Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Blood Pressure and Lipid-Lowering Treatment: Impact on Cardiovascular Outcomes and Influence on Guidelines

1. Summary of the impact (indicative maximum 100 words)

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT; Co-Chairman, Professor Sever) was an investigator designed and led multinational study in which different blood pressure-lowering and lipid-lowering treatment strategies were investigated in an attempt to define optimal programmes for intervention to prevent cardiovascular disease in hypertensive subjects. The outcomes of both the antihypertensive arm and the lipid arm of the trial defined the benefits of more contemporary treatments for hypertensive subjects, including calcium channel blockers, angiotensin converting enzyme inhibitors and statins, which have been incorporated into national and international guidelines (including NICE), and have impacted on current clinical practice in the prevention of cardiovascular disease worldwide.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Peter Sever, Professor of Clinical Pharmacology and Therapeutics (1980-present)
Professor Neil Poulter, Professor of Preventive Cardiovascular Medicine (1997-present)
Professor Simon Thom, Clinical Professor of Cardiovascular Pharmacology (1982-present)

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was conceived and designed by Professor Sever and Imperial colleagues in the late 1990s at a time when there was no clear indication of optimal antihypertensive treatment strategies to prevent cardiovascular disease (particularly coronary heart disease) in patients with raised blood pressure. The ASCOT study was conducted between 1998 and 2005. Since 2005, there have been additional sub-studies and sub-analyses with no fewer than 50 full manuscripts published (64 overall), mostly in high citation journals.

The team at Imperial College, led by Professor Sever and Professor Poulter, designed and managed the international study of 20,000 subjects in collaboration with the Gothenburg Trial Centre (Professor Dahlof and Professor Wedel). The Imperial team established 32 collaborative centres throughout the United Kingdom and Ireland, to recruit, randomise and follow, for an average of 5.5 years of observation, almost 10,000 subjects. In Scandinavia a further 10,000 patients were recruited. In addition to the main trial a 35 sub-studies were undertaken with principal investigators based at Imperial.

The blood pressure arm of the trial (ASCOT-BPLA) tested the specific hypothesis that the newer classes of antihypertensive drug therapy that had become available (the calcium-channel-blocking drugs and the angiotensin-converting-enzyme-inhibitors) would confer greater coronary protection in hypertensive subjects than the most widely used combination therapy for hypertension at the time (beta-adrenoceptor blocking drugs and thiazide diuretics).

The trial included a lipid-lowering arm (ASCOT-LLA) in which a statin was compared in a double-blind fashion with a placebo in patients with normal or modestly raised levels of serum cholesterol. At the time, there were very limited data on the primary prevention of myocardial infarction with statins, and only clear evidence for benefits in patients at high risk associated with substantial elevations of serum cholesterol. The hypothesis in ASCOT was that patients with co-morbidities, such as hypertension, history of smoking, diabetes etc., and cholesterol levels conventionally regarded as being within the normal or near normal range would benefit from lipid-lowering with a statin.

The results of the lipid-lowering arm of the trial (which was stopped prematurely owing to substantial outcome benefits in favour of the statin) demonstrated that both coronary events and strokes were significantly reduced compared with placebo (36% and 27% respectively), that statin use in this context was cost effective, and that there was no evidence of associated side-effects of active treatment. These results defined the benefits of statin therapy in primary prevention of cardiovascular disease (1). The results of the blood pressure-lowering arm of the study demonstrated that the combination strategy of a calcium-channel-blocker and angiotensin-converting-enzyme-inhibitor conferred substantial cardiovascular benefits in terms of reduction in stroke events (23%) and coronary events (14%) in hypertensive patients compared with the more conventional beta-blocker/thiazide regimen and, moreover, those subjects on the optimal treatment strategy were significantly less likely (31%) to develop new-onset diabetes. This defined optimal treatment combinations for anti-hypertensive drugs to reduce stroke and coronary disease outcomes in hypertensive patients (2, 3). In addition to the results of the main trial, sub-study analyses showed that blood pressure variability as opposed to achieved mean blood pressure was a critical determinant of cardiovascular outcomes (4). The analyses also demonstrated the role of specific drug treatments in reducing blood pressure variability (5). The preliminary results of long term outcome benefits on all-cause mortality in the lipid-lowering arm of ASCOT were published in 2011 (6).

3. References to the research (indicative maximum of six references)

(1) Sever, P.S., Dahlöf, B., Poulter, N.R., Wedel, H., Beevers, G., Caulfield, M., Collins, R., Kjeldsen, S.E., Kristinsson, A., McInnes, G.T., Mehlsen, J., Nieminen, M., O'Brien, E., Ostergren, J.; ASCOT investigators (2003). Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet,* 361, 1149-1158. DOI. Times cited: 1802 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 39.06.

(2) Dahlöf, B., Sever, P.S., Poulter, N.R., Wedel, H., Beevers, D.G., Caulfield, M., Collins, R., Kjeldsen, S.E., Kristinsson, A., McInnes, G.T., Mehlsen, J., Nieminen, M., O'Brien, E., Ostergren, J.; for the ASCOT Investigators (2005). Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet,* 366, 895-906. DOI. Times cited: 1143 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 39.06.

(3) Poulter, N.R., Wedel, H., Dahlöf, B., Sever, P.S., Beevers, D.G., Caulfield, M., Kjeldsen, S.E., Kristinsson, A., McInnes, G.T., Mehlsen, J., Nieminen, M., O'Brien, E., Ostergren, J., Pocock, S.; for the ASCOT Investigators (2005). Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). *Lancet*, 366, 907-913. DOI. Times cited: 179 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 39.06.

(4) Rothwell, P.M., Howard, S.C., Dolan, E., O'Brien, E., Dobson, J.E., Dahlöf, B., Sever, P.S., Poulter, N.R. (2010). Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*, 375, 895-905. DOI. Times cited: 231 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 39.06.

(5) Rothwell, P.M., Howard, S.C., Dolan, E., O'Brien, E., Dobson, J.E., Dahlöf, B., Poulter, N.R., Sever, P.S. on behalf of the ASCOT-BPLA and MRC Trial Investigators (2010). Effects of β-blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol*, 9, 469-480. DOI. Times cited: 110 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 23.91.

(6) Sever, P.S., Chang, C.L., Gupta, A.K., Whitehouse, A., Poulter, N.R.; on behalf of the ASCOT

investigators (2011). The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the UK. *Eur Heart J*, 32, 2525-2532. DOI. Times cited: 22 (as at 22nd October 2013 from ISI Web of Science). Journal Impact Factor: 14.09.

Key funding:
- Pfizer Inc (1998-2013; £40 million), Co-Principal Investigators, P. Sever and N. Poulter), Anglo-Scandinavian Cardiac Outcomes Trial, main trial, sub-studies, sub-analyses.
- Laboratoire Servier (1999-2005; £800,000), Anglo-Scandinavian Cardiac Outcomes Trial, main trial.

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare; public policy and services; practitioners and services; economic
Main beneficiaries include: patients; NICE; NHS; international policy makers

In the United Kingdom, one in three adults have hypertension and there are approximately 16 million hypertensive individuals who are at excess risk of cardiovascular events including coronary heart disease (CHD) events and strokes. High blood pressure has been identified by the World Health Organisation (WHO) as the number one risk factor contributing to global death and disability. In its 2002 report, WHO concluded that hypertension contributed to about 50% of CHD events and 75% of strokes. Despite the availability of various treatments, the residual risk amongst hypertensive patients remains high. Outcomes from ASCOT has added new knowledge to the definition of optimal treatment strategies to confer better outcomes for patients with hypertension including: i) primary prevention with statin therapy and ii) optimal blood pressure lowering strategies using combinations of hypertensive drugs.

The results from the ASCOT trial have had a major impact on national and international guidelines for blood pressure and lipid-lowering [1-5]. The 2011 NICE guidelines now advocate the use of calcium channel blockers for first line use in the majority of hypertensive patients [1]. Further, statin therapy is now recommended by NICE as part of the management strategy for the primary prevention of cardiovascular disease for those who are at high risk [2]. Statin therapy is also recommended internationally, as illustrated in the 2011 Canadian Hypertension Education guidelines. The Canadian guidelines recommend the use of statin therapy in hypertensive patients with three or more cardiovascular risk factors, as specified in the ASCOT trial [3; see page 426]. The European (European Society of Hypertension and European Society of Cardiology) guidelines recommend statin therapy for hypertensive patients at moderate to high cardiovascular risk, stating 'the benefit of adding a statin to antihypertensive treatment was well-established by the ASCOT-LLA study' [4; see page 2207].

The increasing use of combinations of antihypertensive drugs including calcium-channel-blockers and angiotensin-converting-enzymes, and the increasing use of statins [1, 2, 4, 5] in the context of the primary prevention of cardiovascular disease is evident from successive iterations of the Heath Survey for England (HSE) 2004, 2006, 2008 and 2011 [6]. The 2011 data from HSE confirms this positive trend which has been associated, amongst other interventions, with the remarkable decline in mortality rates from cardiovascular disease in the United Kingdom (40% reduction in males and 38% reduction in females) [6].

Furthermore, based on ASCOT data, health economic analyses have confirmed both the cost effectiveness of amlodipine-based treatment (about £8,000 per QALY gained) and that of atorvastatin, when used in hypertensive patients (about £10,000 per QALY gained) [7]. These costs are now substantially less due to the availability of generic formulations of the drugs.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] NICE clinical guideline 127. Hypertension: the clinical management of primary hypertension in adults. NCGE (Commissioned by NICE) Update of Clinical Guidelines 18 & 24. Clinical Guide 127: Methods, Guides and Clinical Evidence August 2011.

http://www.nice.org.uk/nicemedia/live/13561/56007/56007.pdf, pp 1 -328 (refer to pp. 248, Imperial research cited). Archived on 22nd October 2013.

[2] Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. (2008; Revised March 2010), NICE Clinical guideline 67. pp 1 – 236 (refer to p145 which advocates the use of statins based on the results from the ASCOT study 2003).
http://www.nice.org.uk/nicemedia/live/11982/40742/40742.pdf. Archived on 22nd October 2013.

[3] Canadian Hypertension Education Programme Guidelines (2011). The 2011 Canadian Hypertension Education Programme Recommendations for the Management of Hypertension: Blood Pressure Measurement, Diagnosis, Assessment of Risk, and Therapy. *Canadian J Cardiol*, 27, 415-433 (refer to Table 9, p 426, Imperial research cited). DOI.

[4] 2013 ESH/ESC Guidelines for the management of arterial hypertension
The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), *European Heart Journal*, 34, 2159-2219 (see pages 2207 and 2208, Imperial research cited) DOI.

[5] NHS National Institute for Health and Clinical Excellence. Prevention of Cardiovascular Disease. NICE public health guidance 25th June 2010. Refer to p.40 (Imperial research cited). http://guidance.nice.org.uk/nicemedia/live/13024/49273/49273.pdf. Archived on 22nd October 2013.

[6] Health Survey for England (2011). Volume 1, Chapter 2 (pp. 3, 4). http://www.hscic.gov.uk/catalogue/PUB09300. Archived on 22nd October 2013.

[7] Lindgren, P., Buxton, M., Kahan, T., Poulter, N.R., Sever, P.S., Wedel, H., Jonsson, B. (2009). Ascot Investigators. The lifetime cost effectiveness of amlodipine-based therapy plus atorvastatin compared with atenolol plus atorvastatin, amlodipine-based therapy alone and atenolol-based therapy alone: results from ASCOT. *Pharmacoeconomics*, 2009, 27, 221-30. DOI