

Impact case study (REF3b)

Institution: London School of Hygiene & Tropical Medicine (LSHTM)
Unit of Assessment: UoA2 – Public Health, Health Services & Primary Care
Title of case study: Improving treatment of hypertension in the very elderly
<p>1. Summary of the impact</p> <p>Hypertension is well known to increase the risk of stroke and other cardiovascular diseases, but up until recently few very elderly people received treatment for it. The first large randomised trial of the pharmacological treatment of hypertension in people aged 80 and over – the Hypertension in the Very Elderly Trial (HYVET) – demonstrated clear benefits of such treatment for this age group. As a direct result of HYVET, changes were made to a number of influential national and international guidelines on the treatment of hypertension, including those published by the UK’s National Institute for Health and Clinical Excellence (NICE).</p> <p>2. Underpinning research</p> <p>Hypertension (high blood pressure) is a major health problem worldwide. The condition is just as prevalent in the developing world as in high-income countries and affects an estimated one in four adults. The incidence of hypertension increases dramatically with age, affecting around 30% of the population aged 40–49 and 75% of those aged over 70. Estimates suggest that about 54% of stroke, 47% of ischaemic heart disease and 25% of other cardiovascular diseases worldwide are attributable to hypertension. Given that heart disease and stroke rank in the top three causes of mortality and disability in the Global Burden of Disease Study, strategies to address hypertension are an urgent priority.</p> <p>While prevention of hypertension through weight control, exercise and diet is desirable, it is difficult to achieve, leaving control by pharmacological treatment as the most effective intervention. Trials have demonstrated the benefit of drug treatment on stroke mortality and morbidity. However these trials included very few people aged 80 years and over and there was concern that treatment for this age group might be harmful.</p> <p>The HYVET was designed to fill the gap in this knowledge and provide evidence for this neglected age group. The trial was particularly important in view of ethical concerns that elderly people were being denied the opportunity to benefit. Conversely, if treatment was harmful this would have major implications for those already on treatment.</p> <p>The HYVET trial was conceived and designed by Professor Chris Bulpitt (Hammersmith Hospital, Imperial College) and Astrid Fletcher (Professor of Epidemiology of Ageing at LSHTM, joined in 1992 as Senior Lecturer) and led on from previous collaborative research in trials of hypertension treatment. HYVET was coordinated from the Hammersmith Hospital. Astrid Fletcher was responsible for the statistical aspects of the trial (including the sample size, trial stopping boundaries and plan of analysis) and of the design of add-on studies (dementia, fracture risk, quality of life). She participated in regular trial monitoring meetings and contributed to the preparation of manuscripts.</p> <p>HYVET was the first large trial of hypertension treatment in the over 80s. Nearly 4,000 patients took part in 195 centres across 13 countries in Western and Eastern Europe, China, Australasia and North Africa. The results showed that pharmacological treatment reduced overall mortality and stroke mortality and the incidence of heart failure.^{3.1} The results also suggested that treatment reduced dementia, although the evidence here – as with three other hypertension trials that had assessed dementia – was inconclusive.^{3.2} When the four trials including HYVET were pooled in a meta-analysis, a significant reduction in dementia from treatment was found, although the size of the reduction was small at 13%. The trial provided reassurance that the trial interventions (a thiazide diuretic and indapamide) had no adverse effects on fracture risk, an important result in the elderly.^{3.3}</p>

3. References to the research

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3.2 Peters, R, Beckett, N, Forette, F, Tuomilehto, J, Clarke, R, Ritchie, C, Waldman, A, Walton, I, Poulter, R, Ma, S, Comsa, M, Burch, L, Fletcher, A and Bulpitt, C for the HYVET investigators (2008) Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial, *Lancet Neurology*, 7(8): 683–689, doi: 10.1016/S1474-4422(08)70143-1. Citation count: 191

3.3 Peters, R, Beckett, N, Burch, L, de Vernejoul, M-C, Liu, L, Duggan, J, Swift, C, Gil-Extremera, B, Fletcher, A and Bulpitt C (2010) The effect of treatment based on a diuretic (indapamide) +/- ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET), *Age and Ageing*, 39(5): 609–616, doi: 10.1093/ageing/afq071. Citation count: 9

Research funding

Bulpitt (Imperial College), Fletcher (LSHTM), Pilot study for Hypertension in the Very Elderly Trial (HYVET), British Heart Foundation, 1994-1996, £150,000.

Bulpitt (Imperial College), Fletcher (LSHTM), Hypertension in the Very Elderly Trial (HYVET), British Heart Foundation 1997-2004, £741,649 and Institut de Recherches Internationales Servier, 2000-2009, £1m+.

4. Details of the impact

The trial results were first published in the *New England Journal of Medicine* in 2008, with an accompanying editorial stating ‘HYVET puts the question of the usefulness of treating hypertension in the very old to rest and provides important guidance to physicians and writers of such guidelines’.^{5.1}

As a result, updated national and international guidelines started to appear from 2009 onwards, all of which cited HYVET as their main source of evidence to support change. While no guideline is binding, in each case these are strong recommendations intended to improve standards, assist in the knowledge and training of health care professionals and help patients make informed decisions about their care.

The 2009 Canadian Hypertension Education Program recommendations for the management of hypertension stated ‘HYVET clearly demonstrates the beneficial effects of antihypertensive therapy in reducing the risk of stroke and death in very elderly patients; these results form the basis of the new recommendation to prescribe antihypertensive therapy regardless of age’.^{5.2}

The 2011 American College of Cardiology and American Hypertension Association published a joint consensus report with the European Society of Hypertension, and a number of American societies for various patient groups and clinical conditions. Emphasising the shift brought about by HYVET, the report was divided into two sections – evidence before the trial and evidence after. The report stated ‘The HYVET results provide clear evidence that BP lowering by drugs is associated with definite CV benefits in patients ≥80 years of age’.^{5.3}

In the UK the most influential guidelines are those from NICE. The revised guidelines prepared in consultation with the British Hypertension Society were published in 2011 based on a meta-analysis of HYVET data – used both in its entirety and divided into patient subgroups. The guidelines provided a firm recommendation to offer treatment to people aged 80 and over with hypertension.^{5.4}

Updated guidelines were also published in a number of other countries including Poland (2012)

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and Russia (2012).^{5.5} Outside Europe, organisations including the Brazilian Society of Hypertension (2010)^{5.6} and the South African Hypertension Society (2011) also published reviewed clinical guidance as a direct result of research findings.

A further influential guideline update was anticipated in mid-2013 in the USA but has been delayed. The eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) will be published by the National Heart, Lung and Blood Institute, part of the US Department of Health and Human Services, and will replace the current 2003 guidelines. The reach of these recommendations extends beyond the USA and they will be seen and adopted by practitioners throughout the developed world.

The HYVET trial has been widely reported by the media, with both the national and medical press picking up on the story and highlighting the positive findings of the trial. In 2008 HYVET was the subject of articles in the *New York Times*, the *Guardian* and the BBC and British Heart Foundation websites, all of which praised the HYVET researchers for addressing the needs of a frequently neglected age group. The *Guardian* article quoted James Goodwin, Head of Research at Help the Aged, as saying the findings had 'serious implications for the treatment of hypertensive people over 80'.^{5.7}

Mentions of HYVET in online clinical resources are too numerous to list but include the *Primary Care Cardiovascular Journal* (2008), *American Medical News* (2009) and *Swiss Medical Weekly* (2012) as well as the influential *F1000* (2008), which highlights recent research of clinical importance.

The HYVET trial has been recognised for its outstanding contribution to research by a number of awards including the Society for Clinical Trials Trial of the Year Award 2009.^{5.8} HYVET was nominated as one of the most important clinical trials of the year in 2009 by Medscape, an online resource for clinicians^{5.9} and recognised in the *F1000* Medicine All time Top 10 in 2009. The American Heart Association voted HYVET among the top 10 major advances in heart and stroke research.^{5.10}

5. Sources to corroborate the impact

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5.5 Karpov, IuA (2012) [New guidelines for hypertension in Russia – a priority of combined treatment], *Terapevticheskiĭ arkhiv*, 84(1): 61–64 (Russian) <http://www.ncbi.nlm.nih.gov/pubmed/22616534> (accessed 28 October 2013) (refers in the abstract to new data from foreign and Russian trials using the antihypertensive drug that was used in HYVET and HYVET included a Russian centre).

5.6 Sociedade Brasileira de Cardiologia, Sociedade Brasileira de Hipertensão & Sociedade Brasileira de Nefrologia (2010) [VI Brazilian guidelines on hypertension], *Arquivos Brasileiros de Cardiologia*, 95(1) (Suppl. 1): 1–51 (Portuguese), http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2010001700001&lng=en&nrm=iso&tlng=pt (accessed 17 October 2013) (section 8 ref. 21).

5.7 Jha, A (2008) Over-80s benefit from blood pressure drugs, *Guardian*, 1 April, <http://www.theguardian.com/science/2008/apr/01/medicalresearch.longtermcare> (accessed 30 September 2013).

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5.9 Black, HR (2009) This year's awards for the most important trials go to ... *HYVET and ACCOMPLISH*, *Medscape Cardiology*, 2 March, <http://www.medscape.com/viewarticle/588818> (accessed 30 September 2013).

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