Institution: The University of Oxford

Unit of Assessment: 2

Title of case study

ANTIPLATELET THERAPY FOR PREVENTING HEART ATTACKS AND STROKES

Summary of the impact

Over the past 20 years, the University of Oxford's Clinical Trial Service Unit (CTSU), within the Nuffield Department of Population Health (NDPH), has conducted some of the world's largest trials and collaborative meta-analyses of trials of antiplatelet therapy, including aspirin, that have together had a major ongoing and incremental impact on the treatment and prevention of cardiovascular disease. They have helped ensure that antiplatelet therapy is widely used both in the acute care of patients with heart attacks and for the secondary prevention of heart attacks and strokes in high-risk patients. This research has been recognised as the gold standard for international guidelines, and has been instrumental in changing prescribing labelling for aspirin.

Underpinning research

In the 1980s a number of trials assessed the effects of antiplatelet drugs (especially aspirin) for the prevention of heart attacks and strokes, but in many cases these trials gave apparently conflicting results. As a consequence there was considerable uncertainty about which types of patients benefited from such treatment. In order to provide better guidance for doctors and patients, the University of Oxford's CTSU initiated collaborative meta-analyses (studies which combine data from a group of original studies) of all trials involving an antiplatelet regimen for the prevention of serious vascular events (heart attacks, strokes and of deaths from vascular disease). The outcome of this effort was the publication by the Antiplatelet Trialists' (APT) Collaboration in 1994 of a series of three important papers, dubbed "The Aspirin Papers" [1-3] by the British Medical Journal. The first of these papers showed conclusively that a prolonged course of antiplatelet therapy could reduce the risk of serious vascular events by about one quarter among a wide range of patients at high risk of vascular disease [1]. The other papers supplemented this evidence by showing also that antiplatelet therapy reduced the risk of vascular occlusion among patients undergoing a vascular procedure [2], and that it reduced the risk of deep venous thrombosis and pulmonary embolism in patients at risk of venous thromboembolism [3].

The recognition of the importance of arterial thrombosis as a cause of death and disability led to a substantial increase in the number of trials involving antithrombotic agents. In 2002, the Antiplatelet Trialists' Collaboration, renamed the Antithrombotic Trialists' (ATT) Collaboration, updated the worldwide evidence from these trials [4]. The ATT Collaboration's analyses reaffirmed the benefits of a prolonged course of antiplatelet therapy for the prevention of serious vascular events, and also demonstrated that intensification of antiplatelet therapy (by adding a second antiplatelet agent to aspirin) yielded further benefits that exceeded any additional risks of bleeding [4]. This strategy was studied, for example, in CTSU's own CCS2-COMMIT (2005) trial of clopidogrel plus aspirin versus aspirin alone among Chinese patients with suspected acute heart attack, which showed that adding clopidogrel to aspirin therapy resulted in additional benefits [5].

Whereas these studies showed clearly that the benefits of aspirin greatly exceed the bleeding risks among patients at high risk of a heart attack or stroke, considerable controversy remained as to whether the benefits exceeded any risks among healthy people. In 2009, the ATT Collaboration published a meta-analysis of six primary prevention trials of aspirin versus placebo, using detailed data on individual participants, in order to quantify the benefits and risks of aspirin at different levels of predicted vascular disease risk [6]. This research showed clearly that the vascular benefits of aspirin do not clearly exceed any bleeding hazards, even among those with risk factors for cardiovascular disease. One reason for this is that the risks of bleeding in an individual tend to mirror their risks of coronary heart disease, so patients deriving greater coronary benefits from

aspirin also tend to suffer from greater risks of bleeding [6]. Like earlier work from the ATT, this research has been influential in guiding clinical practice and has been incorporated into clinical guidelines.

References to the research

[1]. Collins R, Peto R, Baigent C, Sandercock P, Warlow C. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ 308, 81–106 (1994).
PubMed ID: 8298418. ***The first 'Aspirin Paper' showing that a prolonged course of antiplatelet therapy could reduce the risk of serious vascular events by about one quarter among a wide range of patients at high risk of vascular disease.***

[2]. Collins R, Peto R, Baigent C, Sandercock P, Warlow C. Collaborative overview of randomised trials of antiplatelet therapy--II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. Antiplatelet Trialists' Collaboration. BMJ 1994; 308: 159–168.
PubMed ID: 8312766. ***The second 'Aspirin Paper' showing that antiplatelet therapy reduces the risk of vascular occlusion among patients undergoing a vascular procedure.***

[3]. Collins R, Peto R, Baigent C, Sandercock P, Warlow C. Collaborative overview of randomised trials of antiplatelet therapy--III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. BMJ 1994; 308: 235–246.
PubMed ID: 8054013. ***The third 'Aspirin Paper' showing that aspirin reduces the risk of deep venous thrombosis and pulmonary embolism in patients at risk of venous thromboembolism.***

[4]. Baigent C, Sudlow C, Collins R, Peto R. Antithrombotic Trialists' Collaboration Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324: 71–86.
PubMed ID: 11786451. ***A paper from the ATT collaboration showing the benefits of a prolonged course of antiplatelet therapy for the prevention of serious vascular events. This paper also demonstrated that intensification of antiplatelet therapy (by adding a second antiplatelet agent to aspirin) yielded further benefits that exceeded any additional risks of bleeding.***

[5]. Chen, Z. M. et al. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366: 1607–1621.
PubMed ID: 16271642. ***CTSU's CCS2-COMMIT trial of clopidogrel plus aspirin versus aspirin alone, which showed that adding clopidogrel to aspirin therapy resulted in additional benefits in patients with an acute myocardial infarction.***

[6]. Antithrombotic Trialists' (ATT) Collaboration (Writing Committee: Baigent C, Blackwell L, Buring J, Collins R, Emberson J, Godwin J, Hennekens C, Kearney P, Meade T, Patrono C, Peto R, Roncaglioni MC, Zanchetti A.) Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373: 1849–1860.]
PubMed ID: 19482214. ***A meta-analysis of six primary prevention trials of aspirin versus placebo, which showed that the vascular benefits of aspirin do not clearly exceed any bleeding hazards, even among those with risk factors for cardiovascular disease.***

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Programme, the Stroke Association, Chest, Heart and Stroke Scotland, Edinburgh University (Sir Stanley and Lady Davidson Fund), by a Wellcome Training Fellowship, and by Sanofi-Aventis, Bristol-Myers Squibb and AstraZeneca.

Details of the impact

Research into the benefits and risks of antiplatelet therapy has shown that long-term antiplatelet therapy reduces the risk of heart attacks, strokes and deaths due to vascular disease in a wide range of high-risk people. It has also shown that the benefits of aspirin do not clearly outweigh the bleeding risks in healthy people. This work has influenced treatment guidelines nationally and internationally, and has led to changes to medication labelling worldwide. The 3 Aspirin Papers published in the BMJ in 2004 have been cited over 4000 times, and the 2009 ATT paper is listed amongst the most cited articles (793 citations) in The Lancet since 2008 [A].

Public Policy

A number of national and international healthcare policy guidelines for people at high risk of vascular disease have been influenced by CTSU's work on antiplatelet therapy. In particular, the 8th American College of Chest Physicians (ACCP) guidelines [B], published in 2008, are heavily dependent on the ATT for their data synthesis and recommendations as is the report on European Society of Cardiology's Task Force on Antiplatelet Drugs in 2010 [C]. These guidelines were developed with CTSU's assistance (Professor Colin Baigent was a member of both groups) and, taken together, these guidelines have had a major impact on antiplatelet drug use since either the US or the European guidelines are adopted in most countries. The ATT work is also referenced as 'level A' evidence in the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for the management of ST-elevation myocardial infarction [D].

NICE guidance for secondary prevention of myocardial infarction references the ATT collaboration results. This was originally published in 2007 and is planned to be updated before the end of 2013. The draft update (July 2013) references an ATT meta-analysis as the key source of data for antiplatelet trials [E]. The Scottish Intercollegiate Guidelines Network (SIGN) has referenced CTSU's work in a 2013 update to its national clinical guideline on antithrombotics [F], and the 2009 ATT paper is also referenced in a British Hypertension Society 2010 statement regarding the use of aspirin in primary prevention of CVD [G].

Drug Regulation

Following the publication of CTSU's 2009 "aspirin in primary prevention" paper, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued an update to their guidance on aspirin use for primary prevention of thrombotic vascular disease [H]. Directly citing CTSU's research as the motivating factor behind the new guidance, this update warned against the routine use of aspirin in patients at low risk because the benefits of aspirin in these circumstances may not exceed the bleeding risks.

Sources to corroborate the impact

[A]. Most cited articles in The Lancet since 2008, extracted from Scopus. Elsevier website: http://www.journals.elsevier.com/the-lancet/most-cited-articles/. Accessed 5th November 2013. ***The 2009 ATT paper has been cited > 790 times in Scopus since it was published.***

[B]. Patrono C, Baigent C, Hirsh J, Roth G. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008;133:199S–233S. PubMed ID: 18574266. ***The 8th American College of Chest Physicians (ACCP) guidelines, which rely heavily on the ATT for their data synthesis and recommendations. See page 203S.***

[C]. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet J-P, et al. Antiplatelet agents for the treatment and prevention of atherothrombosis. Doi:10.1093/eurheartj/ehr373. PubMed ID: 22019823. ***The European Society of Cardiology's Task Force on Antiplatelet Drugs guidelines from 2010 continue to use the ATT study for their recommendations. Pages 2925-2926.***

[D]. O'Gara PT, Kushner FG, Ascheim DD et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Jan 29;61(4):e78-140. PubMed ID: 23256914. ***These guidelines reference the 2002 ATT paper, referring to it as 'Level A' evidence.***

[E]. C48 MI: secondary prevention: Full guideline. NICE, London 2007 http://guidance.nice.org.uk/CG48/Guidance/pdf/English Draft Updated Guidance (June 2013): http://www.nice.org.uk/guidance/index.jsp?action=download&o=64153 (Accessed 17th September 2013). ***This is the original NICE guideline and the proposed update. The ATT, led by CTSU, provided key evidence for antiplatelet therapy in secondary prevention in the guidelines: see page 318.***

[F]. Scottish Intercollegiate Guidelines Network. Antithrombotics: indication and management. A national clinical guideline. August 2012 (updated June 2013). http://www.sign.ac.uk/pdf/SIGN129.pdf (Accessed 31st October 2013). ***This recently updated SIGN guideline references the 2009 ATT paper.***

[G]. The use of aspirin in primary prevention of cardiovascular disease. Statement from the British Hypertension Society. January 2010. http://www.bhsoc.org/pdfs/Statement%20on%20Aspirin%20Jan10.pdf (Accessed 31st October 2013). ***This BHS statement refers to the 2009 ATT collaborative meta-analysis.***

[H]. MHRA Drug Safety update October 2009: Aspirin: not licensed for primary prevention of thrombotic vascular disease - http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087716. ***The UK Medicines and Healthcare products Regulatory Agency (MHRA) directly cite CTSUs research in this 2009 guidance update on aspirin use for primary prevention of thrombotic vascular disease.***