The effect of rosuvastatin on aortic stiffness in hemodialysis patients; a local addendum to the Aurora study.
Studycode AURORA study: 4522IL/0096

Background: Aortic stiffness is a potent predictor of both cardiovascular and all-cause mortality in patients with end-stage renal disease, a population in which both the cardiovascular and the all-cause mortality are extremely high (Blacher). The aorta shows increased stiffening with loss of renal function (Mourad). This increased stiffening has further been attributed to age, hypertension, elastin degeneration, and atherosclerosis. Aortic stiffness is thought to cause mortality because of its relation with systolic hypertension and subsequent development of left ventricular hypertrophy, which is present in approximately 80% of all hemodialysis subjects, and which is a strong predictor of mortality itself.

Aortic stiffness can be attenuated by ACE-inhibitors, even in dialysis patients (Guerin). To our surprise the aortic compliance could almost be normalized during a short course of ACE-inhibition in hemodialysis patients in whom overhydration was adequately corrected (Vuurmans). Such improvements of the aortic compliance are important. The survival of end stage renal disease patients has been shown to increase when the aortic compliance improves over time (Guerin). This effect was independent of the level of blood pressure reduction and of the use of ACE-inhibitors.
Aortic stiffness has thus been shown to be a potent, and independent, predictor of mortality in dialysis patients. Since it can be estimated relatively easy in a non invasive way by measuring the pulse wave velocity (PWV) over the aorta, its measurement might become a useful tool in clinical nephrology.

Cholesterol lowering with HMG-coA-reductase-inhibitors (statins) has a positive effect on the survival of patients with hypercholesterolemia and patients with known cardiovascular disease. Patients with end-stage renal disease are at very high risk for cardiovascular disease and cardiovascular mortality. Although different statins have been shown to lower cholesterol levels in dialysis patients, their effectiveness in lowering mortality has not been shown in these patients (4Dstudy). Th effect of rosuvastatin on mortality was investigated in the Aurora study, a randomised double blind, placebo-controlled trial in which rosuvastatin is compared to placebo in subjects on hemodialysis.

Little is known on the contribution of hypercholesterolemia to the development of aortic stiffness. Most studies have shown little or no effect of LDL-cholesterol levels on aortic PWV. Recently artifc stiffness was found to be increased in subjects with familial combined hyperlipidemia (ter Avest). Also in ESRD hypercholesterolemia is not an independent predictor of aortic PWV (Blacher).
Trials in which the PWV was measured before and after initiation of lipid lowering therapy with HMG-coA-reductase-inhibitors have shown conflicting

results. No effects were observed in a 4 week trial with simvastatin in hypercholestrolemic subjects (Shige). Twelve weeks of treatment of hypertensive hypercholesterolaemic subjects even caused an increase of the aortic PWV by 8 % (Raison)!
Only one paper describes positive effects of lipid lowering therapy on aortic PWV. This study was performed in hemodialysis patients. Treatment of 22 diabetic hemodialysis patients with fluvastatin resulted in a decrease of the aortic PWV from 19.91 ± 1.62 m/s to 17.09 ± 1.34 m/s 6 months after initiation of therapy with fluvastatin. In the control group the aortic PWV increased from 19.69 ± 1.40 m/s to 23.26 ± 1.90 m/s in these 6 months (8, Ichihara)
Since start of the study effects of cholesterol lowering therapy has been shown in patients with type 2 diabetes (mukherjee).

The present study we investigated the effect of rosuvastatin on the aortic stiffness, as measured with PWV, in hemodialysis patients within the Aurora study (Fellström). The presented sub-study was performed in a single center.

Methods:
Patients:
Ten to twelve hemodialysis patients participating in the Aurora study.

Measurements:
- Blood pressure (automated, Omron M5)
- Aortic PWV using tonometry with the Sphygmocor
- Augmentation index derived from pressure wave recording at carotid artery using Sphygmocor.

Aortic pulse wave velocity is measured using two applanation-tonometers. The time difference between the arrival of the pressure pulse at the carotid and the fernoral artery, divided by the distance between those two measurement sites, yields the pulse wave velocity over the aorta. The aortic pressure wave, reconstructed from carotid or radial artery pressure waves, using the above mentioned techniques, is analysed to study the timing and the intensity of reflected pressure waves.

Measurement were performed at the start of the study, and 1, 3, 6 and 12 months after starting therapy.
Since the hemodialysis procedure itself not only affects hemodynamics considerably (Bos), but also the aortic PWV (Vuurmans, unpublished data), measurements will be performed before hemodialysis.
Mean blood pressure was calculated using a newly derived formula (Bos, Verrij). Mean pressures are given since mean pressures are the distending pressures, affecting aortic stiffness, and thus PWV.

Sample size calculation:

Assuming a standard deviation of the aortic PWV of 2.25 m/s and a clinically relevant difference of 6.0 m/s, eight subject will have to be studied to test the hypothesis that rosuvastatine improves aortic PWV at a significance level of 0.05 and a power of 80%.

Results:
All eight patients participating in the St Antonius Hospital participated in the substudy. Four subjects were on active drug treatment (1female, 3 male, mean age 66 years), 4 used placebo (3 female, 1 male, mean age 70 year). Three patients on active treatment completed the first year of the study in which the sub-study measurements were performed. One patient stopped taking the active medication after 6 months (t=12 months not used in analysis), because of muscle pain. In the placebo group one patient stopped taking study medication because of an allergic reaction of the skin.

Blood pressure did not change significantly during the study (table 1, figure 1).
Pulse wave velocity did not differ between the 2 treatment groups and did not change during the study either (table 1, figure 2).
The augmentation index tended to be higher in the placebo group., and did not change significantly over time in either group.

Discussion

We investigated the effect of rosuvastatin on the aortic stiffness in hemodialysis patients. We did not observe a significant effect of rosuvastatin on aortic stiffness as measured with PWV.

Hemodialysis patients often show advanced vascular disease. Vascular disease in hemodialysis patients is not only characterized by atheroma formation of the intima, but also by changes in the media of elasic arteries. The media is often calcified. It is likely that the use of cholesterol lowering therapy mainly affects the atheroma formation of the media, whereas elastic properties are mainly determined by properties (elastine, calcification) of the media (Mc Donalds).

Arterial stiffness is directly determined by blood pressure. The mean pressure serves as the distending pressure of arteries (mc Donalds). Changes in PWV should therefore be seen in the light of changes in blood pressure. In our study changes in blood pressure (table 1, figure 1) did explain some, but not all changes in PWV (table 1, figure 2)

Limitations
The number of subjects studied was low. This certainly affected the power of the study. We met the (surprisingly low) number of subjects needed according to the power calculation at inclusion. However 2 subjects dropped out.
We aimed to recruite a much higher number of participants. We were confronted with the fact that many hemodialysis patients were not willing to participate in a study in which they were required to take additional medication

on top of the often considerable number of drugs to be taken already for routine medical care.

We did not observe an effect of rosuvastatin on aortic stiffness in hemodialysis in a study which was underpowered.

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Table 1. Blood Pressure, pulse Wave Velocity (PWV) and Augmentation Index during the study (timepoints 0,3,6 and 12 months)

	Active treatment	Placebo
Base Line BP		
systole	157	159
diastole	84	75
mean	113	109
Mean pressure		
t = 0	113	109
t = 3	124	120
t = 6	115	107
t = 12	120	101
PWV		
t = 0	16,0	14,9
t = 3	13,2	11,2
t = 6	14,2	11,1
t = 12	9,4	9,5
Augmentation index		
t = 0	0,21	0,39
t = 3	0,25	0,52
t = 6	0,25	0,33
t = 12	0,20	0,44

Figure 1. Mean blood pressure during the study.

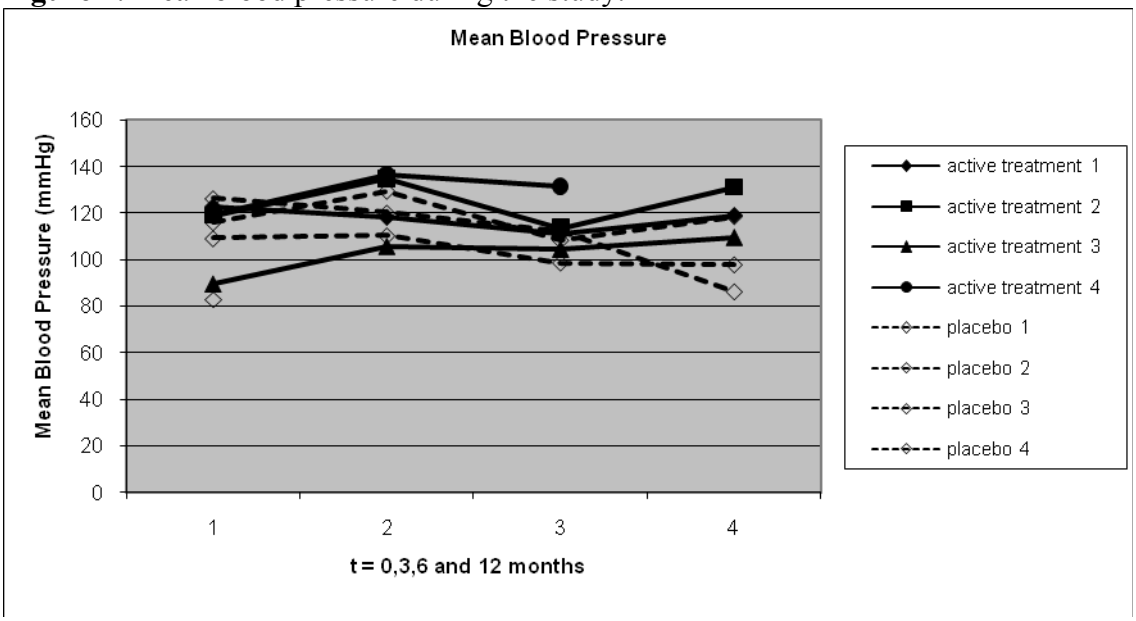

Figure 2. Pulse Wave Velocity during the study

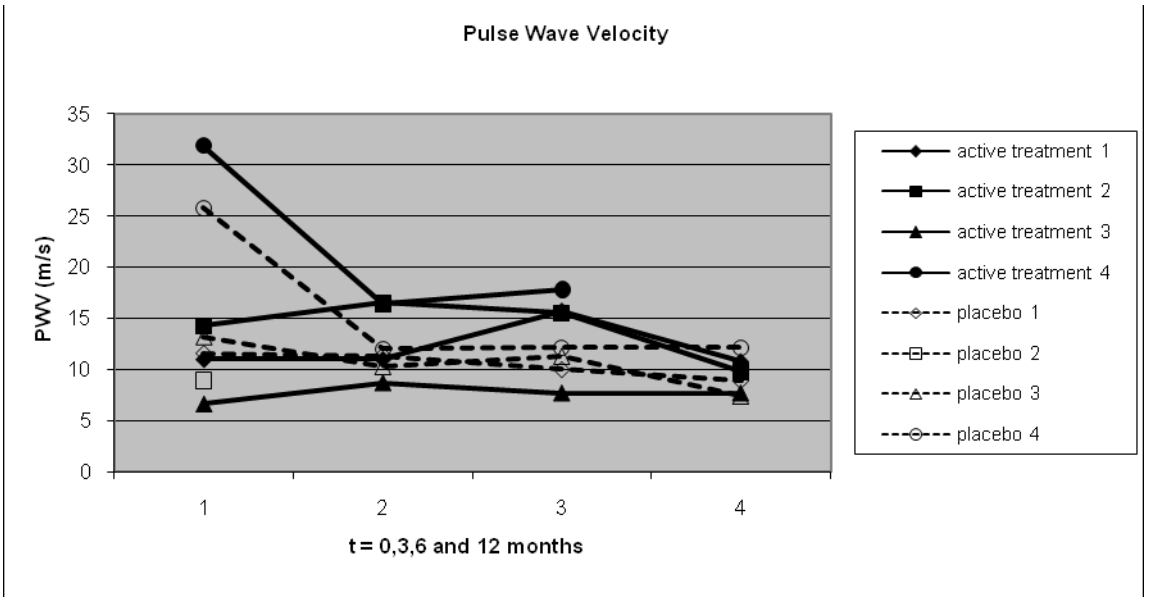

Figure 3. Augmentation Index during the study