Correspondence

Is it time for a re-assessment of EECP in the UK?

Dear Sirs,

External enhanced counter pulsation (EECP) is a validated, safe, non-invasive treatment for angina and heart failure. To date, more than 300,000 people worldwide have been treated, with 15,000 involved in clinical trials. The 2013 European Society of Cardiology (ESC) Guidelines on the Management of Stable Coronary Artery Disease[1] give EECP a level 2a recommendation, meaning that the treatment should be considered for patients with refractory angina. The recommendation was made following a review of published data on the mechanisms of action and clinical benefits of EECP. The ESC concluded that the results of these studies prove the concept and clinical effectiveness of EECP.

EECP and its invasive counterpart, the intra-aortic balloon pump (IABP), began parallel development in the late 1950s and both are now clinically established in North America, China, Russia, India and the Middle East. By contrast, EECP remains largely unknown in the UK, with only three active treatment centres. In 10 years, less than 800 UK patients have received treatment. The majority of UK cardiologists have little or no clinical experience with EECP and in primary care it remains almost completely unknown.

The effects of EECP treatment on the left heart and coronary circulation are identical to those of the IABP. Both reduce afterload and myocardial oxygen demand. EECP also augments arterial blood flow to other organs such as the brain, kidneys and skin and, by enhancing venous return to the right heart, increases both preload and cardiac output.

Possible mechanisms of action include improved diastolic left ventricular (LV) filling, improved endothelial function, coronary collateral recruitment, neurohormonal and cytokine changes, neovascular growth, improved microvascular function and peripheral muscle training. There is ongoing research in all these areas. The increased volume and velocity of coronary blood flow increases endothelial shear stress, leading to a rise in nitric oxide levels and falls in endothelin-1, B-type natriuretic peptide and asymmetric dimethyl arginine. These changes are sustained for many weeks after a course of treatment. There are also falls in levels of cytokines, such as TNF–α and MCP-1. Improvements in endothelial function, arterial stiffness and flow mediated vasodilatation occur in active EECP, but not sham EECP-treated individuals. After one hour of active EECP there is a significant rise in platelet cyclic guanosine monophosphate (GMP) levels, equating to increased nitric oxide synthase activity. Exercise and stress lead to a rapid rise in peripheral blood endothelial progenitor cell numbers, but this rise is blunted in the elderly and in the presence of endothelial dysfunction. EECP causes a rise in peripheral blood populations of bone marrow derived endothelial progenitor cells and a rise in monocyte/macrophage derived endothelial-like cells. These cells secrete vascular endothelial growth factors (VEGF) stimulating angiogenesis. Some of the benefits of treatment are through peripheral muscle training, suggesting an important role for EECP in cardiac rehabilitation. Treatment also affords prolonged one-to-one contact time with trained therapists, which may provide additional psychological support.

Symptoms and exercise improved

EECP improves symptoms and exercise capacity. It reduces angina class, heart failure level and nitrate consumption in 80% of cases of refractory angina, with more than 60% maintaining benefit five years after a single 35-hour course. Treatment reduces hospital readmission rates and visits to emergency departments, outpatient clinics and GP surgeries. It has been shown to be cost effective.

Other, non-cardiac conditions may benefit from EECP, including peripheral vascular disease, erectile dysfunction, renal impairment, chronic venous ulcers and even sleep apnoea and depression. It can improve functional recovery after ischaemic stroke and may enhance the effects of thrombolysis when used in acute thrombo-embolic cerebrovascular events.

In the UK in 2009, EECP was subjected to a systematic review and economic analysis,[2] with the conclusion then that there was not enough firm evidence to recommend its use in standard clinical practice. Much of what we know about its mechanisms of action has been published since that review, leading to the recent ESC recommendations. It is therefore time for the use of EECP in the UK to be re-assessed.

Conflict of interest

RR runs the EECP unit at Alexander House Private Medical Clinic in Wimbledon, London, and has received honoraria from Vasomedical Inc. USA.

Robin Roberts
Consultant Cardiologist
15 Princes Road, Wimbledon, London, SW19 8RQ

(robinhroberts@aol.com)

References

1. Montalescot G, Sechtem U, Achenbach S, *et al*. The task force on the management of stable coronary artery disease of the European Society of Cardiology. 2013 ESC guidelines on the management of stable coronary artery disease. *Eur Heart J* 2013;**34**:2949–3003. http://dx.doi.org/10.1093/eurheartj/eht296

2. McKenna C, McDaid C, Suekarran S, *et al*. Enhanced external counterpulsation for stable angina or heart failure: a systematic review and economic evaluation. *Health Technol Assess* 2009;**13**. http://dx.doi.org/10.3310/hta113240

Aggressive risk factor modification: 30 year follow-up of IHD and non-haemorrhagic stroke

Dear Sirs,

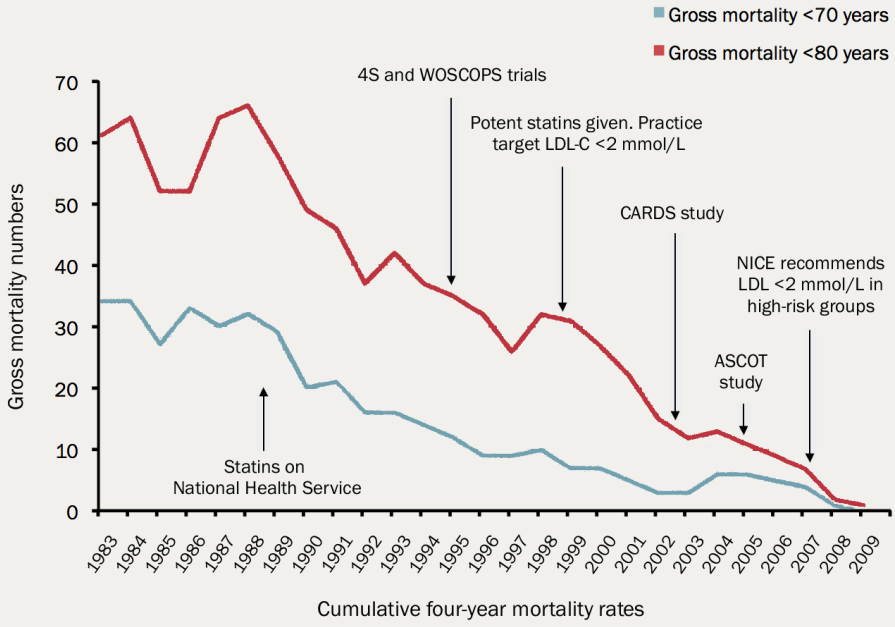
In a single doctor's practice in a high-risk area of South Sheffield, aggressive measures were taken to prevent ischaemic heart disease (IHD) and non-haemorrhagic stroke (ST) since 1980. Four cardinal risk factors were detected: smoking, diabetes, hypertension and cholesterol. Smoking, diabetes and hypertension were treated critically using standard guidelines and applying the latest evidence available independent of cost from 1980 onwards. Mortality from IHD has been known for many years to be directly related to the level of serum cholesterol and more specifically to the low-density lipoprotein (LDL) cholesterol. It was assumed therefore that as levels of LDL cholesterol approached zero then IHD mortality would almost be abolished. Diet, fibrates and cholestyramine were used as lipid-lowering therapy until 1988 after which statins were introduced on an intensive scale for all standard high-risk patients and those with a 20% risk of atherosclerotic vascular disease (AVD) under 70 years (British National Formulary).

Following the publication of the 4S (Scandinavian Simvastatin Survival Study) and WOSCOPS (West of Scotland Coronary Prevention Study) studies in 1995, simvastatin was given to patients with a 15% AVD risk under 80 years.

From the year 2000, atorvastatin and rosuvastatin were supplied to patients who failed to achieve an LDL cholesterol <2.0 mmol/L. Where statin side effects were experienced low doses of rosuvastatin 5 mg daily or less were given. All death records were retained and summarised from 1981 and divided into IHD, ST, malignancy and other. Population densities in decades were recorded.

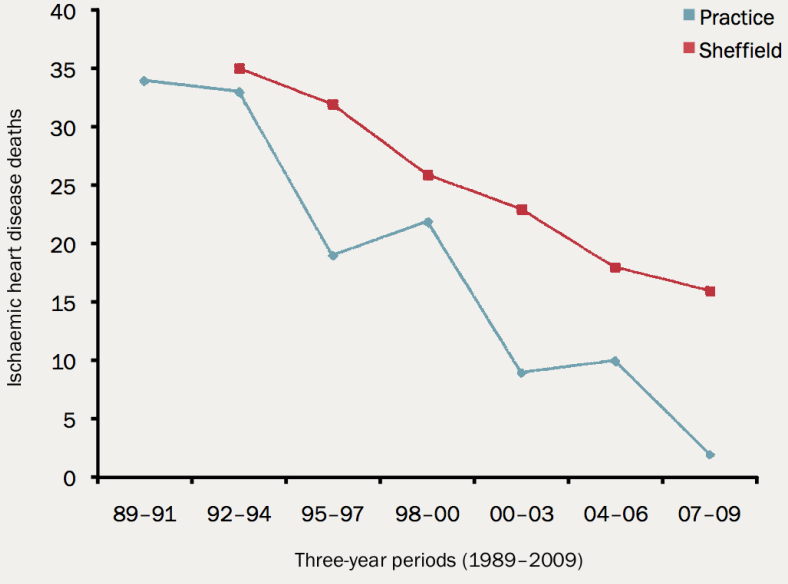
By reference to **figure 1**, using a four-year cumulative record of IHD and ST deaths, we can see that by 2008 in patients under 70 years, mortality was abolished and virtually abolished in those under 80 years. The fall in mortality follows closely the introduction of statins and the increasing progress towards more aggressive treatment to achieve an LDL cholesterol <2.0 mmol/L. Those in the over 70 age group were only offered statins from

Figure 1. Mortality gross numbers of atherosclerotic vascular disease and stroke four-year cumulative progression (1981–2010)



Key: 4S = Scandinavian Simvastatin Survival Study; ASCOT = Anglo Scandinavian Cardiac Outcomes Trial; CARDS = Collaborative Atorvastatin Diabetes Study; LDL-C = low-density lipoprotein cholesterol; NICE = National Institute of Health and Care Excellence; WOSCOPS = West of Scotland Coronary Prevention Study

Figure 2. The comparative mortality from ischaemic heart disease in a Sheffield practice population aged under 80 years, compared with the whole of Sheffield



1995 onwards and only gained full treatment after 2000. This is reflected in their mortality level falling at a much later time than the under 70 age group (**figure 1**).

Comparing IHD and ST mortality in the first 10 years from 1981 in our practice, to the levels in the whole of Sheffield, we found these were roughly parallel (**figure 2**). After 1990 the mortalities began to diverge markedly with increasing difference until 2010. Whilst in Sheffield mortality in the last four years of the study period had approximately halved, compared with the first 10 years, the mortality in the practice was abolished in the under 70 age group and almost abolished in the 70–79 age group in the same period (see **figure 2**).

These data demonstrate that aggressive correcting of the lipid profile if actively pursued nationally would almost abolish mortality and morbidity for IHD and non-haemorrhagic ST. This would not only benefit patients, but would also be likely to be highly cost effective in saving hospital, general practitioners and social costs in treating the consequences of an event.

The present national policy as advocated by the National Institute for Health and Care Excellence and other authorities gives too little statin therapy at too late a stage in life and should be urgently amended

Acknowledgment

JR would like to acknowledge the help provided by Dr Anthony Wierzbicki of Guy's & St Thomas' Hospital, London.

Dr John Revill
General Practitioner
Lowedges Clinic, 7 Lowedges, Sheffield, S8 8LW

Assessing the clinical benefits of drugs for dyslipidaemia

Dear Sirs,

A recent editorial in the *New England Journal of Medicine*[1] highlights several challenging issues in the development of new treatments for lipid disorders. There is now uncertainty regarding the regulatory approach of approving drugs on the basis of favourable lipid effects and evaluating clinical benefit after approval.

In numerous trials and several meta-analyses of outcome trials, the reduction of low-density lipoprotein (LDL) cholesterol has been shown to be associated with outcome benefit.[2–4] Most of these studies have been performed with statins. The first demonstration of efficacy in lowering LDL cholesterol to reduce cardiovascular morbidity, however, was achieved with bile acid sequestrants.[5] A reduction of LDL cholesterol by 1 mmol/L results in a 20% reduction of cardiovascular events regardless of its baseline levels.[3,4] LDL cholesterol is one of the best validated end points in medicine. Therefore, while the benefit of reducing LDL-cholesterol can be quantified, the benefit risk assessment of new interventions to reduce LDL-cholesterol is mainly influenced by the risk profile of a new drug. In the ILLUMINATE trial, torcetrapib failed to demonstrate benefit despite a 25% reduction in LDL cholesterol, because an increase in blood pressure induced by torcetrapib could not offset the benefit in reducing LDL cholesterol.[6]

In the absence of a safety signal, the expected benefit of a new intervention can be realised in the target population through long-term trials with clinical end points, to be conducted post-authorisation

Gilbert Wagener
Transcrip Partners
400 Thames Valley Park Drive, Reading, RG6 1PT

(gilbert.wagener@transcrip-partners.com)

References

1. Hiatt WR, Smith RJ. Assessing the clinical benefits of lipid disorder drugs. *N Engl J Med* 2014;**370**:396–99. http://dx.doi.org/10.1056/NEJMp1313866

2. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.

3. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**:1267–78. http://dx.doi.org/10.1016/S0140-6736(05)67394-1

4. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–81. http://dx.doi.org/10.1016/S0140-6736(10)61350-5

5. Tyroler HA. Cholesterol and cardiovascular disease. An overview of Lipid Research Clinics (LRC) epidemiologic studies as background for the LRC Coronary Primary Prevention Trial. *Am J Cardiol* 1984;**54**:14C–19C. http://dx.doi.org/10.1016/0002-9149(84)90851-8

6. Bartler PJ, Caulfield M, Eriksson, M *et al*. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;**357**:2109–22. http://dx.doi.org/10.1056/NEJMoa0706628