

Risk factors for HE at univariate analysis were HCV positivity, VKA therapy at time of KTx and KTx year class 1998-2003, as compared to more recent years. **AAT at KTx was not associated with HE**, neither with a single drug therapy (50.0% vs. 39.2%, p = 0.595) nor with a double drug therapy (0% vs. 1.5%, p = 0.670).

Patients with an HE were more likely to develop a delayed graft function (66.7% vs. 23.1%, p = 0.0001) and acute rejection (33.3% vs. 12.7%, p = 0.020).

Mean transfused units per patient were higher in patients on VKA (4.0±4.4 vs. 2.0±3.7, p = 0.001) and in those on AAT (2.3±2.8 units on single AAT vs. 2.4±2.5 units on dual AAT vs. 1.7±2.6 units in patients without any AAT; p = 0.003). ***Risk factors for the number of transfused blood units were both AAT and VKA***, age, duration of dialysis, HCV positivity and previous CVE.

CVE occurred in 32/911 (3.5%), including 12 graft artery or vein thrombosis (11 graft losses) and 3 fatal events

Patients with CVE were older (55.9 ± 9.9 vs. 51.0 ± 12.5 p=0.044), had a higher PTH (256.8±160.2 pg/mL vs. 175.1±178.1 pg/mL, p=0.002), were more likely on cinacalcet (47.6% vs. 9.3%, p<0.0001), had had more likely a CVE before transplant (29.0% vs. 9.0%, p=0.0002) and were more likely to have received KTx over the period 2008-2013 (56.2% vs. 29.6%, p=0.004) than patients without eCVE.

These risk factors for CVE were confirmed at the univariate regression, while **AAT use was not associated with CVE** .

Patients with CVE were more likely to have a DGF (42.9% vs. 23.5%, p = 0.041), to receive more transfusions (4±3.2 vs. 2.1±3.4, p < 0.0001) and to have a higher serum creatinine at discharge (2.6±1.1 vs. 2.0±0.8 mg/dL, p = 0.012).

Multivariate Analyses

Multivariate Logistic model for Hemorrhagic events (n=21/911)				
	Ref.	OR	95% CI	p
KTx year 1998-2003 KTx year 2004-2008	KTx year 2009-13	5.83 2.95	1.24 - 27.44 0.61 - 14.21	0.03 0.18
HCV positive	Negative	2.69	0.94 - 7.72	0.07
Vit. K Antagonist	No AAT, No VKA	7.09	2.03 - 24.77	0.01
Any Antiplatelet th.	No AAT, No VKA	1.89	0.71 - 5.06	0.20

Multivariate Logistic model for CV events (n=21/911)				
	Ref.	OR	95% CI	p
KTx year 2004-2008 KTx year 2009-2013	KTx year 1998-2003	3.17 3.79	0.38 - 26.51 0.45 - 30.53	0.29 0.22
Cinacalcet before KTx	No cinacalcet	7.93	3.00 - 20.95	<0.001
History of CVE	No prev. CVE	4.18	1.62 – 10.95	0.003

CONCLUSIONS

1. **Our results suggest that AAT are not associated with a higher risk of HE or CVE, while patients on VKA have a higher risk of HE,** due to probably the early start of LMWH which is needed for compelling and unmodifiable indications to anticoagulation (ie: mech. valve).
2. Therefore, as bleeding due to VKA or to its bridge therapy are an unmodifiable risk factors for HE, *patients with an indication to a life-long anticoagulation should be informed about their increased risk of minor and major HE, including the risk of early graft loss or death.*
3. Unexpectedly we found that CVE are associated to cinacalcet before transplantation: it is possible that patients on cinacalcet have had a more severe hyperparathyroidism yielding eventually to a more diffuse vascular damage. Moreover we usually do not use cinacalcet soon after KTx and in some patients there may be a rebound increase of PTH and calcium, with a potentially severe vascular and cardiac toxicity. However since this finding was very unexpected, *we need further trials evaluating the role of cinacalcet use at KTx and its withdrawal after KTx.*

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