DABIGATRAN *VS* WARFARIN TREATMENT: EFFECTS ON BONE VOLUME AND STRUCTURE IN RATS

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INTRODUCTION and AIMS

Warfarin acts as a vitamin K antagonist inhibiting the effects of Vitamin K-Dependent Proteins (VKDPs) including Bone Gla Protein (BGP or Osteocalcin),which acts to mantain normal bone mineralization and Matrix Gla Protein (MGP), which acts to prevent vascular calcifications (VC). The aim of this study was to compare the impact of warfarin and dabigatran on bone and vascular calcifications, in rats with normal renal function.

METHODS

Rats received for 6 weeks orally administered Dabigatran etexilate-supplemented chow (1.0mg/g) or Warfarin in drinking water (starting from 0.6 mg/kg rat to achieve the desired INR between 2 and 3). Controls (Untreated): rats were fed a placebo diet containing 8 mg of Vitamin K3 per gram of chow. Diluted thrombin time (Hemoclot) tests were conducted at the end of the study for all three experimental groups. Femur, tibia and vertebrae were evaluated for immuno-histochemical and morphometric analysis of bone remodelling. Samples of aorta and iliac arteries were preserved for histological examination (Von Kossa and Alizarin red).

RESULTS

Histomorphometric results of femur and vertebra analysis showed for structural parameters decreased bone volume and increased trabecular separation in rats treated with warfarin compared to control and rats treated with dabigatran. The difference was statistically significant *(see Table)*. In addition, vertebra analysis showed that trabecular number differed significantly between the two treatment groups. No significant differences in osteoblast activity and resorption parameters were observed among groups, except for maximum erosion depth, which was higher in warfarin treated rats compared to dabigatran and control groups, suggesting a more pronounced osteoclastic activity.
Furthermore in the vertebra analysis warfarin treatment was associated with significantly higher Bone Formation Rate/Bone Surface (BFR/BS) and AcF than in dabigatran treated and control rats, suggesting that warfarin may cause an increased turnover characterized by increased remodeling cycles, with stronger osteoclast activity with respect to other groups. In the femur analysis, warfarin was associated with significantly higher Activation Frequency (AcF) versus dabigatran-treated and control rats, suggesting a significantly increased turnover .
There were no differences among the three groups of rats in arterial calcium deposition either in the aorta or in the iliac arteries. I moved femur analysis comments to end, since you have quite a few data points to highlight from the vertebra analysis.

Table

Table . Histomorphometric parameters of structure in femur analysis

	Warfarin	Dabigatran	Controls
Bone Volume/Tissue Volume (%)	27.32±8.95*#	42.42±9.77	43.66±6.55
Trabecular Thickness (µm)	64.13±23.22	85.39±10.92	66.16±17.42
Trabecular Number (#)	4.42±0.32	4.36±1.54	4.46±2.17
Trabecular Separation (µm)	199.21±57.15**##	111.74±33.97	129.03±31.81
Osteoid Surface/Bone Surface (%)	1.31±0.68	2.19±1.61	2.94±2.03
Osteoid Thickness (µm)	16.38±10.12	17.13±6.61	19.46±7.75
Osteoblast Surface/Bone Surface (%)	0.28±0.10	0.87±0.57	0.55±0.26
Erosion Surface/Bone Surface (%)	1.10±0.91	1.19±0.77	1.67±0.68
Max. Erosion Deep (µm)	76.49±36.35	46.49±22.75	75.59±23.46
Osteoclast Number/Tissue Volume (%)	1.09±0.16	1.72±0.60	2.06±1.41

** p ≤ 0.05 vs Dabigatran*
***p ≤ 0.005 vs Dabigatran*
#p ≤ 0.05 vs Controls
##p ≤ 0.005 vs Controls

CONCLUSIONS

This study demonstrates that treatment with warfarin was associated with significantly decreased bone volume, increased trabecular separation and higher turnover than in dabigatran treated and control rats. These findings suggest for the first time in literature that dabigatran has a better bone safety profile than warfarin, as warfarin treatment affects bone reducing trabecular size and structure, increasing turnover and reducing mineralization. These differences could translate into lower incidence of fractures in dabigatran treated patients both in general population and in patients with chronic kidney disease.

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M) Dialysis. M3) Cardiovascular complications in in CKD 5D.

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