Long-term use of angiotensin-converting enzyme inhibitors to modify endothelial dysfunction: a review of clinical investigations

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Authors' objectives
To review clinical studies assessing the effect of long-term, oral angiotensin-converting enzyme (ACE) inhibition on endothelial dysfunction in specific disease syndromes and to identify areas requiring further research.

Searching
MEDLINE and Current Contents were searched as of February 2000 (no search terms listed). In addition the bibliographies of articles were examined for further studies. No attempts were made to locate unpublished material.

Study selection
Study designs of evaluations included in the review
Due to the paucity of double-blind, randomised, placebo-controlled trials the review also included other types of studies with less formal clinical designs, such as prospective uncontrolled studies, crossover studies and retrospective studies. Studies reported in abstract form were not included in the review.

Specific interventions included in the review
Orally administered ACE inhibitors including perindopril (2-8mg), captopril (25-150mg), enalapril (5-30mg), cilazapril (2.5-10mg), temocapril (2-4mg), lisinopril (10-20mg), benazepril (5-10mg) + amlodipine, imidapril (5-15mg), quinapril (20-40mg) +/- nifedipine, fosinopril (10mg), ramipril (0.625-10mg). Comparators included placebo, no ACE inhibitor control and other drugs including amlodipine (2.5-15mg), atenolol (50-100mg), carvedilol (25-50mg), triamterene (50mg) + hydrochlorothiazide (25mg), and losartan (50mg). Studies were excluded if they were based on systemic infusion or single, oral doses of ACE inhibitors.

Participants included in the review
Patients with endothelial dysfunction including patients with a variety of conditions such as coronary artery disease, dyslipidemia, hypertension, diabetes (type I and II), congestive heart failure, and immunoglobulin A nephropathy (IgAN).

Outcomes assessed in the review
No outcomes were defined a priori. Endothelium-mediated outcomes were reported in the review including: dilatory responses in conduit or resistance vessels, measures of coagulant and fibrinolytic factors, soluble adhesion molecules, endothelin-I, systemic and glomerular barrier functions and renal blood flow. Studies of ACE inhibition and exercise-induced flow changes or reactive hyperemia are not included in this review unless other measurements specifically implicating endothelium-dependent processes were also undertaken. In addition studies measuring only microalbuminuria were excluded.

How were decisions on the relevance of primary studies made?
This is a single author review. The author does not state how the papers were selected for the review, or if any other individuals assisted in the selection of studies.

Assessment of study quality
No formal assessment of study validity was performed. However, some aspects of study quality were discussed including randomisation, blinding, control groups and study size. This is a single author review. The author does not state how papers were assessed for validity, or if any other individuals assisted in the assessment.
Data extraction
The following data were extracted: study characteristics, patient population, drug interventions, duration of active therapy, key methodology, and the main outcomes regarding endothelial function. This is a single author review. The author does not state how data were extracted for the review, or if any other individuals assisted in the data extraction.

Methods of synthesis
How were the studies combined?
A narrative synthesis was used.

How were differences between studies investigated?
Some differences between studies were discussed qualitatively. Studies were grouped according to the specific disease conditions (coronary artery disease, dyslipidemia, hypertension, diabetes, congestive heart failure, and immunoglobulin A nephropathy).

Results of the review
Forty-three studies (over 1638 participants in total) were included in the review. Fifteen of the studies were double-blind randomised controlled trials (RCTs).

1. Hypertension (19 studies (581 participants), 6 double-blind RCTs, 8 cohort, 3 single blind cohort, 1 observational and 1 retrospective study).

Two studies both undertaken in previously untreated hypertensive patients assessed the response of renovascular endothelium. One showed ACE inhibitors can restore or enhance the vasodilatory response to infusion of L-arginine, and the other showed that ACE inhibitors are effective within three months. One of the studies suggested that this efficacy can be sustained for 1.5 to 10yrs.

Three studies assessed endothelial function of the conduit artery, reporting the reversal of dysfunction after active therapy for only 5 to 6mths.

Five studies measured circulating substances as indicators of endothelial function. One of the studies demonstrated improved conduit artery endothelial function in addition to enhanced insulin sensitivity and fibrinolytic state. A further two of the studies measured endothelin-1 and reported discordant findings.

Only one study investigated the role of basal synthesis of nitric oxide in forearm resistance vessels and reported the normalisation of response after only 6wks in newly diagnosed hypertensive patients without any evidence of target organ damage. In contrast three further studies failed to show any major role of calcium channel blocking agents in improving endothelial dysfunction in spite of effective blood pressure lowering. One further study demonstrated an inverse correlation between blood pressure reduction and basal levels of both nitric oxide and bradykinin during one-month treatment with lisinopril.

Finally, three studies that assessed the functional properties of small, resistance arterioles using gluteal biopsy and direct in vitro assessment showed concordant decreases in media:lumen ratios in patients treated with ACE inhibitors, but not when other agents were used. Both also report some mild abnormalities of endothelial function, which mildly improved after 2-3yrs of treatment with ACE inhibitors.

2. Diabetes (11 studies (444 participants), 4 double-blind RCTs, 2 double-blind crossover, and 5 cohort studies).

The active treatment arms of these studies included 41 or fewer patients. Two studies assessed barrier function and report concordant positive results. One study looked at type I and the other at type II diabetes. Another study demonstrated a decrease in plasma thrombomodulin after 1.5yrs of ramipril therapy (type I and II diabetes). The remaining studies assessed some aspect of vasodilatory function. Three reported a benefit with regards to resistance vessel endothelial function in either type I or type II diabetic patients, and negative findings in type I diabetic patients were reported in a further two studies that assessed brachial (conduit) artery dilatation. In contrast one additional study demonstrated an improvement in femoral (conduit) artery dilatation after only one week of treatment in type I diabetic
patients with microalbuminuria.

3. Congestive heart failure (3 studies (number of participants unclear), 2 double-blind RCTs and 1 cohort study).

The three studies were very heterogeneous and included very few participants (minimum of n=69). One study based on tissue-plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) measurements was negative. A second study showed short-term positive effects in symptomatology, resistance vessel endothelial function and soluble adhesion molecule levels, but only in a small number of symptomatic patients. The final study showed a slight worsening of in vitro endothelium-dependent relaxation of small resistance vessels in patients treated for 6-43mths with ACE inhibitors.

4. Coronary artery disease (6 studies (495 participants), 3 double-blind RCT, 1 RCT, 1 cohort, and 1 double-blind crossover study).

Three of the studies pertained to stable patients who had had recent myocardial infarctions and the remainder were stable patients with angiographically documented coronary artery disease. All of the studies reported positive results and suggested that ACE inhibitors improve endothelium-mediated coronary conduit function and endothelium-mediated fibrinolytic function after relatively brief courses of therapy (1-6mths).

5. Dyslipidemia (2 studies (66 participants), both double-blind placebo-controlled trials).

One study showed ACE inhibitors improved forearm resistance vessel endothelial function in patients with hypercholesterolemia (average LDL in range of 4.5mmol/L in spite of lipid lowering therapy). The second study showed ACE inhibitors abrogated post-prandial endothelial dysfunction compared to losartan which only marginally deteriorated the condition.

6. Immunoglobulin A nephropathy (2 studies (52 participants), both cohort studies).

Both studies were consistent in demonstrating a beneficial effect of ACE inhibitors on endothelium-related functions, namely von Willebrand factor (vWF) levels and improvement in the glomerular barrier to large, but not small, dextran particles. Whether these effects were correlated with conduit or resistance artery effects in other vascular beds is not known.

Authors' conclusions
ACE inhibitors appear to improve endothelial dysfunction in patients with coronary artery disease, dyslipidemia, hypertension and IgAN. Conflicting evidence exists in studies of patients with congestive heart failure and diabetes. Further trials are required to clarify and define the prevalence of endothelial dysfunction and the predictors of response in all of these conditions.

CRD commentary
This review is based on a search of two electronic databases. The search terms used are not stated and as no attempts were made to locate unpublished data there is a risk of publication bias. All of the inclusion criteria are quite broad including the type of study design. Very few methodological details are provided and it is unclear how studies were selected for inclusion and the data extracted. In particular this is a single author study and it is unclear whether additional individuals were involved in these processes. This may introduce bias into the review.

The quality of the studies was not formally assessed, although some design issues relating to randomisation, controls and blinding are reported in the data tables. The data tables also adequately summarise a number of other study details and demonstrate the wide range of study designs included in the review. The use of a narrative review is therefore appropriate given the wide range of studies, which are subgrouped into the different disease states. Some of the differences contributing to the heterogeneity between studies are also discussed along with other issues that could affect the review. Overall, the findings would appear to be reasonable although they should be treated with caution given the limitations of the review outlined above.
Implications of the review for practice and research
Practice: The author did not state any implications for practice.

Research: The author states a number of implications for further research. Trials are needed to determine the true prevalence of endothelial dysfunction in various disease states; to see if therapy can be tailored and outcomes improved by identifying such patients; to establish whether dysfunction exists in conduit arteries or resistance arterioles, or both; to determine which other aspects of endothelial dysfunction are amenable to therapy; to clarify which factors predict beneficial responses to ACE inhibitors; and to determine which ACE inhibitors are most efficacious. In addition, prospective, randomised, double-blind parallel trials are required in hypertensive patients using both basal and stimulated nitric oxide outcomes. These trials should also compare the relative effectiveness of different ACE inhibitors. There is also a need in diabetic patients for well-designed trials of longer duration that measure many of the complicated abnormalities and characteristics of diabetes that may be linked to endothelial function and therapy.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.