Institution: The University of Manchester

Unit of Assessment: 1

Title of case study:
Improved management of population cardiovascular risk in diabetic patients

1. Summary of the impact

The Collaborative Atorvastatin Diabetes Study (2004), led by researchers at the University of Manchester (UoM), established the efficacy of statin therapy in the prevention of atherosclerotic cardiovascular disease (CVD) among patients with diabetes. The research challenged the previously held view that, since CVD risk is markedly raised in people with diabetes even when blood cholesterol levels are normal, statins were unlikely to be beneficial for this group. These key findings have informed clinical guidelines governing the use of statin therapy in the UK (NICE, SIGN) and internationally (American Heart Association and the American Diabetes Association, ESC, EAS), ensuring that statins are now considered for all diabetic patients.

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

Background

A number of trials (e.g., Scandinavian Simvastatin Survival Study, *Lancet* 1994) established the value of statins in preventing CVD in non-diabetic patients. However, diabetologists were reluctant to extrapolate this evidence to diabetic patients because diabetes does not typically cause raised cholesterol. In addition there were earlier adverse experiences with less effective and possibly harmful lipid-lowering medication and a disinclination to add to complex treatment regimens for glycaemia and blood pressure control.

Collaborative Atorvastatin Diabetes Study (CARDS)

Key researchers at UoM:

- **Paul Durrington** (Professor of Medicine, 1995-2009; Honorary Professor of Medicine, 2009-date)
- **Michael Mackness** (Research Fellow, 1998-1999; Lecturer, 1999-2002; Senior Research Fellow, 2002-2003; Reader, 2003-2008)
- **Valentine Charlton-Menys** (Research Associate, 1999-2010)
- **Michael France** (Honorary Lecturer, 2007-date)

Durrington and Fuller (University of London) raised funding from Diabetes UK (DUK) to convene a committee to design a trial of lipid lowering specifically in type 2 diabetes. The committee comprised the Director of R and D from DUK, a representative of the Department of Health (DH), Neil (Oxford), Hitman (London) and Betteridge (London). A large, scientifically rigorous trial was designed, with substantial funding provided by industry as well as DH and DUK. Parke Davies provided funding, atorvastatin and placebo. **Durrington** led the central laboratory, which was managed initially by **Mackness** and later by **Charlton-Menys**. **Durrington** also joined the Steering Committee.

After a pilot investigation in secondary prevention, the key trial to test the hypothesis that in primary prevention a statin could decrease CVD risk began in 1998. By then, it was becoming obvious from transnational epidemiology that there was no lower threshold below which low-density lipoprotein (LDL) ceased to be a risk factor for CVD. Therefore the target of the new primary prevention study was aimed at patients with lower LDL levels. The participants were 2838 type 2 diabetic patients with LDL cholesterol ≤4.14mmol/l and no clinical evidence of CVD, attending 132 centres in the UK and Ireland. They had at least one risk factor for CVD besides diabetes, most commonly mild hypertension.

Key findings:

1. The trial was terminated in 2003 after 3.9 years (2 years early) by the Safety Monitoring

Committee because of a substantial highly significant lower CVD event rate on the active treatment.
2. The mean pre-treatment LDL cholesterol was 3mmol/l and the average decrease on atorvastatin was 1.2mmol/l (1). This produced a 37% decrease in CVD incidence (P<0.001) due to reductions of 36% in acute coronary events, 31% in coronary revascularisation and 48% in stroke (2-5).
3. All-cause mortality declined by 27%, which just failed to reach statistical significance (P=0.059) for the whole trial, but was highly significant in its final year (2).
4. Adverse active treatment effects were no more frequent than on placebo (for example, albuminuria incidence was not increased, 6).

The CARDS database and biobank (created in Manchester), which includes DNA, serum and urine, continues to generate significant scientific findings about aspects of atherosclerosis and metabolic responses to statin treatment.

3. References to the research

1. Colhoun HM, Betteridge DJ, **Durrington PN**, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, **Mackness MI**, **Charlton-Menys V**, Fuller JH on behalf of the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in Type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS); a multicentre randomised placebo controlled trial. *Lancet*. 2004; 364: 685-96. DOI: 10.1016/S0140-6736(04)16895-5

2. Colhoun H, Betteridge DJ, **Durrington PN** et al. Rapid emergence of effect of atorvastatin on cardiovascular outcomes in the Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetologia*. 2005; 48: 2482-2485. DOI: 10.1007/s00125-005-0029-y

3. Raikou M., McGuire A., Colhoun HM, Betteridge DJ, **Durrington PN**, Hitman GA, Neil HAW, Livingstone SJ, **Charlton-Menys V**, Fuller JH. Cost effectiveness of primary prevention of CVD with atorvastatin in type 2 diabetes: results from the Collaborative Atorvastatin Diabetes, Study (CARDS). *Diabetologia.* 2007; 50: 733-740. DOI: 10.1007/s00125-006-0561-4

4. **Charlton-Menys V**, Betteridge DJ, Colhoun H, Fuller J, **France M**, Hitman GA, Livingstone SJ, Neil HA, Newman CB, Szarek M, Demicco DA, **Durrington PN**. Apolipoproteins, cardiovascular risk and statin response in type 2 diabetes: the Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetologia*. 2009; 52: 218-225. DOI: 10.1007/s00125-008-1176-8

5. **Charlton-Menys V**, Betteridge DJ, Colhoun H, Fuller J, **France M,** Hitman GA, Livingstone SJ, Neil HA, Newman CB, Szarek M, DeMicco DA, **Durrington PN**. Targets of statin therapy: LDL cholesterol, non-HDL cholesterol, and apolipoprotein B in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS). *Clinical Chemistry*. 2009;55:473-80. DOI: 10.1373/clinchem.2008.111401

6. Colhoun HM, Betteridge DJ, **Durrington PN**, Hitman GA, Neil HA, Livingstone SJ, **Charlton-Menys V**, Demicco DA, Fuller JH; CARDS Investigators. Effects of Atorvastatin on Kidney Outcomes and Cardiovascular Disease in Patients with Diabetes: An Analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *American Journal of Kidney Diseases*. 2009; 54: 810-819. DOI: 10.1053/j.ajkd.2009.03.022

4. Details of the impact

See section 5 for corroborating sources S1-S10.

Context and pathways to impact

Statistics published by DUK show that CVD is the cause of death in 52% of people with type 2 diabetes and 44% with type 1. Within 5 years of its onset (and many people are not diagnosed until then) CVD risk in type 2 diabetes is the same as in non-diabetic people who have already had a

myocardial infarction. The additional risk is higher still in diabetic compared with non-diabetic women. Within 5 years of diagnosis stroke risk is doubled. The publication of CARDS in 2004 (1) therefore attracted great interest both in scientific journals and lay press. The initial *Lancet* report has over 2500 citations, and DUK set new target levels of LDL cholesterol of <2mmol/l, to be achieved with statins if necessary, which were widely broadcast.

Reach and significance of the impact

Impact on national and international clinical guidelines

Following publication of the findings, DUK rapidly ensured that new guidelines for statin use in diabetes were incorporated in the Joint British Societies second recommendations (JBS2, 2005) (S1). The recommendations state that all type 2 diabetic patients aged ≥40 years (and also some younger patients with particularly adverse risk factors) should receive statin treatment to achieve an LDL cholesterol <2mmo/l. The DUK recommendations were further extrapolated to include type 1 diabetes, but this was on the basis of their CVD risk and the practicality of implementation when the distinction between the two types was often blurred in general practice.

The British Heart Foundation endorsed the JBS2 recommendation (S2), but the Association of British Clinical Diabetologists (ABCD) was one of a number of groups to challenge the CARDS conclusions. The arguments were that the patients randomised in CARDS were atypical, particularly in their high CVD risk. In fact, they were subsequently shown to be at high risk, but no more than typical diabetic patients. There was initial reluctance to accept that an apparently low LDL cholesterol target for statin treatment was justified by CARDS. In fact, in CARDS the mean LDL cholesterol had been decreased from around 3mmol/l (the average in middle-aged Britons is 3.7mmol/l) to under 2mmol/l.

These arguments were overcome and the guidance issued by ABCD, NICE and SIGN (2007-2010) (S3, S4) is essentially the same as JBS2 (S1). The guidance was strengthened by a meta-analysis by Kearney and colleagues largely drawing on data from CARDS and the Heart Protection Study, which was a mixed primary and secondary trial of the less effective simvastatin, and which included a diabetic cohort (S5).

North American guidelines were modified to take account of the new evidence provided by CARDS (S6) and European recommendations rapidly followed (S7, S8).

Improved management of diabetes

The acceptance of the CARDS findings is now universal and statins are an essential part of diabetic management. Indeed statin targets are generally easier to achieve than recommended goals for glycaemia or blood pressure. Proof of benefit and evidence of cost-effectiveness is stronger for statin therapy than any other aspect of type 2 diabetes management (S9).

The full impact of CARDS on global health is difficult to evaluate precisely, but it is likely to be vast. Many of the 400 million people with diabetes globally inhabit countries that are not affluent. However, now that both simvastatin and atorvastatin are out of patent, many more of the 2 million CVD deaths occurring annually in diabetes worldwide should be preventable (S10).

5. Sources to corroborate the impact

S1. Joint British Societies' Guidelines on Prevention of Cardiovascular Disease in Clinical Practice (JBS2). *Heart*. 2005; 91 Suppl V: 1-52 DOI: 10.1136/hrt.2005.079988

S2. British Heart Foundation Factfile Jan 2006: Joint British Societies' Guidelines on Prevention of Cardiovascular Disease in Clinical Practice: Risk Assessment. http://www.bhsoc.org/files/5013/3363/9191/Factfile_2006_JBS2_Guidelines_on_the_Prevention_of_Cardiovascular_Disease_in_Clinical_Practice.pdf

S3. Feher MD, Winocour PH. On behalf of the Association of British Clinical Diabetologists (ABCD). ABCD position statement on lipid modifying drug therapy in diabetes. *Practical Diabetes International*. 2007; 24: 458-462 (published jointly with Scottish Intercollegiate Guidelines

Network). See SIGN 116 Management of diabetes. Summary of recommendations. http://www.sign.ac.uk/guidelines/fulltext/116/index.html).

S4. National Institute for Health and Clinical Excellence (NICE) clinical guideline 67. Lipid modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Developed by the National Collaborating Centre for Primary Care. Issue date: May 2008 (reissued March 2010) http://www.nice.org.uk/nicemedia/pdf/CG67NICEguideline.pdf

S5. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Baigent C, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet.* 2008; 371: 117–25. DOI: 10.1016/S0140-6736(08)60104-X

S6. Buse JB., Ginsberg HN., Bakris GL et al. Primary prevention of cardiovascular disease in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation.* 2007; 115: 114-126 DOI: 10.1161/ CIRCULATIONAHA.106.179294

S7. Graham I, Atar D, Borch-Johnsen K et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *European Heart Journal*. 2007;28: 2375-2414. DOI: 10.1093/eurheartj/ehm316

S8. Catapano AL et al. ESC/EAS Guidelines for the management of dyslipidaemias, The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *European Heart Journal*. 2011; 32: 1769–818 DOI: 10.1093/eurheartj/ehr158 and *Atherosclerosis*. 2011; 217: 3-46.

S9. Annemanns L, Marbaix S, Webb K et al. Cost effectiveness of atorvastatin in patients with type 2 diabetes mellitus: a pharmacoeconomic analysis of the collaborative atorvastatin diabetes study in the Belgian population. *Clinical Drug Investigation*. 2010; 30: 133-42. DOI: 10.2165/11531910-000000000-00000

S10. International Diabetes Federation. Global Guideline for Type 2 Diabetes (2012). www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf