Institution: Queen Mary University of London

Unit of Assessment: A1 (Clinical Medicine)

Title of case study:

Cardiovascular outcomes research: blood pressure and lipid lowering

1. Summary of the impact

Caulfield co-led and was a principal investigator (PI) on **Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).** Hitman co-led and was a PI on **Collaborative AtoRvastatin Diabetes Study (CARDS).** These studies dramatically changed national and international guidance for diabetes, hypertension and cholesterol, leading to widespread and far-reaching changes in management of common and potentially fatal risk factors. For example, the proportion of hypertensive patients in England with good BP control (<140/90) rose from 52% in 2006 to 62% in 2011; the mean total cholesterol level of the population has fallen by 0.5 Mmol/L between 1998 and 2011.

2. Underpinning research

Caulfield and Hitman transformed the prevention of cardiovascular disease (CVD) by leading seminal RCTs for treatment of high blood pressure (BP) and lowering cholesterol in patients with hypertension (25% of adults in Western countries) and type 2 diabetes (6% of the UK).

2a. Using the best drug combinations to lower BP: contribution to ASCOT

The **Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),** an independent investigator-led study 1997-2007, tested the impact of combinations of anti-hypertensive and lipid lowering drugs on cardiovascular outcomes in 19,000 individuals. Caulfield was Co-PI on the steering group from 1997. He designed, piloted and actively disseminated primary care recruitment procedures. His group optimized the (then novel) electronic case record file before UK-wide deployment so data could be remotely uploaded in real time. Queen Mary used this as a platform to develop an East London partnership of 120 GP practices, serving 500,000 people, enabling the team to recruit and follow 1157 (making this the largest site in the trial) of the 9000 UK ASCOT participants with 33% from minority ethnic groups and 99.8% followed up over 5-7 years (income £2M).

The ASCOT Blood Pressure Arm demonstrated that a combination of amlodipine/ perindopril was superior to a beta blocker/ thiazide regimen in hypertension, with 11% reduction in all cause mortality [1,2]. Over the life of the trial, BP fell from a mean of 163/94 to 136/77 (fall of 27-25/17-16) mm Hg. There was a difference in BP between the two arms of 2.7/1.9 mm Hg, reflecting the effectiveness of the amlodipine/perindopril combination relative to the older combination of beta-blocker/thiazide. At the end of ASCOT, 53 percent of non-diabetic people with hypertension (over 10,000) had reached the target of <140/90. After 5.5 years follow-up, 82 more people were alive and there were 240 fewer cardiovascular events or procedures in the amlodipine/perindopril arm.

b) Cholesterol lowering in patients with hypertension and diabetes whose LDL cholesterol levels were average or below average. *Prior to this trial, it was not recommended to treat 'normocholesterolaemic' patients who had hypertension and/or diabetes.*

Findings from ASCOT Lipid Lowering Arm (LLA). This arm was terminated early at 3.3 years because of a reduced incidence of non-fatal myocardial infarction and fatal coronary heart disease by 36% and 27% in stroke in those receiving atorvastatin 10 mg [3,4]. From the trial it was estimated that the absolute risk reduction was 3.4/1000 patient years. Benefits of atorvastatin were seen at one year into the trial and persuaded the Steering Committee that the placebo group and those on active treatment should be offered statins because the BP arm was continuing and this would allow us to test whether earlier treatment was associated with greater benefit. This enabled our subsequent findings: individuals receiving statins later in the trial did not get the same benefits as those treated early. These ASCOT subjects were previously untreated. After a median of 11 years after initial randomization and ~8 years after closure of LLA, follow-up of outcomes shows that all-cause mortality (n=520 and 460 in placebo and atorvastatin, respectively) remains significantly lower in those originally assigned atorvastatin (HR 0.86, CI 0.76-0.98, P=0.02). Cardiovascular deaths were fewer, but not statistically significant (HR 0.89, CI 0.72-1.11, P=0.32)

possibly due to statin treatment in the placebo group; and non-cardiovascular deaths were significantly lower (HR 0.85, CI 0.73-0.99, P=0.03) in those formerly assigned atorvastatin. It appears that the legacy effect of originally being assigned to atorvastatin may contribute to long-term benefits on all-cause mortality.

Contribution to CARDS (Collaborative AtoRvastatin Diabetes Study): Hitman was co-PI and rotating chair of the academically led CARDS Study in type 2 diabetes [5]. He helped design the study, seek funding from Diabetes UK, NHS and Pfizer and had close involvement in the management and success of the study. Underpinning research from CARDS involved 2,838 people with type 2 diabetes and low to moderate cholesterol levels; the first such study to focus only on people with diabetes. CARDS was terminated at the 2nd interim analysis showing overwhelming benefit with atorvastatin that significantly reduced cardiovascular events (37%); there was also a 48% reduction in stroke [5]. To date CARDS has resulted in 19 peer reviewed publications, including recently in JAMA [6] and Lancet, and is consistently quoted as the seminal work on cholesterol lowering in diabetes.

c) The dangers of elevating HDL using Torceptrapib:. As a result of the ASCOT study, Caulfield joined the **ILLUMINATE steering committee for design and leadership** of a large-scale pre-license outcome trial of the addition of torceptapib to atorvastatin in high-risk patients with cardiovascular disease [7]. This drug elevated high-density lipoprotein cholesterol levels by blocking Cholesterol Ester Transfer Protein but also had the unwanted effect of elevating BP. In 2007 the ILLUMINATE Trial was stopped prematurely due to excess cardiac and non-cardiac deaths in the torceptrapib arm. This early finding has shaped and enabled continued development of this class in other cardiovascular outcome trials.

3. References to the research

This research was reported in a series of papers (>30) from 2002 onward, mainly in the Lancet and New England Journal of Medicine. The papers listed below have been cited between 250 and 3500 times. The findings led to changed guidance from 2005 onwards.

1. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M et al; for the ASCOT investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus an atenolol adding thiazide as required in the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005; 366: 907-13.
2. Poulter NR, Wedel H, Dahlof B, Sever PS, Beevers DG, Caulfield M et al; ASCOT Investigators. 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 2005; 366: 907-13.
3. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M et al; ASCOT investigators. 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): multicentre RCT. Lancet 2003;361:1149-58.
4. Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR; ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the U.K. European Heart Journal 2011; 32: 2525-32.
5. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA et al; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364: 685-96.
6. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, Simes RJ, Durrington P, **Hitman GA** et al Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA. 2012; 307:1302-9
7. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M et al; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. New England Journal of Medicine 2007; 22: 357: 2109-22.

4. Details of the impact

4a: Change in national and international guidance for hypertension

The 2011 NICE Hypertension Guideline CG127 was a partial update to guidance from 2006 and Caulfield served on the Guideline Development Group [8]. The 2011 analysis including data derived from ASCOT confirmed that beta-blockers were usually less effective than a comparator drug at reducing major cardiovascular events, particularly stroke, and showed excess rates of new onset diabetes and should be used at step 4. Importantly, the results from the ASCOT BP Lowering Arm when combined with new data made a strong case for a further modification to the Pharmacological Treatment algorithm. This is summarised in section 12.3 page 208 of that guideline and indicated that a combination of a calcium channel blocker and angiotensin converting enzyme inhibitor at step 2 therapy, first trialled in ASCOT, was superior in preventing cardiovascular outcomes [8]. Step 2 of the algorithm was changed to reflect this and a meta-analysis showing that calcium channel blockers (CCB) were superior to thiazide diuretics in stroke prevention changed priority at step 1 for over 55s to CCBs. The NICE Hypertension Guideline also cites publications, also based upon ASCOT, showing differential effects of antihypertensive treatments on blood pressure variability as an independent predictor of clinical outcomes as a further rationale for the CCB recommendation at step 1 (CCBs were most effective at reducing variability). In the **European Society of Hypertension Guideline 2009,** ASCOT alongside other new data supported the recommendation for equal consideration of CCBs and ACE inhibitors [9].

4b: Change in national and international guidelines for lipid lowering

ASCOT and CARDS changed lipid-lowering guidance for primary prevention of cardiovascular disease in people with hypertension and for those with type 2 diabetes over 40 years old who (due to lack of peer reviewed evidence) had not been offered such drugs previously.

The Cholesterol Trialists Meta-analysis [10] informed the NICE Technology Appraisal (TA094) and Guideline on lipid lowering (CG67) and NCCPC/RCGP revision 2 [11, 12]. Heavily influenced by ASCOT and CARDS, it showed that within a year of therapy, people begin to benefit and over 5 years this translates into an overall reduction of about one fifth per mmol/L of LDL cholesterol reduction (48 fewer per 1000 having major vascular events among those with pre-existing CHD at baseline, compared with 25 per 1000 if no such history). This benefit is reflected in national (NICE) [13] and also international guidance, including American Diabetes Association, European Diabetes Association, European Society of Cardiology and Joint American and European Societies [14,15].

4c: Change in patient outcomes

Hypertension. Following NICE Hypertension Guideline CG34 in 2006 the most recent Health Survey for England 2011 (chapter 3, figure 3G page 10 and table 3.12 page 31) shows evidence of improved treatment rate (12% improvement in men and 5% in women). The proportion of patients with good BP control (<140/90) has risen from 52% in 2006 to 62% in 2011, and older people in particular are more tightly controlled [16]. This improvement is likely to be due partly to ASCOT (reflected in NICE CG34) and also to the Quality and Outcomes Framework in primary care.

Cholesterol. From the Health Survey for England, mean levels of total serum cholesterol were lower in men than women (5.1 and 5.2 mmol/L respectively) in 2011 [16]. On page 2 in chapter 2 on cardiovascular disease the 2011 survey reports 44% of men and 43% of women had total cholesterol levels below 5 mmol/L (the 'audit level' for those with CVD, diabetes or hypertension who are on drug treatment), while only 14% and12% respectively had levels below 4 mmol/L (current target for same group). Since 1998 there has been a fall in mean total cholesterol of 0.5 mmol/L in men and women, accompanied by a rise in prescriptions in England from 52,190,000 in 2008 to 61,649,000 in 2011 (page 89 Table 3.1 in BHF Heart Statistics 2012 [17]). This reflects the influence of lipid lowering studies such as ASCOT, CARDS and cholesterol trialists' meta-analysis on lipid guidelines and thus on implementation. In Europe, mean cholesterol varies between 50-70% above 5.2 mMol/l and 20-29% above 6.2 mMol/L which means the findings of ASCOT and CARDS if accompanied by prevalence rates between 30-40% for hypertension and 6-8% for diabetes have broad impact for large numbers of the European population [17].

4d: Professional education

Caulfield has been active in promoting continuing professional development of health professionals [15]. Hitman and Caulfield have given international tours to disseminate the findings of ASCOT and CARDS to health professionals and as expert advisors to groups developing national guidelines.

4e: Patient and public engagement

Caulfield chaired a steering group that produced a National Health Service Patient Decision Aid for the Department of Health between September 2012-March 2013. This is designed to explain the management of blood pressure and specifically the NICE Guidance on Hypertension that derives from the ASCOT study. It is intended to answer what patients frequently ask and help them to build an understanding of what to expect and why it is important. During ASCOT and ILLUMINATE the researchers held regular open question and answer "Town Hall" meetings with participants and their families. The engagement of the patients and public in CV research as a direct result of ASCOT and ILLUMINATE at this Centre has led to patient production of videos, animations and personal statements to encourage participation in new trials. As a direct result of their experience in ASCOT, the patients have acted as champions of a national electronic volunteering system for trials called Mediguard. Annual meetings are held for all participants involved in the ASCOT and ILLUMINATE Trials. This has created a highly engaged 'patients and public engagement' group who propose, advise and support clinical trials at Queen Mary.

5. Sources to corroborate the impact

8. NICE Guideline for Hypertension 2011, update from 2006 (CG34). See section 1.4, page 17. http://www.nice.org.uk/nicemedia/pdf/cg034niceguideline.pdf
9. Mancia G, Laurent S, Agabiti-Rosei E et al., Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. Journal of Hypertension 2009; 18: 308-347. PMID: 19838131.
10. 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. (update Lancet 2010; 376: 1670-81).
11. NICE Lipid Modification Guidance 2008 (CG67) http://www.nice.org.uk/nicemedia/live/11982/40742/40742.pdf
12. NICE Technology Appraisal 2006 (TA094) http://www.nice.org.uk/nicemedia/live/11564/33151/33151.pdf
13. NICE guidance for type 2 diabetes May 2011 and last updated April 2013 http://pathways.nice.org.uk/pathways/diabetes#path=view%3A/pathways/diabetes/managing-blood-lipids-in-type-2-diabetes.xml&content=close
14. American Diabetes Association Standards of Medical Care in Diabetes 2013 care.diabetesjournals.org/content/36/Supplement_1/S11.full
15. International Diabetes Federation guidance on cardiovascular risk http://www.idf.org/webdata/docs/GGT2D 12 Cardiovascular risk.pdf (chapter 12)
16. Health Survey for England 2011 (see chapter 2 on CVD and 3 on hypertension) http://www.hscic.gov.uk/catalogue/PUB09300
17. British Heart Foundation Statistics 2012: Coronary Heart Disease in UK http://www.idf.org/webdata/docs/GGT2D 12 Cardiovascular risk.pdf and cardiovascular disease in Europe (see Chapter 8 Blood pressure and 9 Cholesterol) http://www.bhf.org.uk/publications/view-publication.aspx?ps=1002098
18. NICE Hypertension Guideline Web stream from the British Hypertension Society for Health Professionals led by Caulfield (President 2009-11). http://www.bhsoc.org/stream/index.html.
19. Patient and public involvement (examples):
    How to volunteer. http://www.whri.qmul.ac.uk/whricrc/
    Experiences: http://www.whri.qmul.ac.uk/whricrc/takepart/patientexperiences/index.html
    e-volunteering for trials: http://www.whri.qmul.ac.uk/whricrc/takepart/registerwithus/index.html