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Possible superiority of angiotensin II type 1 receptor blockers in patients with Marfan syndrome. Do we have a dose-related effect?

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Introduction:
Dilatation of sinus of valsalvae (SV) is the most common pathology in Marfan syndrome (MFS). To prevent aortic complications, initiation of medical therapy is often necessary. Due to pathogenesis of MFS medical therapy with angiotensin II type 1 receptor blockers (ATII) was expected to be highly effective. Now first published large randomized trials demonstrate that ATII is not superior to prophylaxis with betablockers (BB).
Nevertheless dosing of ATII in childhood is variable and has not been investigated yet. To ensure best impact on connective tissue, different doses may be necessary and could potentially prove that ATII is superior to BB.

Methods:
Since 2008 we investigated 343 patients (11.12±5.71 y) with suspected MFS whereas 132 patients were diagnosed. Thereby 82 showed indication for prophylactic treatment (n(ATII)=56, n(BB)=26)). To evaluate dose related impact we retrospectively divided patients in ATII groups (A:0.5-1.0, B:>1.0-1.5, C:>1.5 mg/kg/d) to measure progression of SV dilatation (Z-score) via echocardiography. The ATII groups showed no difference regarding age, gender and indication for therapy.

Results:
Mean follow up period in group A(n=31), B(n=38) and C(n=19) after initiation of ATII was 29.88±21.24 months (BB 48.10±43.35). Z-score decreased in all groups after follow-up period (Table1). Using linear regression rate of change between the three groups with different ATII dose did not show linear correlation.

Table1: Z-score of SV before (SV1) and after (SV2) treatment with BB, ATII, different ATII dose.

Group	Follow-up [months]	Z-Score SV1	Z-Score SV2	N	P (Z-score)
BB	48.10±43.35	2.54±1,70	2.14±1.36	26	p=0.067
ATII (overall)	29.88±21.26	1.74±1.03	1.31±1.31	56	P=0.001
ATII 0.5-1mg/kg/d (A)	14.26±12.01	1.71±1.07	1.12±1.45	31	P=0.003
ATII 1-1.5mg/kg/d (B)	08.32±08.38	1.70±1.03	1.48±1.31	38	P=0.060
ATII >1.5mg/kg/d (C)	14.68±12.68	1.89±1.04	1.82±1.03	19	P=0.567

Conclusions:
This selective and non-randomized collective indicates a tendency towards the superiority of ATII prophylaxis in children with MFS. In contrast to recently published data therapy with ATII seems to be more effective, but there is no proof for a dose related effect. And it seems that non-responders to ATII exist as enhancement of dose does not correlate with decrease of SV dilatation. To estimate effective dosing and reasons for possible non-responding further, larger pharmacokinetic and pharmacodynamic studies are indispensable.