Vasodilator therapy in patients with aortic insufficiency: a systematic review
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CRD summary
This review investigated the long-term effect of vasodilators for asymptomatic patients with chronic aortic insufficiency. The authors concluded that the role of vasodilators in this context remains to be determined. Despite a number of methodological weaknesses, the conclusions of the review are generally supported by the evidence presented.

Authors' objectives
To assess the long-term effect of vasodilators for asymptomatic patients with chronic aortic insufficiency (AI).

Searching
MEDLINE, Current Contents and the Cochrane Library were searched to October 2006 for eligible studies; the search terms were reported. Reference lists from retrieved articles and recent review articles were also examined. The search was restricted to publications in the English language.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a minimum follow-up of 4 weeks were eligible for inclusion.

Specific interventions included in the review
Studies that compared vasodilators (hydralazine, calcium-channel blockers and angiotension-converting enzyme (ACE) inhibitors) with at least one comparison intervention (placebo or digoxin) were eligible. The vasodilators in the review included hydralazine (daily dose 150 to 300 g), ACE inhibitors (captopril 75 mg and enalapril 20 to 40 mg) and calcium-channel blockers (felodipine 10 mg and nifedipine 40 mg). These were compared head-to-head, or with digoxin or placebo, for durations ranging from 12 weeks to 7 years.

Participants included in the review
Studies that enrolled participants with chronic asymptomatic AI of at least moderate severity and with normal function of the left ventricle were eligible. The authors excluded studies with a substantial proportion of participants with mild chronic AI or with severe left ventricular (LV) systolic dysfunction at baseline. The participants in most of the included studies had AI that was described as at least moderate, significant, or grade II. In one study up to 29% of the participants had mild disease only.

Outcomes assessed in the review
Studies that assessed either clinical outcomes or haemodynamic and structural parameters were eligible. The latter included left ventricular ejection fraction (LVEF), LV end-systolic or end-diastolic volume index (LVESVI and LVEDVI, respectively), LV end-systolic or end-diastolic dimension (LVESD and LVEDD, respectively), regurgitant fraction, fractional shortening and LV mass.

The clinical outcomes reported in the review were rate of progression to aortic valve replacement (AVR) over 6 to 7 years' follow up, and post-operative LVEF after AVR. Haemodynamic and structural outcomes were as listed above, plus blood-pressure, mean wall stress and reduction in grade of AI.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The following aspects of study validity were assessed: evidence of allocation concealment, number of patients screened
for enrolment, use of a placebo group, extent of blinding and the proportion of participants followed up. The authors
stated that a standardised abstraction form was used to collect data on trial quality, but did not state how many reviewers
performed the quality assessment and whether they made decisions independently.

Data extraction
The authors stated that a standardised abstraction form was used, but did not state how many reviewers performed the
data extraction and whether they made decisions independently.

For clinical outcomes, data were reported as the proportion of each group experiencing the event or as a mean
percentage and standard deviation, with a p-value for differences between the groups. For haemodynamic and structural
parameters, the outcomes were expressed in tables with symbols denoting whether parameters of interest increased,
decreased or remained unchanged in each intervention group.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative, grouped by outcome and type of intervention.

How were differences between studies investigated?
Individual differences between the studies were highlighted in the body of the text.

Results of the review
Ten RCTs (n=544) were included.

In terms of study quality, none of the included studies provided evidence of allocation concealment. Seven studies were
double-blinded with a placebo arm; the remaining 3 studies were unblinded head-to-head comparisons. Six studies
followed up over 90% of the participants, while follow-up in the other four ranged from 55 to 87%. The number of
patients screened for enrolment was not reported in the review.

Clinical outcomes. Two RCTs reported clinical outcomes. One double-blinded RCT (n=143) found that patients on
nifedipine had a significantly lower rate of progression to AVR than patients on digoxin after 6 years' follow-up (34%
+/- 6 versus 15% +/- 3, p=<0.001). Post-operative LVEF was significantly higher in the nifedipine arm (65% +/- 4
versus 58% +/- 8, p=0.04).

One unblinded RCT (n=95) found no statistically significant difference in the rate of progression to AVR between
patients on enalapril, nifedipine or placebo. An on-treatment analysis did not change this finding. Haemodynamic and
structural outcomes.

ACE inhibitors versus placebo (2 randomised comparisons, n=63 and 20): no difference was found in haemodynamic
or structural parameters at follow-up.

ACE inhibitors versus other vasodilators (3 randomised comparisons): 1 RCT found no difference between enalapril
and nifedipine (n=64), while another RCT (n=70) found enalapril significantly more effective at reducing LVESVI and
LVEVDI than hydralazine; the third study (n=25) found that captopril significantly reduced LVEDD and the grade of
AI (p=<0.01), while no difference was noted in the nifedipine group. No other statistically significant findings were
reported in these studies.

Calcium-channel blockers versus placebo (2 RCTs): an RCT comparing nifedipine with placebo (n=70) reported
significant improvements in LVEDVI, mean wall stress, LVEF and LV mass in the intervention group, with no
significant changes in the placebo group. A study of felodipine versus placebo (n=16) reported significant
improvements in LV mass and regurgitant fraction in the intervention group, but no difference on several other
parameters.

Calcium-channel blockers versus other vasodilators (3 RCTs): a comparison of nifedipine versus digoxin (n=143)
showed improvements in LVESVI, LVEF and LV mass in the nifedipine group compared with the digoxin group. As noted already, two other randomised comparisons found no statistically significant benefit for nifedipine compared with ACE inhibitors (n=64 and n=25).

Hydralazine versus placebo (3 RCTs): one RCT (n=14) found that LV mass increased significantly with hydralazine but not with placebo (p=<0.05). Another RCT (n=37) found that hydralazine improved LVESVI, LVEDVI and LVEF in comparison with placebo, but other measures were unchanged in both groups. A third RCT (n=54) found statistically significant reductions in LVESVI and LVEDVI and improvements in LVEF with hydralazine but not with placebo. LV mass was unchanged in either group.

Further analyses were reported in the paper.

**Authors' conclusions**
Most studies failed to indicate any consistent improvement with the long-term use of vasodilators on haemodyamic and structural outcomes. Data on clinical outcomes were scanty and inconsistent. There was no indication of harm from long-term use of vasodilators, apart from one report of an increase in LV mass with hydralazine; however, studies may have been too small to assess harms. The role of vasodilators in the management of asymptomatic patients with chronic AI remains to be determined.

**CRD commentary**
The review question and inclusion criteria were clear and there was sufficient descriptive detail about the primary studies. The literature search was adequate, although it is possible that studies were missed because of the language restriction; the authors did not attempt to assess publication bias. There were insufficient details of the study selection, data extraction and quality assessment processes to establish whether decisions were made independently by more than one reviewer, in order to minimise the potential for bias in the review process. Generally, the data extracted from the primary studies were presented clearly in the text and/or the tables. However, the use of symbols to represent effect estimates in the results table was not clearly explained, and in some cases neither the table nor text indicated whether the results were statistically significant. There was some inconsistency in sample numbers between the table and text. Despite these methodological weaknesses, the overall conclusions of the review are supported by the evidence presented.

**Implications of the review for practice and research**
Practice: Routine use of vasodilators in the management of asymptomatic patients with chronic AI cannot be recommended on current evidence.

Research: Well-designed clinical studies with easily reproducible assessment measures, adequate blinding and standardised referral protocols are urgently needed to ascertain the role of vasodilators in the management of patients with chronic AI. Such studies should focus on clinical outcomes such as overall survival time or time to AVR. Other issues to be addressed include appropriate dosing, different classes of vasodilator, and the potential for harm.

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