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Beneficial effect of high dose statins on the vascular wall in patients with repaired aortic coarctation?☆,☆☆

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ABSTRACT

Background: Carotid intima–media thickness (CIMT) is a marker for atherosclerosis. Adult post-coarctectomy patients (CoA) demonstrate an increased cardiovascular risk and increased CIMT compared to controls. This study evaluates the effect of high dose statins on the change in CIMT and cardiovascular risk.
Methods: We designed a multicenter, prospective, randomized, open label trial with blinded endpoint (PROBE design) to evaluate the effect of three year treatment with atorvastatin 80 mg on CIMT and cardiovascular risk. Primary endpoint was CIMT measured by B mode ultrasonography. Secondary endpoints were mortality and morbidity due to cardiovascular disease and serum lipids.
Results: 155 patients (36.3 ± 11.8 years, 96 (62%) male) were randomized (atorvastatin = 80, no treatment = 75). There was no significant effect of atorvastatin on the change in CIMT (treatment effect −0.005, 95% CI, −0.039–0.029; P = 0.76). A significant effect on serum cholesterol and LDL levels was found (− 0.71, 95% CI, − 1.16 to − 0.26; P = 0.002 vs − 0.66, 95% CI − 1.06 to − 0.26; P = 0.001). There was no difference in secondary outcome measures. Baseline CIMT was higher in hypertensive compared to normotensive CoA. (0.69 ± 0.16 mm vs 0.61 ± 0.98 mm; P = 0.002). Hypertension (ß = 0.043, P = 0.031) was the strongest determinant CIMT.
Conclusion: Three year treatment with atorvastatin does not lead to a reduction of CIMT and secondary outcome measures, despite a decrease in total cholesterol and LDL levels. Hypertensive CoA demonstrate the highest CIMT and the largest CIMT progression. Blood pressure control should be the main focus in CoA to decrease cardiovascular risk.

1. Introduction

Aortic coarctation (CoA) is a typical discrete aortic narrowing distal to the left subclavian artery [1]. Despite surgical or percutaneous repair, CoA patients demonstrate a significant premature morbidity and mortality [2–4]. Several studies have shown that the main cause of death in CoA is premature coronary atherosclerosis [2,5–8].

Carotid intima media thickness (CIMT) is known to be a reproducible marker for atherosclerosis and is associated with future cardiovascular risk and the occurrence of cardiovascular events in the general population. Moreover, it is known that CIMT might reflect smooth muscle hypertrophy or hyperplasia [9–12]. Previous studies demonstrated an increased CIMT in both children and adult CoA patients, even in normotensive CoA and in those after early repair, which might reflect the increased cardiovascular risk. Moreover, these data demonstrate that an aortic coarctation seems to be part of a

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generalized arteriopathy instead of only a localized narrowing of the thoracic aorta [13–15].

In the general population, traditional risk factors such as hypertension and cholesterol levels have been proven to be important determinants for CIMT progression [9,16]. Moreover, LDL cholesterol levels are one of the key determinants for CIMT as confirmed by a linear relationship between LDL cholesterol levels and CIMT [17]. A meta-analysis across several trials demonstrated that statin therapy resulted in an average decrease of CIMT progression of 0.012 mm/year together with a 52% risk reduction for cardiovascular disease [11,18]. Shukla et al. demonstrated that low-dose statins reduced progression of atherosclerosis reflected by the change in CIMT over time in patients with acquired coronary heart disease and normal lipid values independent of lipid lowering [19].

Brili et al. demonstrated that a four-week treatment with atorvastatin in CoA significantly improved endothelial function and decreased serum levels of proatherogenic inflammatory cytokines [20,21]. These data are intriguing as CoA patients have increased circulating levels of proinflammatory cytokines and adhesion molecules, which have a well-established role in atherogenesis development [22]. However, the benefit of statin treatment on the vascular wall and cardiovascular risk in CoA patients has never been investigated. Therefore, the aim of our study was to evaluate the beneficial effect of statin therapy on the change in CIMT over time in CoA. Secondary endpoints included mortality and morbidity due to cardiovascular disease, aortic diameters, blood pressure, and serum cholesterol levels.

2. Methods

2.1. Study overview

We designed a multi-center, prospective, randomized open label study with blinded endpoints (PROBE-design) to evaluate the effect of three year treatment with high dose atorvastatin on the change in CIMT in CoA. Six tertiary referral centers in the Netherlands participated in this trial. Potential candidates were identified via the CONCOR database, a national database and DNA bank of adult patients with congenital heart disease [23,24]. The study complies with the Declaration of Helsinki; locally appointed ethics committees have approved the research protocol and informed consent was obtained from all subjects prior to their participation in the study. The trial design including the power-calculation is registered at: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1065.

2.2. Study population

Adult patients after successful coarctation (CoA) repair followed in one of the participating centers (Academic Medical Centre Amsterdam, VU University Medical Centre Amsterdam, University Medical Centre Utrecht, Radboud University Medical Centre Nijmegen, University Medical Centre Groningen and Leiden University Medical Centre) were eligible to participate in the study. Inclusion and exclusion criteria are detailed in Table 1. If a patient met all inclusion and none of the exclusion criteria, the patient was invited to the outpatient clinic for a detailed explanation of the study and asked for informed consent.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
Patients after surgical repair of aortic coarctation
Age 18 years or older
Informed consent and assent of participant, parent or legal guardian as applicable
Exclusion criteria
Incapable of giving informed consent
Hypersensitivity to atorvastatin or any of its help substances
Current treatment with anti-lipemic drugs
Indication for treatment with statins based on the CBO-guideline for cardiovascular risk management.
Raised plasma transaminases level > three times limiting value
Raised CPK level > five times limiting value
Myopathia
Pregnant or nursing women (a pregnancy test is offered to every female patient within the fertile age)
Desire to have children within the study period

CBO = The Dutch Institute for Health Care Improvement; CPK = creatininefosfokinase.

2.3. Interventions

Participating patients randomized for medication started on study medication when all baseline examinations had been performed. Patients in the atorvastatin group started on 80 mg once daily. After 3 months blood analyses were performed. The use of co-medication during the study was closely monitored.

2.4. Blinding and randomization

Patients were randomized according to a computer generated randomization sequence using randomly permuted blocks of 6 or 4, stratified by site. Eligible patients were randomly assigned to atorvastatin 80 mg once a day or no prescription of atorvastatin. If randomization indicated use of atorvastatin, medication was prescribed by the investigator. Patients obtained the prescribed atorvastatin from their local pharmacy.

2.5. Sample size calculation

Sample size calculation was based on the primary endpoint (per subject averaged carotid mean IMT); a standard deviation (of the means of the difference of paired replicate observations) of 0.10 mm; and a considered clinically relevant difference of 0.05 mm carotid IMT between groups (2-sided alpha = 0.05; beta = 0.2). Based on these assumptions we calculated that 128 patients are required to obtain 80% power to detect a difference of 0.05 mm in IMT between the treatment groups. To accommodate for a 10% dropout, the inclusion of at least 150 patients was advised.

2.6. Outcome measures

At baseline study measures (i.e. medical history, physical examination, B-mode ultrasonography of the carotid arteries, 24-hour ambulatory blood pressure monitoring, echocardiography, exercise testing, CMR imaging, blood analysis) were obtained in all participating patients. These study measures were repeated after a 3 year follow-up. Physical examination and blood analysis were repeated after a 1.5 year follow-up. Study protocols at baseline after 1.5 years and after three years of follow-up were identical. Medical history included parameters such as, type of coarctation repair, age at repair, the presence of associated congenital cardiac abnormalities, re-operation, medical therapy and cardiovascular disease risk factors.

2.7. Clinical data and definitions

2.7.1. B-mode ultrasonography of the carotid artery (CIMT imaging)

CIMT imaging was performed at baseline and after a three year follow-up. Images were acquired according to a standardized protocol, and obtained from the arterial wall segments of the right and left common carotid arteries, carotid bulbs and internal carotid arteries. Two well-trained and experienced sonographers blinded to all clinical information performed all measurements of ultrasound scans. An Acuson 128XP ultrasound instrument (Acuson, Mountain View, CA) was used. Standard views of 2-by-2 cm were imaged of each arterial segment that was saved as a DICOM still image. All scans were analyzed off-line in a core lab. Validated software was used (eTRack), as extensively published before. The primary endpoint was defined as the per subject aggregate of available IMT measurements at a given time point in the study.

2.7.2. Ambulatory blood pressure monitoring (24 h ABPM)

All patients underwent 24 h ABPM at baseline and at follow-up. An automatic ambulatory blood pressure monitor (Spacelabs 90207, SpaceLabs Inc, Redmond, WA) was placed on the right arm. The right arm was used to avoid operation-related blood pressure disturbances. Blood pressures were measured at regular intervals of 15 min at daytime and 30 min at nighttime. Patients were considered hypertensive when mean daytime systolic blood pressure was ≥135 mm Hg and/or diastolic blood pressure was ≥85 mm Hg or if patients were on antihypertensive medication, in accordance with the JNC 7 Report [25].

2.7.3. Exercise testing

Exercise testing was performed in all patients at baseline and was repeated after a 3 year follow-up. All patients underwent a maximal, symptom limited, standardized treadmill exercise test, following the Bruce protocol. During the exercise test, blood pressure was measured