

# **Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis**

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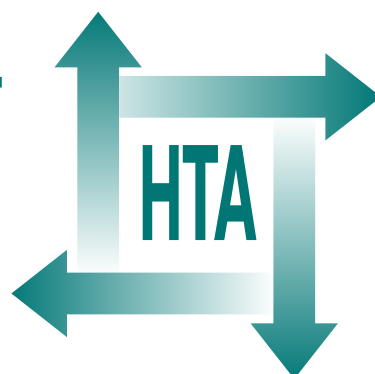
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## ***Executive summary***

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## Executive summary

### Background

Stable angina is managed primarily through education and lifestyle advice, drug therapy and vascular surgery. Some patients exhibit symptoms that are not optimally controlled with the (apparently) optimal medication and surgical options available (termed refractory angina). Enhanced external counterpulsation (EECP) is a technique that can be used to improve symptoms in chronic stable angina. However, the role of EECP has not yet been well defined; its use in patients with mild heart failure has also been investigated following positive outcomes in patients with both angina and heart failure in two medium-sized multicentre studies.

### Objectives

The primary objectives were: (1) to determine the clinical effectiveness and cost-effectiveness of EECP compared with usual care and placebo for refractory stable angina and heart failure; and (2) to undertake analyses of the expected value of information (EVI) to assess the potential value of future research on EECP.

### Methods

A systematic review of the evidence of the clinical effectiveness of EECP was performed. Searches were undertaken to identify relevant published and unpublished clinical and cost-effectiveness literature. The website of the main EECP manufacturer, Vasomedical, was also searched. Update searching was conducted in March 2008 on selected databases.

Randomised controlled trials (RCTs), non-RCTs, cohort studies with a contemporaneous control group (i.e. not historical controls) and case-control studies of patients with refractory stable angina or heart failure were included. Usual care (drugs, cardiac rehabilitation, revascularisation) or placebo (sham EECP) were the comparators. The results of the included studies were discussed in a narrative synthesis.

A broad range of studies was considered for inclusion in the review of cost-effectiveness, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included. The quality of studies was assessed according to a checklist updated from that developed by Drummond and Jefferson (1996).

A decision model was developed to evaluate a strategy of EECP treatment compared with no treatment in adults with chronic stable angina. This was used to estimate the cost-effectiveness of EECP, in terms of cost per quality-adjusted life-year, under a range of assumptions. Decision uncertainty associated with this analysis was presented and used to inform future research priorities using value of information analysis.

### Results

#### Clinical effectiveness

Five studies were included in the review. There was one RCT – the Multicenter Study of Enhanced External Counterpulsation trial (MUST-EECP) ( $n = 139$ ) – and three non-randomised controlled studies of EECP for angina (one comparison of two registries and two small comparisons with usual care). For heart failure there was one RCT – the Prospective Evaluation of EECP in Congestive Heart Failure (PEECH) study ( $n = 187$ ).

The MUST-EECP RCT compared angina patients randomised to either EECP or sham EECP. Time to greater than or equal to 1-mm ST segment depression (exercise-induced ischaemia) was statistically significantly improved in the EECP group compared with the control group, mean difference 41 seconds [95% confidence interval (CI) 9.10–73.90]. There was no statistically significant difference between the EECP and control groups in the change in exercise duration from baseline to end of treatment, self-reported angina episodes per day or daily nitroglycerin use, and the clinical significance of the limited benefits was unclear.

There were more withdrawals due to adverse events (AEs) in the EECP group than in the control group, as well as a greater proportion of patients with adverse events [relative risk (RR) 2.13, 95% CI 1.35–3.38]. There were some weaknesses in the internal validity of this trial and limitations in the generalisability of the results because of the substantial exclusion criteria and large proportion of participants with Class I or II disease; patients seen in clinical practice may exhibit angina more severe than this. There was also a lack of data about long-term outcomes.

The three non-randomised studies compared EECP with elective percutaneous coronary intervention (PCI) and usual care. These studies were of poor quality. There was a high risk of selection bias in all three studies; therefore, the results need to be treated with considerable caution. The study comparing an EECP registry with a PCI registry reported similar 1-year all-cause mortality in both groups.

In the PEECH trial, patients with heart failure were randomised to EECP or to usual care (pharmacotherapy only). At 6 months post treatment, the proportion of patients achieving at least a 60-second increase in exercise duration was higher in the EECP group (RR 1.39, 95% CI 0.89–2.16,  $p = 0.016$  from logistic regression that factored site and baseline), but the proportion with an improvement in peak  $\text{VO}_2$  was similar in both groups, mean difference 0.30 (95% CI –0.53 to 1.13). The clinical significance of this is unclear. The proportion of patients in the EECP group with an improvement in New York Heart Association classification was higher at 6 months (RR 2.25, 95% CI 1.25–4.06), as was the mean exercise duration, mean difference 34.6 (95% CI –4.86 to 74.06). For most outcomes, the results at 6 months reflected those at 3 months except for improvement in quality of life with EECP, which was lower at 6 months than at 3-month follow-up. There were more withdrawals in the EECP group than in the control group as a result of AEs (RR 1.05, 95% CI 0.67–1.66). There were some limitations in the generalisability of results of the trial, and the 6-month follow-up period provided limited data on long-term outcomes.

### Cost-effectiveness

The review of cost-effectiveness evidence found only one unpublished cost–utility analysis, which, from a UK NHS perspective, had a number of important limitations.

The base-case analysis for a population of patients with angina severity similar to participants in the MUST-EECP trial demonstrates that the long-term maintenance of quality of life benefits of EECP is central to the estimate of cost-effectiveness. If quality of life benefits of EECP are assumed to be maintained for no more than 1 year after treatment, EECP does not appear to be cost-effective, as defined by the National Institute for Health and Clinical Excellence's cost-effectiveness threshold range (National Institute for Clinical Excellence, 2004). In contrast, if quality of life benefits are maintained over a lifetime, the cost-effectiveness of EECP appears clear, with a resulting incremental cost-effectiveness ratio well below conventional thresholds. The base-case analysis, based on pooled expert beliefs about the durability of quality of life benefits, suggests that EECP is cost-effective (incremental cost-effectiveness ratio = £18,643) for this patient population, but the probability is around 0.5, indicating high uncertainty in the estimate. Value of information analysis suggests that future research in this area is likely to be of significant value.

### Conclusions

The results from a single RCT do not provide firm evidence of the clinical effectiveness of EECP in refractory stable angina. Further, higher quality RCTs are required to investigate the benefit of EECP in terms of time to ST segment depression, exercise duration, angina frequency and patients' requirements for nitroglycerin, and whether these outweigh the common adverse effects associated with this intervention.

Similarly, the results from a single RCT in heart failure do not provide firm evidence of the clinical effectiveness of EECP. Statistically significant modest benefits were seen in terms of exercise duration and New York Heart Association classification; however, their clinical significance is unclear. These effects need to be investigated in further RCTs.

To date, the impact of EECP on mortality or major adverse cardiovascular events has not been investigated in angina or heart failure.

EECP is cost-effective if the observed quality of life benefits are assumed to continue throughout a patient's lifetime. However, there remain

uncertainties around the longer-term effects of the intervention.

### **Suggested research priorities**

In order to draw firmer conclusions regarding the effectiveness of EECP, further RCTs in both angina and heart failure are warranted. For angina, the value of information analysis suggests that future research in this area is likely to be of significant value. This research should be directed towards obtaining more precise estimates of the quality of life following EECP treatment and the duration over which these benefits are expected to be maintained.

Long-term follow-up trials assessing quality of life from EECP in both refractory stable angina and heart failure are required. There is also an important need to establish the efficacy of EECP

in patients with truly refractory severe angina, who have much more severe symptoms than patients in the MUST-EECP study. The design of any future trial should take account of existing angina guidelines, such as SIGN 2007 (Scottish Intercollegiate Guidelines Network, 2007), and ensure correct selection of patients for EECP therapy, i.e. only after education, comprehensive rehabilitation and real optimisation of medication. The investigation of adverse effects should be an important outcome in any future RCT.

### **Publication**

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The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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