# Long-Term Effect of Inhibition of the Angiotensin-Converting Enzyme (ACE) on Cavernosal Perfusion in Men with Atherosclerotic Erectile Dysfunction: A Pilot Study

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**ABSTRACT**

***Introduction.*** Impaired perfusion of the corpora cavernosa is considered an important causal factor of erectile dysfunction (ED) in the aging male with atherosclerosis.

***Aim.*** On the basis of this notion, we hypothesized that inhibition of angiotensin-converting enzyme (ACE) may have a structural beneficial effect on cavernosal perfusion and subsequently on erectile function in men with impaired cavernosal perfusion.

***Methods.*** A total of 59 men with atherosclerotic ED (mean age, 60.0 ± 6.8 years) and impaired cavernosal perfusion, as demonstrated with penile-pharmaco duplex ultrasonography, were randomized between an ACE inhibitor and placebo treatment arm. The minimum period of intervention was 26 weeks (26–46 weeks). The goal of the study was to demonstrate an improvement of (i) cavernosal arterial perfusion demonstrated by a decrease of blood flow velocity waveform; and (ii) erectile function in the erection domain of the International Index of Erectile Function.

***Results.*** Cavernosal perfusion improved significantly (paired samples *t*-test, $P < 0.05$) in both study arms, but the improvement did not differ significantly (ANOVA, $P > 0.05$) between both arms. The number of sexually active men increased, and the severity of ED decreased in both groups.

***Conclusion.*** Although a persisting improvement of cavernosal perfusion by at least a 6 month-administration of an ACE inhibitor in men with advanced atherosclerotic ED could not be demonstrated in this pilot study, the beneficial effect on cavernosal perfusion, sexual activity, and erectile function in all participants of this study is remarkable. This pilot study warrants a follow-up study in sexually more active men with ED and less advanced atherosclerosis to show that ACE inhibition may result in persisting improvement of cavernosal perfusion.

***Key Words.*** Erectile Dysfunction; Angiotensin-Converting Enzyme Inhibition; Quinapril

## Introduction

Erectile dysfunction (ED) is a multifactorial condition with physiological and psychological–social components. As it has been observed that the prevalence of ED is higher in men with atherosclerosis, impaired perfusion of the corpora cavernosa is considered an important physiological factor, more precisely a manifestation of cavernous endothelial dysfunction and subsequent hypertrophy and proliferation of cavernosal vascular smooth muscle cells in the aging male [1–6].

In the early 1990s, inhibition of angiotensin-converting enzyme (ACE) has been shown to improve endothelial function and to prevent progression of general atherosclerosis [7,8]. Acute and persisting effects of ACE inhibition have been postulated to explain these observations—the former by the reduction of the vasoconstrictive effects of angiotensin, the promotion of nitric oxide released by the endothelium, and the

inhibition of bradykinin degradation [9,10], and the latter by structural remodeling of the endothelium [11] and the reduction of hypertrophy and proliferation of vascular smooth muscle cells [12,13].

Relying on these data, we hypothesized a persisting beneficial effect of ACE inhibition on cavernosal perfusion and subsequently on erectile function. In this clinical study, we sought to demonstrate a reduction of acceleration time of the blood flow velocity waveform in the cavernous artery 6 weeks following the discontinuation of a 6-month treatment with quinapril in men with proven impaired cavernosal perfusion. The secondary objective was to show an improvement of erectile function.

#### Patients and Methods

This study was conducted at the urology outpatient department of the University Medical Center Nijmegen from January 2001 to March 2002. The ethics committee approved the study, and a written consent was obtained from all patients. The intake of men with ED included medical and sexual history, physical examination, biochemical analysis, penile-pharmaco duplex ultrasonography (PPDU), and measurement of the intima media thickness (IMT) of the common carotid artery. PPDU and IMT measurements were performed as previously described [14]. Moreover, the patients were asked to fill in the International Index of Erectile Function (IIEF) questionnaire [15]. Biochemical analysis included a serum lipid spectrum, glucose, and creatinin.

We selected patients with complaints of ED and impaired cavernosal perfusion as demonstrated with PPDU. Recent literature [14] shows that an acceleration time of >100 ms was considered to be indicative of impaired cavernosal perfusion. Patients younger than 35 years and older than 75 years of age were excluded—the former, because cavernosal vascular insufficiency is rare among men younger than 35 years; the latter, because, based on previous experience with this age group, a low compliance was expected. Exclusion criteria were men with penile implants; heart failure or low ejection fraction; uncontrolled hypertension (not responding to blood pressure-lowering therapy); hypotension; nephropathy or renal artery stenosis; abnormal kidney function (creatinine <110 μmol/L); presenting dehydration during physical examination; taking diuretic medication; myocardial infarction or stroke within 4 weeks before the study started; hypersensibility for ACE inhibitor substances; participating in any other trial; in the opinion of the investigators had medical, psychiatric, or substance abuse disorders that were likely to affect the subject's ability to complete the study, or precludes the subject's participation; and a history of malignancy in the past 5 years.

The primary end point was cavernosal acceleration time as measured during PPDU. The secondary end point was erectile function as determined by the erection domain of the IIEF questionnaire.

The study population group was randomly assigned to either treatment with an ACE inhibitor [quinapril (Acupril$^{TM}$)] (daily, 20 mg) or placebo. Quinapril was chosen from the wide range of ACE inhibitors because the Trial on Reversing Endothelial Dysfunction had shown convincingly that 6 months of treatment with quinapril improves endothelial function in large and small vessels of normotensive patients (Mancini et al.) and is associated with a significant improvement of flow-mediated vasodilatation following 8 weeks of treatment [16].

The intervention phase lasted for at least 26 weeks (maximum 46 weeks), depending on the date of enrollment. Follow-up visits were scheduled at day 14, week 4, and 2 months following the end of the intervention phase and included measurement of blood pressure, filling in the IIEF questionnaire, assessment of penile cavernosal perfusion with PPDU, and measurement of the carotid intima media thickness to evaluate the effect of the intervention on general atherosclerosis.

During the study, patients were allowed to use erection-enhancing medication such as sildenafil or intracavernous self-injection with papaverine/phentolamine prior to sexual intercourse. In order to make an unbiased assessment of the persisting effect of ACE inhibition on cavernosal perfusion possible, the patients were asked to refrain from erection-enhancing medication for a period of 2 months following the conclusion of the intervention phase, prior to the final assessment. At each visit, patients were interviewed and asked for adverse events. Moreover, blood pressure was measured twice on the right arm after a period of 10 minutes of rest, in supine position, and once immediately after standing.

Two persons were responsible for various components of the trial. The physician (T.S.) who was responsible for all baseline and end-point mea-