Institution: University of Dundee
Unit of Assessment: UoA1 Clinical Medicine
Title of case study: The use of aspirin as a primary prophylaxis against cardiovascular events in patients with Diabetes

1. Summary of the impact

An eight year MRC-funded clinical trial led by the University of Dundee and run throughout Scotland (16 hospitals, 188 GP Surgeries) exploring aspirin in diabetes for primary cardiovascular event prevention, where clinical practice had evolved without evidence.

- **NHS**: Implementation of results in general practices, hospitals, and Health Boards globally, by ceasing to prescribe aspirin as primary prevention in diabetes.
- **Policy**: Resulted in major changes to international Guidelines globally e.g. American Diabetes Association Guidelines, Australian, New Zealand and Canadian Guidelines and Scottish Intercollegiate Guideline Network (SIGN).
- **Improved Patient Care and Health Outcomes**: Reduction in aspirin prescribing with decrease in adverse events, reduction in concomitant proton pump inhibition prescribing.
- **Internationalisation**: Implementation worldwide, by doctors and pharmacists with reports in lay publications, radio programmes, TV interviews and patient targeted websites.

2. Underpinning research

Background: Clinical decision making should, where possible, be based on evidence. An example of clinical practice reliant on guidelines with an incomplete evidence base is the use of low-dose aspirin for primary prevention of cardiovascular disease (CVD) events in diabetes mellitus.

Cardiovascular disease is a major global health problem. The website of the World Health Organisation estimates that 17.3 million people died from CVD in 2008, and by 2030 more than 23 million people will die annually. Vascular disease is the major cause of morbidity and mortality in diabetes mellitus. Aspirin has a wide publication base of evidence as a useful agent for secondary prevention of CVD. Antioxidants have little evidence base apart from in retrospective population studies, but are popular with patients and with alternative therapists.

Prior to our study, numerous national and international associations recommended low-dose aspirin for patients with diabetes. Our MRC-funded underpinning research work (1998-2007) [i] was carried out at the University of Dundee and led by Professor Jill **Belch** (Professor of Vascular Medicine, Ninewells Hospital and Medical School, Dundee 1987 to date). The Prevention Of Progression of Arterial Disease And Diabetes (POPADAD) trial tested the hypothesis that aspirin and/or antioxidants were more effective than placebo in reducing the development of CVD events. Twenty-seven hospital centres took part in the study, supported by 188 GP surgeries. Of 8730 patients with diabetes mellitus who were screened, 1276 were enrolled into the study of aspirin versus placebo versus antioxidant. CVD events were the primary outcome. The results showed no difference between aspirin and placebo or antioxidant and placebo, and the finding that aspirin does not reduce CVD events in patients with diabetes and no previous CVD is now embedded in the NHS and also in national and overseas healthcare Guidelines.

Research Question: Secondary prevention of CVD events and mortality can be achieved in patients with diabetes by aspirin therapy. What was not known is whether primary prevention with aspirin was effective, despite recommendations for this treatment in many published Guidelines.

What This Study Adds: This trial provides no evidence to support the use of either aspirin or antioxidants in primary prevention of CVD events and mortality in the diabetes mellitus population studied. It thus questions the evidence base for these Guideline recommendations.

Additional Impact in other areas: As well as changing medical practice, our data were exploited further in later collaborative work with the University of Oxford, whereby this study formed part of a meta-analysis showing that aspirin reduced both the development and metastases of cancer [ii-iv].

Conclusion: Since the trial's publication two further studies, the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) study [v] and the meta-analysis by the Anti-Thrombotic Trialist (ATT) Collaboration, have validated the results. The latter showed that primary prevention of vascular events with aspirin is of uncertain value, whereas the risk of major episodes of haemorrhage may increase. The POPADAD study has been incorporated into meta-analyses [vi] and, with the JPAD trial and ATT analysis, forms a convincing evidence base.

3. References to the research

i. **Belch** JJF, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R (2008) Prevention of Progression of Arterial Disease and Diabetes Study Group, Diabetes Registry Group, Royal College of Physicians Edinburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *Brit. Med. J.* **337**, 1030-1033 (DOI: 10.1136/bmj.a1840).

ii. Rothwell PM, Fowkes FGR, **Belch** JJF, Ogawa H, Chew E, Warlow CP, Peto R, Meade TW (2011) Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomized trials. *Lancet* **377**, 31-41 (DOI: 10.1016/S0140-6736(10)62110-1).

iii. Rothwell PM, Wilson M, Price JF, **Belch** JJF, Meade TW, Mehta Z (2012) Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet* **379**, 159-601 (DOI: 10.1016/S0140-6736(12)60209-8.

iv. Rothwell PM, Price JF, Fowkes GR, Zanchetti A, Roncaglioni MC, Tognoni G, Lee R, **Belch** JJF, Wilson M, Mehta Z, Meade TW (2012) Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* **379**, 1602-1612 DOI: 10.1016/S0140-6736(11)61720-0.

v. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators (2008) Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* **300**, 2134-41 (DOI: 10.1001/jama.2008.623).

vi. Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, Rosenson RS, Williams CD, Wilson PW, Kirkman MS; American Diabetes Association; American Heart Association; American College of Cardiology Foundation (2010) Expert Consensus Document: Aspirin for Primary Prevention of Cardiovascular Events in People with Diabetes. *J. Am. Coll. Cardiol.* **55**, 2878-2886 (DOI:10.1016/j.jacc.2010.04.003).

Funding

- **Belch** J, Cairns J, Fowles G, Hawthorne V, Jung RT, McEwan S, Newton RW and Smith A: The Prevention of Progression of Asymptomatic Diabetic Arterial Disease (POPADAD) Study: A Multicentre study; Medical Research Council, (66 months from August 1997) £1,065,576.
- **Belch** J, Cairns J, Hawthorne V, Jung RT, Newton RW, Smith A, McEwan S, and Prescott R: The Prevention of Progression of Asymptomatic Diabetic Arterial Disease (POPADAD) Study; Medical Research Council (12 month extension from February 2003) £268,389.

4. Details of the impact

This study has delivered an evidence base regarding the use of aspirin in diabetes and is now embedded at the heart of national and international Guidelines. The 2008 *BMJ* publication [i]

reported on the results of this trial. The impact of this initial study was immediate with much publicity worldwide; lay press, radio and television discussions and reports were made throughout 2009-11. Further changes to national and international Guidelines were made over the next 3-4 years taking these data into account (see below). It created a global change in prescribing practice for patients with diabetes that provided value to frontline clinical teams in both primary and secondary care. It represents one of the major changes in the care of people with diabetes internationally over the past 5 years. Further, editorials reviewed this article favourably (e.g. [1,2]) using the evidence from this trial to give advice to readers. The BMJ voted the publication second most impactive study published by them in 2008. It also received 6 stars for clinical impact from the American College of Physicians [3], who summarise the best new evidence for internal medicine from over 130 clinical journals using a worldwide panel of >5000 physicians to assess the clinical relevance and newsworthiness of rigorous studies.

Government Policy Impact and Guidelines (National and International): UK Primary Care Guidelines changed as a result of our findings [4], as have those abroad. UK and international Guidelines for medically-related specialities such as Pharmacy [5] and the Drug and Therapeutic Bulletin have been influenced, quoting POPADAD as the reason for change. The recent SIGN Guidelines on the management of diabetes took the trial findings into account when making its recommendations (http://www.sign.ac.uk/pdf/sign116.pdf). In addition the new USA recommendations, from a joint statement of the American Diabetes Association, the American Heart Association, and the American College of Cardiology, essentially call for tighter criteria for aspirin use in diabetes quoting the trial (http://circ.ahajournals.org/content/115/1/114.long). Dr Sue Kirkman, a member of the writing committee, is quoted: "The previous recommendations had been that pretty much anybody with diabetes over the age of 40 should be on aspirin, but there…is less of a general recommendation for aspirin than there used to be, and this is based on some of the newer studies that have come out". Further the respected US Preventative Services Task Force [6] recommended on aspirin use, based on the trial. The Canadian, New Zealand and Australian Diabetes Guidelines [7] also changed in response to the trial as did those of the European Society of Cardiology [8]. The Clinical Guidelines Task Force of the International Diabetes Federation Global Guideline for the care of people with Type 2 diabetes around the world has also incorporated the findings from POPADAD [9]. The ATT Collaboration updated their recommendations for aspirin in primary prevention after considering the results from POPADAD and two later trials [v,vi]. They concluded that the benefit of aspirin appeared to outweigh its risks when used for secondary, but not primary, prevention.

Improved Patient Care and Health Outcomes: The findings have also been integrated into UK [10] and global [various non-English-language websites] healthcare as an exemplar of a clinically relevant study. Aspirin has significant side effects associated with its use in CVD prevention. Even mild adverse events such as dyspepsia can be a major issue, requiring additional prescriptions of antacids and proton pump inhibitors. In the ATT Collaboration meta-analysis [vi], aspirin allocation for primary prevention increased major gastrointestinal and extracranial bleeds, and this has been confirmed by others. Aspirin was associated with a 55% relative risk increase in major bleeding. Reducing aspirin prescribing reduces these risks and will have impacted on the diabetes population previously considered for aspirin primary prevention. There is also a question regarding increased CVD events in patients on proton pump inhibitors and aspirin, though this may be due to reduced effectiveness of the aspirin produced by the antagonist.

NHS Cost Impact: Although aspirin is relatively cheap, there are 251,000 people with diabetes in Scotland alone, of which about 50% will have no evidence of CVD. Thus there will be potential savings to the NHS as aspirin prescribing falls and also for associated proton pump inhibitor usage which will be substantial over time.

Impact in other clinical areas: More recently this work has underpinned a number of meta-analyses including the effect of aspirin on long-term risk of death due to cancer and cancer metastasis [ii-iv]. This work in cancer has also been the subject of editorials in high impact journals and produced much interest in the lay press, expressed via radio and TV items.

Pubic Engagement, Media Coverage: The findings have also formed the basis for public engagement and debate on use of aspirin in diabetes [11]. This debate has appeared in tweets,

blogs and on lay websites, there have been discussions in newspaper articles, radio and TV shows in all the continents of the world.

5. Sources to corroborate the impact

Examples of Editorials on the clinical trial findings

1. Krantz MJ, Berger JS, Hiatt WR (2010) An aspirin a day: are we barking up the wrong willow tree? *Pharmacother.* **30**, 115–118 (DOI:10.1592/phco.30.2.115).
2. Nicolucci A (2011) Recommending Aspirin for Primary Prevention in Diabetic Patients: What May We Conclude? *Ther. Adv. Chronic Dis.* **2**, 157–160 (DOI: 10.1177/2040622311400116).
3. Farkouh ME (2009) ACP Journal Club. Aspirin and/or antioxidants did not prevent CV events in diabetes and peripheral arterial disease. *Ann. Int. Med.* **150**, JC1-8 (DOI:10.7326/0003-4819-150-2-200901200-02008).

Examples in Primary Care

4. **UK:** http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20081111120515749131;
Canada: Allan GM, Ivers N and McCorkack J (2010) Type 2 diabetes and ASA. *Canadian Family Physician* **56**, 664; http://www.cfp.ca/content/56/7/664.full;
USA: Crawford-Faucher A (2009) Secondary Prevention of Cardiovascular Events in Diabetes. *Am. Fam. Physician.* **80**, 1000; http://www.aafp.org/afp/2009/1101/p1000.html.

Pharmacy Impact

5. UK: Burrill, P. (2009) Aspirin and the primary prevention of cardiovascular disease. Pharmacy in Practice September 2009, 109-111; http://www.pharmacyinpractice.com/archive/2009-volume-19-issue-3/8-PIP-Cardiovascular-special-section-3-Sept09.pdf;
USA: http://dig.pharm.uic.edu/faq/ada.aspx.

Additional International Guidelines/Recommendations influenced by the trial

6. U.S. Preventive Services Task Force recommendation statement (2009) Aspirin for the prevention of cardiovascular disease *Ann. Intern. Med.***150**, 396–404 (DOI:10.7326/0003-4819-150-6-200903170-00008).
7. Canadian Diabetes Association (2013) Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can. J. Diabetes* **37**: s1-212 (DOI:10.1016/j.jcjd.2013.01.009) and subsequent articles; PHARMAC and the NZ Guidelines Group (2011) The Use of Antithrombotic Medicines in General Practice: A Consensus Statement. *Best Practice J. NZ* **39**:11-2 (http://www.bpac.org.nz/BPJ/2011/october/antithrombotic.aspx).
8. European Society of Cardiology Task Force on diabetes, pre-diabetes, and cardiovascular diseases and European Association for the Study of Diabetes (2013) ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur. Heart J.* **34**, 3035-87 (DOI:10.1093/eurheartj/eht108).
9. IDF Clinical Guidelines Task Force (2006) Global guideline for type 2 diabetes: Recommendations for standard, comprehensive, and minimal care. *Diabet. Med.* **23**, 579-93 (DOI: 10.1111/j.1464-5491.2006.01918.x).
10. Report on changed Guidelines:
http://www.eguidelines.co.uk/eguidelinesmain/gip/vol_12/feb_09/begg_popadad_feb09.php.

Lay Impact

11. http://apvascular.blogspot.co.uk/2011/02/in-popadad-study-bmj-2008-it-was-found.html;
http://the-brillo-pad.blogspot.co.uk/2009/03/aspirin-ineffective-for-primary.html;
http://www.clotcare.com/aspirin_and_diabetes.aspx;
http://www.ethiopianreview.com/news/135701.