Systematic review of trials using vasodilators in pulmonary arterial hypertension: why a new approach is needed


CRD summary
The review concluded that the impact of vasodilators on long-term survival in pulmonary arterial hypertension remained uncertain. Limitations in review design meant conclusions drawn from most of the analyses should be interpreted with caution, but since most studies did not assess long-term survival the authors’ cautious overall conclusion appears likely to be reliable.

Authors' objectives
To assess the effectiveness of approved treatments for pulmonary arterial hypertension.

Searching
EMBASE, MEDLINE and CINAHL were searched for studies published in English between January 1985 and April 2009; this was an update review (see Other publications of Related Interest).

Study selection
Randomised controlled trials (RCTs) of patients with idiopathic pulmonary arterial hypertension (and related conditions) treated with epoprostenol, prostacyclin analogues, endothelin receptor antagonists or phosphodiesterase-type-5 inhibitors were eligible. The main outcome measures were total mortality and exercise capacity assessed by the six-minute walk test; haemodynamic effects were also assessed.

Around three-quarters of included participants were functional class III or IV according to the New York Heart Association classification. Mean baseline six-minute walk tests were around 345 metres. A variety of drugs and doses were studied. Most trials were placebo-controlled. Most trials used exercise capacity (mostly by six-minute walk test) as the primary outcome. Mean trial duration was 14 weeks.

The authors did not state how many reviewers selected studies.

Assessment of study quality
The authors did not state that they assessed study quality.

Data extraction
Intention-to-treat data were extracted in order to calculate relative risks (RR) or mean differences with 95% confidence intervals (CI). Standard errors were estimated when not published. When a trial had no events in one or more groups, 0.25 was added to event counts and 0.5 to group sizes. Multi-arm trials of different doses had active arms combined.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Meta-analyses to calculate pooled relative risks or weighted mean differences (WMD) were performed using a fixed-effect model weighted by inverse variance. When significant heterogeneity was found a random-effects model was used. Cochran Q test was used to assess heterogeneity. Sensitivity/subgroup analyses assessed the effect of drug category, disease severity (estimated using the median value of the six-minute walk distance at baseline) and mortality rates (below and above the median mortality of all trials). Linear regressions were performed and included looking at the association of total mortality with baseline exercise capacity and with change in exercise capacity during follow-up. Publication bias was assessed by funnel plot.

Results of the review
Twenty-six RCTs (n=3,519) were included. Sample sizes ranged from 16 to 470 participants.

**Exercise capacity:** All treatments produced a statistically significant increase compared with placebo or control. Epoprostenol and prostacyclin analogues had a WMD of 35.4m (95% CI 17.3 to 53.5; nine trials), endothelin receptor antagonists a WMD of 46.1m (95% CI 38.1 to 54.2; eight trials) and phosphodiesterase-type-5 inhibitors a WMD of 33.8m (95% CI 24.8 to 42.7; six trials). There was significant heterogeneity for the epoprostenol and prostacyclin analogues analysis (but not for other analyses). Pooled WMD for all three drug types was 38.5m (95% CI 29.9 to 47.2; 23 trials). Subgroup analyses showed no differences in effect size.

**Mortality:** None of the individual drug types showed a statistically significant reduction in mortality, but pooling all three types produced a significant result (RR 0.61, 95% CI 0.38 to 0.98; 23 trials) that represented a reduction in all-cause mortality of 39% (95% CI 2% to 62%). A reduction in mortality was seen in trials that included patients who were functional class IV (RR 0.58 95% CI 0.35 to 0.96; 16 trials), but not in trials that excluded these patients. There was no significant statistical heterogeneity.

**Haemodynamics:** All three types of treatment showed a significant improvement in pulmonary vascular resistance and pulmonary artery pressure (result details were provided), but this represented only a 6% decrease from baseline. The was no evidence of publication bias. Further results were reported.

**Authors' conclusions**
The impact of vasodilators on long-term survival in pulmonary arterial hypertension remained uncertain.

**CRD commentary**
The review question was supported by appropriate inclusion criteria. Three electronic databases were searched to identify relevant studies. The restriction to studies published in English meant that relevant studies may have been missed. The authors did not appear to have used suitable methods (such as independent duplicate processes) to reduce risks of reviewer error and bias during study selection and data extraction. Study quality was not assessed, which meant it was not possible to evaluate the strength of the evidence. Not all study details were presented clearly (for example, it was often unclear what comparator treatments were used). Suitable methods were used to pool data and assess heterogeneity. The review had three main flaws: a lack of study quality assessment; an absence of methods to reduce the risk reviewer error and bias; and the possibility that relevant studies were missed during the searches. Results of the shorter-term analyses should be interpreted with caution. However, the authors' cautious overall conclusion appears likely to be reliable, since most studies did not assess long-term survival.

**Implications of the review for practice and research**
**Practice:** The authors stated that patients needed to be informed that no proven long-term treatment existed.

**Research:** The authors made numerous recommendations that included: adoption of new trial designs that better address clinical benefits; use of new end points that incorporated best understanding of the disease and not those that were easy to administer; and use of longer durations of study and other strategies to clarify whether survival was affected.

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Record Status
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.