2017 Scientific Conference

Aspirin: 120 years of innovation

14th September 2017

Charité – Berlin Museum of Medical History

8.00am - 5.30pm

Increasing the knowledge & understanding of Aspirin

Welcome

The International Aspirin Foundation welcomes you to our 28th Scientific Conference, but more importantly we are here to celebrate 120 years since the synthesis of acetylsalicylic acid, and what more prestigious venue than the former lecture hall of Charité – Berlin Museum of Medical History.

Professor Peter Rothwell, outgoing Chair of the International Aspirin Foundation's Scientific Advisory Board together with the other board members – Professors Carlo Patrono and Mike Gaziano, Dr Ruth Langley & Dr Andy Chan - have developed an exciting programme. This unique meeting brings together experts to discuss the implications of trials and other research in mechanisms, prevention and treatment across multiple diseases.

I would like to give special thanks to Peter, who in 2015 formally took on the role of Chair of the Scientific Advisory Board and we are indebted to him for the enormous amount of support he has given The Foundation, particularly given his clinical and research responsibilities. During his reign we have increased the members of the Scientific Advisory Board and are delighted to have additional support from Professor Lina Badimon (Spain), Dr John Chia (Singapore) and Professor Junbo Ge (China).

Sharing knowledge is vital and we are delighted that with the good grace of modern technology we are able to have 300 medical doctors join the conference via a live link to China in our East meets West session.

This important meeting provides a platform where professional colleagues can discuss and debate future uses of aspirin in an open manner.

We trust the setting of our Scientific Conference will inspire you and we look forward to seeing you all again the in future.

Pippa Hutchison MSc
Executive Director

From the Chair of the International Scientific Advisory Board and Scientific Conference

Peter Rothwell
Oxford University, Oxford, UK

"The International Aspirin Foundation has organised many influential scientific meetings since it was founded by Nick Henderson over 40 years ago. The 2017 Scientific Conference, organised by Pippa Hutchison, the Executive Director, reflects The Foundation's continuing aim of increasing awareness of research on aspirin by stimulating the distribution and exchange of information and discussion.

We are extremely fortunate to have a truly world-leading group of speakers who will review some of the most interesting areas of current research and practice. I am honoured to chair the meeting and look forward to supporting Carlo Patrono as he takes over as the next Chairman of the International Scientific Advisory Board".

From the Chair elect of the Aspirin Scientific Advisory Board

Carlo Patrono
Rome, Italy

In celebrating the 120th anniversary of the synthesis of acetylsalicylic acid, the International Aspirin Foundation (IAF) wants to help the medical/scientific community take a look back on its second life as an anti platelet agent, as well as looking at its future as a novel tool for the integrated prevention of cardiovascular disease and some forms of gastrointestinal cancer.

As incoming Chair of the Scientific Advisory Board of the IAF, I'm looking forward to one day of global science as well as to the role that the IAF is going to play in interpreting the results of ongoing clinical trials and promoting new research - both basic and clinical - into acetylsalicylic acid's multifaceted benefits for mankind.

Programme

Session One

8.35 - 10.00

Update on CVD & Stroke: East meets West - Chair: Professor Junbo Ge

The disease burden of cardiovascular disease and major strategy of primary prevention in China – Dong Zhao

Antiplatelet therapy for stroke prevention in China – Yongjun Wang

Acute effects of aspirin in TIA and stroke – Peter Rothwell

Primary prevention in US and Europe and forthcoming trials – Mike Gaziano

Session Two

10.30-12.30

Oncology - Chair: Dr Ruth Langley

Aspirin for the Primary Prevention of Colorectal Cancer – Andrew Chan

Lynch syndrome & experience of implementing secondary prevention – John Burn

Aspirin for Cancer Prevention and Cure – Is the Time Now? – John Chia

Summing up & Chairing discussion about clinical implications – Ruth Langley

Session Three

2.30-3.30

Mechanism of Action - Chair: Professor Carlo Patrono

The aspirin-sensitive platelet lipidome: beyond thromboxane A2 – Valerie O'Donnell

PK/PD determinants of the interindividual variability in the antiplatelet response: aspirin "resistance" revisited – Bianca Rocca

Session Four

4.00-5.00

Bleeding on aspirin - Chair: Professor Lina Badimon

What is the risk of bleeding? – Peter Rothwell

Causes of bleeding and strategies for prevention – Chris Hawkey

Meeting concluding remarks: Professor Carlo Patrono

Speakers

Professor Sir John Burn FRCP, SRCPE, FRCOG, FRCPCH, FMedSci

Professor of Clinical Genetics, Newcastle University, UK

Professor Sir John Burn obtained an MD with distinction, a first class honours degree in human genetics from Newcastle University, where he has been Professor of Clinical Genetics since 1991 and a consultant specialist since 1984. He led the regional NHS Genetics Service for 20 years and helped to create the Centre for Life which houses an education and science centre alongside the Institute of Genetic Medicine and Northgene Ltd, the identity testing company he launched in 1995. He chairs DNA device company QuantuMDx. He was knighted in 2010, chosen as one of the first 20 'local heroes' to have a brass plaque on Newcastle Quayside in 2014. He received the Living North award in 2015 for services to the North East 2000 – 2015. He is also a non-Executive Director of NHS England.

Dr Andrew T. Chan MD, MPH

Associate Professor of Medicine, Harvard Medical School, USA
Email: ACHAN@mgh.harvard.edu

Andrew T. Chan, MD, MPH is an Associate Professor of Medicine at Harvard Medical School (HMS), Chief of the Clinical and Translational Epidemiology Unit, and the Program Director for gastroenterology training at Massachusetts General Hospital (MGH). As a clinical gastroenterologist, Dr. Chan specializes in familial gastrointestinal cancer syndromes and cancer prevention. Dr. Chan is a leading investigator in the epidemiology of colorectal cancer and other digestive diseases, with a focus on chemoprevention with aspirin and the gut microbiome. An elected fellow of the American Society of Clinical Investigation, his work is supported by the National Cancer Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the American Gastroenterological Association (AGA), the Damon Runyon Cancer Research Foundation, and the Crohn's and Colitis Foundation of America. He has published over 280 papers in the field of colorectal cancer and other chronic digestive diseases in leading journals, including the New England Journal of Medicine, Journal of the American Medical Association, Lancet, Science Translational Medicine, Gastroenterology and Gut. In 2016, he was recognized with a Top Ten Clinical Research Achievement award by the Clinical Research Forum. Dr Chan is a section editor for Gastroenterology, serves on the editorial board of Cancer Prevention Research and Cancer Epidemiology Biomarkers and Prevention, and is vice-chair of the Gastrointestinal Oncology Section of the AGA.

Speakers

Professor J Michael Gaziano MD, MPH

Principal Investigator, Million Veteran Program and Scientific Director of the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Heathcare System; Chief, Division of Aging, Brigham and Women's Hospital, Professor of Medicine, Harvard Medical School; all in Boston, Massachusetts, USA.

Dr. Gaziano is a preventive cardiologist and internationally recognized chronic disease epidemiologist whose research interests include the epidemiology of chronic diseases using large data sources. He has a particular interest in the lifestyle, metabolic, biochemical and genetic determinants of common chronic disease such as cardiovascular disease and cancer.

A centerpiece of his research involves the conduct of observational studies and trials that are imbedded in a health care system and the curation of electronic health data from many sources. He serves as one of two PIs of the Million Veteran Program (MVP), a project that will enroll one million veterans into a longitudinal cohort with stored biospecimens, self-reported data and the rich electronic clinical and administrative data available in the VA. To date over 580,000 veterans have been enrolled into MVP. He is principal investigator of the Physicians' Health Study, a large-scale trial-based cohort of over 29,000 physicians followed for over 30 years. He has also served as PI, Co-PI or co-investigator on a number of other cohort studies and large-scale trials. He serves on advisory committees for the Precision Medicine Initiative and the UKBiobank.

Dr. Gaziano oversees several fellowship programs and teaches advanced epidemiology at the Harvard School of Public Health. He has published over 550 journal articles, reviews, book chapters and books. He has also served as an Associate Editor for the Journal of the American Medical Association. He is a Fellow of the Royal College of Physicians.

Professor Christopher Hawkey

Professor of Gastroenterology, Faculty of Medicine & Health Sciences,
Nottingham University, UK

Christopher Hawkey is Professor of Gastroenterology at the Nottingham Digestive Diseases Centre. His main interests are in the field of non-steroid anti-inflammatory drugs and inflammatory bowel disease. In both areas his approach is to try to identify targets in small exploratory studies and then evaluate them in large and/or outcomes studies.

Speakers

Professor John Whay-Kuang Chia

MBBS (Singapore), MRCP (UK) FAMS (Medical Oncology)

Senior Consultant Medical Oncologist at the Department of Medical Oncology, National Cancer Centre, Singapore

Dr John WK Chia is Senior Consultant, at the National Cancer Centre Singapore. Graduating from the National University of Singapore, he later obtained his Membership of the Royal College of Physicians in Edinburgh in 2002 and upon completing his Oncology Boards, he underwent fellowship training in "Immunotherapy for Solid Tumors" - with Malcom Brenner at the Centre for Cell and Gene Therapy, Baylor College, Houston, for the development of cancer vaccines and adoptive T-cell therapy. He undertook a second clinical fellowship in with Prof Stan Kaye at The Royal Marsden Hospital London from 2011 to 2012 in the advanced management of Gynecological cancers.

Dr Chia is active in clinical trial research; and has developed and/or led numerous clinical trial studies– including immune check-point inhibitors, cancer vaccines, adoptive T cell therapy, and small molecule targets for cancer and he holds scientific research grants both locally and internationally.

Professor Valerie O'Donnell PhD

Professor of Biochemistry and Co-Director of the Systems Immunity Research Institute, Cardiff University, UK

Dr Valerie O'Donnell is Professor of Biochemistry and Co-Director of the Systems Immunity Research Institute, Cardiff University. She uses mass spectrometry to uncover new lipids involved in inflammatory processes, and is funded by British Heart Foundation and Wellcome Trust. She is an ERC Advanced Investigator. Following a PhD in Bristol, studying enzymology of NADPH oxidase in neutrophils, she completed post doctoral fellowships in Bern, Switzerland and with Bruce Freeman and Victor Darley-Usmar at University of Alabama at Birmingham. She moved to Cardiff in 1999 on a Wellcome Trust CDA Fellowship. Her research group studies vascular inflammation, applying informatics, machine learning and statistics to global analysis and discovery lipidomics projects which aim to uncover new mechanisms of lipid signaling in disease.

Speakers

Professor Bianca Rocca MD PhD

Professor of Pharmacology at the Catholic University School of Medicine in Rome, Italy

Prof. Rocca trained as Postdoctoral Fellow at the Center for Experimental Therapeutics, University Pennsylvania of Philadelphia (USA) with Prof. Garret A. FitzGerald. Prof. Bianca Rocca is member of the Editorial Board of the 'European Heart Journal-Cardiovascular Pharmacology', listed in the Top Italian Scientists, she has co-authored over 100 articles with over 5500 citations in peer-reviewed journals, including: Nature Medicine, Science, Blood, Circulation, Journal of Clinical Investigation, PNAS (USA), Annals of Internal Medicine, ATVB, Nature Clinical Practice in Cardiovascular Medicine, JACC, European Heart Journal, Diabetes. She has been appointed by the European Society of Cardiology as the Chairperson of the Working Group on Thrombosis (2016-2018). Her H-index is 36. Main scientific topics of interest are: antiplatelet drugs, eicosanoids, primary haemostasis, platelets, non-steroidal anti-inflammatory drugs, cardiovascular diseases.

Professor Peter M Rothwell MA MB ChB, MD PhD FRCP FESO FRSB FMedSci

Head of the Centre for the Prevention of Stroke and Dementia
and Professor of Clinical Neurology, Oxford, UK

Peter qualified in medicine from the University of Edinburgh in 1987 and after completing his early postgraduate clinical training he moved to Oxford as Clinical Lecturer in Neurology in 1996. He was awarded an MRC Senior Clinical Fellowship in 1999 and set up the Stroke Prevention Research Unit in 2000, which now employs over 40 research staff. He was awarded a Professorship in 2004 and was elected a fellow of the Academy of Medical Sciences in 2008, a National Institute of Health Research Senior Investigator in 2009 and a Wellcome Trust Senior Investigator in 2011. He has published over 400 scientific papers and several books. His research interests include primary and secondary prevention of stroke, the effects of blood pressure on the brain, and the risks and benefits of aspirin.

Peter is clinically active, working as a Consultant Neurologist for the Oxford University Hospitals Trust.

Speakers

Professor Yongjun Wang MD, PhD

Chief physician, professor, doctoral tutor, vice president of Beijing Tiantan Hospital affiliated to Capital Medical University, Beijing, China

Executive vice president or Chairmen: Chinese Stroke Association, Chinese Society of Neurology, Stroke Prevention and Control Society, Chinese Preventive Medicine Association.

Editor of journals: Chinese Journal of Stroke, Chinese Journal of Internal Medicine, CNS Neuroscience & Therapeutics, Stroke, a member of the World Stroke Organization.

Research interests: cerebrovascular disease clinical and applied basic research work. He published CHANCE study which was adopted by AHA/ASA 2014 "Guidelines for the Prevention of Stroke in Patients With Stroke and TIA", and "2014 Chinese Guidelines for the Secondary Prevention of Ischemic Stroke and TIA". He has published more than 100 SCI papers as the first author or corresponding author.

Award: the first prize of Beijing Science and Technology Award, the first prize of Science and Technology of the Chinese Preventive Medicine Association, the first prize of Science and Technology Progress Award of Ministry of Education, the outstanding achievement award of "2014 WuXi PharmaTech Life Chemistry Research Award". "Beijing scholar" in 2015.

Dr Dong Zhao MD

Chief physician, PhD, doctoral tutor, deputy director of Beijing Institute of heart lung and blood vessel disease, director of epidemiology research department, An Zhen Hospital, Beijing, China

Experts Committee member for: Disease Control of the Ministry of Health, National Cardiovascular Center, Chinese Society of Cardiology, Cardiovascular Disease branch of Chinese Physicians' Association, International Society of Atherosclerosis.

Vice chairman for: Chinese Society for prevention of chronic diseases, Cardiovascular Disease Branch of Chinese Female Physicians' Association.

Involved in Chinese Guidelines and international guidelines update: Prevention and Treatment of Hypertension, Prevention and Treatment of Dyslipidemia, Guideline for Cardiovascular Disease Prevention. World Health Organization Guidelines for cardiovascular disease prevention and American Heart Association guidelines of Cardiovascular Disease Prevention in women. Published more than 200 hundreds papers in professional journals.

Award: the first prize of Scientific Progress Award of the Ministry of Education in 2011, the Chinese Medical Prize in 2013, the second prize of Scientific and Technological Progress in Beijing City in 2005.

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Session One

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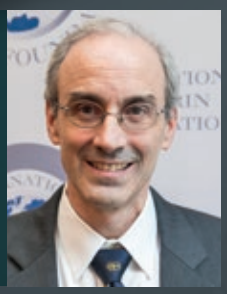

The disease burden of cardiovascular disease and major strategy of primary prevention in China

Dong Zhao

Capital Medical University affiliated Beijing Anzhen Hospital, Beijing Institute of Heart, Lung and Blood Vessel Disease

In China, cardiovascular disease (CVD) is a leading cause of death. In 2012, CVD accounted for 41 and 39% of the total deaths in urban and rural populations respectively.[1] A 2013 study published in Lancet on the rapid health transition in China from 1990 to 2010 showed that stroke and ischemic heart disease (IHD) came first and second out of 235 causes of death. In 2010, China had an estimated 1.73 million deaths from stroke and 0.95 million deaths from IHD.[2]

The trend in IHD mortality rate differs from that of stroke. In the previous 20 years, IHD had a 120.3% increase in crude mortality rate and a 31.6% increase in age-standardized mortality rate. It jumped from the seventh leading cause of years of life lost in 1990 to the second in 2010. [2]In Chinese urban populations, IHD has replaced stroke as the leading cause of death. According to a World Bank report, the estimated number of patients with IHD in China will increase from 8.1 million in 2010 to 22.6 million in 2030.[1-3] For stroke, several studies reported a notable decrease in the age-standardized mortality rate and disability adjusted life year (DALY).[2,4] However, the decreasing stroke mortality rate is likely caused by an increased survival rate in hospitalized stroke victims rather than a decreased incidence of stroke.[5] The World Bank report also predicts a substantial increase in the number of stroke patients, from 8.3 million in 2010 to 32 million in 2030.[3]

What is the impact of CVD deaths on the life expectancy (LE) of Chinese people? Two recently published papers provided answers for this question.[6-7] They analyzed the effect of total CVD deaths and cerebrovascular disease deaths on life expectancy in the Chinese population, using recent mortality data from the National Disease Surveillance Point System on more than 70 million Chinese (6% of the total population of China). This sample is nationally representative in age, gender, and regional distribution. According to the study, in 2010 the Chinese LE at birth was 73.2 years. The top five major causes of death in the Chinese population result in a total 10.6 year reduction in LE. CVD deaths reduced LE by 4.8 years, malignant tumors by 2.7 years, injury and poisoning by 1.5 years, respiratory diseases by 1.2 years, and perinatal diseases by 0.46 years. The study also found that 34.8% of the loss of life expectancy (LLE) from CVD deaths in men and 21.7% in women, was from the premature CVD deaths of people aged 25–64 years.

Premature CVD deaths contributed more to LLE in rural areas (30.7%) than in urban areas (23.3%). Of the 4.8 year LLE caused by CVD, 2.3 years (47%) was from stroke, 1.2 years (25%) from IHD, and 1.3 years from other forms of CVD. In rural men, 51.1% of the LLE from CVD deaths was caused by stroke death, and more than 30% was attributed to premature death in people aged <65 years. However, IHD deaths contributed more to LLE in urban men and women than in rural men and women. Based on the study, a 27.4% reduction in CVD mortality would increase LE at birth by 1 year in the Chinese population, if there were no changes in the mortality rates of all other diseases.

Several published studies have tried to identify the key determinants of the current CVD trend in China.[3,8] Aging and population growth will explain at least half of the increase in CVD over the coming 20 years, and unfavorable trends in smoking, blood pressure, cholesterol, diabetes, and obesity are key determinants for the CVD epidemic in future. In 2012, the China National Plan for NCD [Non-Communicable Disease] Prevention and Treatment was issued with clearly defined targets for CVD prevention. [9] Several areas in CVD prevention have been identified as development priorities for public health policies and actions. The major strategies in CVD primary prevention include promotion of healthy diet and physical activities, tobacco control, hypertension control, LDL-C lowering and anti-thrombotic treatment by aspirin among high risk people. However, the greatest challenge is how to effectively implement these plans in CVD prevention practice.

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Antiplatelet therapy for stroke prevention in China

Yongjun Wang

In China, a randomized, double-blind, controlled trial (the CHANCE trial) enrolling 5170 patients from 114 hospitals between October 2009 and July 2012 was performed to assess the efficacy and safety of combined treatment of clopidogrel and aspirin versus aspirin alone in minor ischemic stroke and TIA. The CHANCE trial showed that treatment with clopidogrel plus aspirin for 21 days, followed by clopidogrel alone for a total of 90 days, is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage among patients with minor stroke or TIA treated within 24 hours after symptom onset [1] [2]. In current guidelines for the early management of patients with acute ischemic stroke published by both Chinese Medical Association, combination of clopidogrel and aspirin is recommended for initiation within 24 hours of a minor stroke or TIA and continuation for 21 days based on the results of the CHANCE trial. Although antiplatelet drugs are easy to use, inexpensive, and well tolerated, adherence to antiplatelet drugs in Chinese population is not optimal, as anticipated. As the ChinaQUEST study demonstrated, antiplatelet use declined from 81% at the time of hospital discharge to 66% at 12 months post-stroke [3].

Following the publication of the CHANCE trial, more researches on antiplatelet drugs were performed in China in the recent 4 years:

Early dual antiplatelet therapy for acute minor stroke or TIA

The benefits and safety associated with combination of clopidogrel and aspirin have received much concern. A meta-analysis assessing clinical trials about dual versus mono antiplatelet therapy confirmed that dual therapy was more effective than monotherapy in reducing risks of early recurrent stroke for patients with acute non-cardioembolic ischemic stroke or TIA[4]. To investigate the appropriate therapeutic time window, our group analyzed patients treated within 12 hours, and found that the benefit of dual antiplatelet therapy also exist compared with mono therapy[5]. While efficacy of dual antiplatelet therapy has been proven, the issue of haemorrhagic complications has always been of concern. Our subgroup analysis concluded there was no overall significant difference in the rate of intracranial haemorrhages between dual and mono antiplatelet therapy groups. However, dual antiplatelet therapy may increase the risk of non-intracranial haemorrhages in patients with minor strokes[6]. To figure out the short-term time course of benefits and risks, our results suggest it is within the first 2 weeks that clopidogrel–aspirin treatment may have a benefit of reducing stroke risk outweighing the potential risk of increased bleeding compared with aspirin alone [7]. Furthermore, in comparison with aspirin alone, the combined treatment of clopidogrel and aspirin not only decreases the 90-day risk of stroke without increasing hemorrhage, but also reduces 1-year risk of stroke without increasing hemorrhage [8].

The clopidogrel drug genome

The association between CYP2C19 genetic variants and clinical outcomes of patients with minor stroke and TIA treated with clopidogrel remains unclear. In order to find the answer, our group tested genotypes of CYP2C19 in 2933 CHANCE patients, and found 58.8% of them were carriers of loss-of-function alleles (*2,*3) [9].Compared with aspirin alone, the combination of clopidogrel and aspirin reduced the risk of a new stroke only in the subgroup of patients who were not carriers of the CYP2C19 loss-of-function alleles. A recent meta-analysis also showed carriers of CYP2C19 loss-of-function alleles(*2,*3,*8) are at greater risk of stroke and composite vascular events than non-carriers among patients with ischemic stroke or TIA treated with clopidogrel[10]. Both findings support a role of CYP2C19 genotype in the efficacy of this treatment. The level of glycated albumin (GA) may have an effect on the role of CYP2C19, and clopidogrel-aspirin when compared with aspirin alone reduced stroke recurrence only in non-carriers of CYP2C19 loss-of-function allele(*2,*3) and normal GA levels[11].

Biomarkers can predict outcomes and treatment effect

Our group had made some efforts to analyze the association between biomarkers and recurrent stroke. Among patients with acute minor stroke or TIA, high hsCRP levels can predict recurrent stroke and poor functional outcome [12], and elevated sCD40L levels can independently predict recurrent stroke[13]. Glycated albumin could be a potential biomarker to predict the effects of dual and single antiplatelet therapy[14].Furthermore, both impaired fasting glucose(IFG) and diabetes mellitus(DM) were associated with an increased

risk of stroke [15]. What's more, higher levels of Lp-PLA2 activity(Lp-PLA2-A) in the acute period are associated with increased short-term risk of recurrent vascular events [16]. We also examined the impact of kidney function on treatment effect for stroke patients. Results show clopidogrel plus aspirin could decrease new stroke in patients with normal kidney function and mild chronic kidney disease (CKD), but no extra benefit was observed in those with moderate CKD[17].

Antiplatelet therapy effect depends on neuroimaging features

The impact of imaging patterns on treatment among stroke patients was given a lot of attention. CHANCE sub-study confirmed both multiple infarctions and intracranial arterial stenosis(ICAS) were associated with an increased risk of 90-day ischemic stroke in patients with minor stroke or TIA, and indicated the presence of both imaging features had a combined effect[18]. However, there was no significant difference in the response to dual or mono antiplatelet therapy between patients with and without ICAS [19].

Dual antiplatelet therapy improves functional outcome and quality of life

Consistent with a reduction in the rate of disabling stroke in the dual antiplatelet therapy, the combination of clopidogrel and aspirin appears to be superior to aspirin alone in improving the 90-day functional outcome[20]. Since stroke recurrence was associated with poor HRQOL (Health-Related Quality Of Life) in patients with minor strokes or TIA , interventions focusing on controlling risk factors and prevention of worsening of neurological function may prevent poor HRQOL in these patients[21].

The mystery of smoking in stroke patients

The role of smoking on treatment among stroke patients remains controversial. Compared with patients who never smoked, current smokers with a recent minor stroke or transient ischemic attack had a greater benefit in stroke prevention at 90 days from clopidogrel [22]. However, large prospective trials are needed to confirm this enhanced effect of clopidogrel in stroke patients.

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Effects of aspirin on risk and severity of early recurrent stroke after TIA and ischaemic stroke

Peter M Rothwell

The risk of major stroke is up to 10% in the days after a transient ischaemic attack (TIA) or minor stroke without appropriate treatment.[1-4] Urgent medical treatment appears to reduce that risk by as much as 80%,[5,6] but many patients delay seeking medical attention, often for several days or weeks, even when they make a correct self-diagnosis.[7,8] Public education campaigns have decreased delays to presentation after major stroke,[9,10] but there has been little improvement after TIA or minor stroke.[11] In a recent population-based study in the UK, half of recurrent strokes in the days after a TIA occurred prior to medical attention being sought for the initial event,[11] and the situation is likely to be worse in many parts of the developing world in which access to emergency services is limited.

Antithrombotic treatment is important in the immediate management of most acute ischaemic vascular events.[12,13] Since aspirin is available in many households public education materials recommend self-administration by patients who develop acute chest pain, in addition to seeking immediate medical attention.[14,15] However, pre-hospital self-administration of aspirin is discouraged after stroke,[15] due to concern about effects on possible intracerebral haemorrhage. However, haemorrhage is a rare cause of TIA symptoms and it accounts for less than 5% of minor strokes.[16,17] Although public education should continue to persuade people with transient neurological symptoms to seek medical attention immediately, where this is possible, self-administration of aspirin after transient unfamiliar symptoms might also be appropriate, particularly in rural settings or in less developed countries where access to medical services will be delayed.

There are, however, few published data from randomised trials on the effect of aspirin on risk of early recurrent stroke after TIA and minor stroke, and no data on severity. Evidence of apparently major benefits of urgent medical treatment more generally comes only from observational studies.[4,18] Randomised trials of aspirin vs. placebo in longer-term secondary prevention showed only a 13% relative reduction in risk of recurrent stroke.[12,13,19] Trials of short-term treatment of hospitalised acute stroke also reported a 13% reduction in the 4 week risk of recurrent stroke or intracerebral haemorrhage, but the effect of aspirin on risk or severity of recurrence after more minor stroke was not reported.[20-22] Yet, observational studies suggest potentially substantial early benefits of aspirin after TIA or minor stroke. In the EXPRESS study, urgent treatment with antiplatelet drugs, BP-lowering, and statins reduced the early risk of stroke by 80%,[5,6] much of which benefit was hypothesised to have been due to aspirin.[5] Severity of recurrent cerebral events was also reduced in EXPRESS, which might also have been due to aspirin.

In the absence of published randomised evidence of the effect of aspirin on risk and severity of early recurrent stroke after TIA and minor stroke, individual patient data and original paper records on early outcomes were recently reviewed and re-analysed from all available trials of aspirin vs. placebo in secondary prevention after TIA or ischaemic stroke.[23] To more reliably estimate the very early time-course of onset of effects of aspirin, risk of recurrent ischaemic stroke was also studied in trials of aspirin in treatment of acute stroke, stratified by severity of the pre-randomisation neurological deficit. To inform on possible mechanisms of action, the time-course of the interaction between effects of aspirin and dipyridamole in secondary prevention of stroke was also determined.

Among 15,778 patients in 12 trials of aspirin vs. control in secondary prevention, aspirin reduced the 6-week risk of major ischaemic vascular events by 70-80% (disabling or fatal ischaemic stroke - HR=0.29,0.20-0.43, p<0.0001; acute myocardial infarction - HR=0.22, 0.09-0.53, p=0.0008), with greatest benefit in patients with TIA or minor stroke (disabling or fatal ischaemic stroke: 0-2 weeks-HR=0.07, 0.02-0.31, p=0.0004; 0-6 weeks-HR=0.19, 0.11-0.34, p<0.0001).[23] The effect of aspirin on early recurrent ischaemic stroke was due partly to a substantial reduction in severity (modified Rankin score – mRs - shift analysis: OR=0.43, 0.26-0.72, p=0.001). These effects were independent of dose, patient characteristics or aetiology of TIA or stroke. Some further reduction in risk of ischaemic stroke on aspirin only vs control accrued from 6-12 weeks, but benefit after 12-weeks was limited (stroke risk-OR=0.97, 0.84-1.12, p=0.67; severity-mRS 'shift' OR=1.00, 0.77-1.29, p=0.97). In contrast, dipyridamole plus aspirin vs aspirin alone had no effect on risk or severity of ischaemic stroke within 12-weeks (OR=0.90, 0.65-1.25, p=0.53; mRS shift: OR=0.90, 0.37-1.72, p=0.99), but did reduce risk thereafter (OR=0.76, 0.63-0.92, p=0.005; disabling or fatal ischaemic stroke - OR=0.64, 0.49-0.84, p=0.001). In trials of aspirin versus control in major acute stroke (40,531 participants in 3 trials), the reduction in risk of recurrent ischaemic

stroke was most evident in patients with less severe baseline deficits (interaction-p=0.014), and was substantial by the second day after starting treatment (2-3 days-HR=0.37, 0.25-0.57, p<0.0001).

These findings confirm that timely medical treatment substantially reduces the risk of early recurrent stroke after TIA and minor stroke and identify aspirin as the key intervention. The considerable early benefit from aspirin warrants public education about self-administration after possible TIA. The previously unrecognised effect of aspirin on severity of early recurrent stroke, the diminishing benefit with longer-term use, and the contrasting time-course of effects of dipyridamole have implications for understanding mechanisms of action.

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Primary Prevention in US and Europe and Forthcoming Trials

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Aspirin is one of the most widely use medications. It is commonly use in cardiovascular disease for both acute treatment and prevention. In the setting of acute cardiovascular events such as myocardial infarction (MI) and stroke aspirin has clear benefit for the treatment of aspirin in the acute setting

The benefits of aspirin in the secondary prevention of cardiovascular disease (CVD) have been conclusively demonstrated in many trials among patients with all types of cardiovascular disease. The Antithrombotic Trialists' Collaboration reviewed 287 trials. Compared with placebo, those assigned to aspirin or other antiplatelet agents had an approximately 22 percent reduction in the combined outcome of serious vascular thrombotic events (non-fatal MI, non-fatal stroke or vascular death) and had clear reductions in MI (34%), Stroke (25%) and vascular death (15%) . Antiplatelet therapy was protective in high-risk patients, with previous MI, stroke, or transient cerebral ischemia; unstable or stable angina; peripheral artery disease; and indicated clear benefits of aspirin at doses higher than 75 mg per day and uncertain effects of aspirin at lower doses. (Antithrombotic Trialists' Collaboration, 2002)

The risk/benefit analysis is more complicated for those who do not yet have demonstrated CVD but who may be at risk of initial cardiovascular events. Aspirin as well as other antiplatelet agents lower the risk of cardiovascular events by reducing the tendency toward thrombus formation. This same effect of aspirin and related agents on platelet function also increase the risk of bleeding

Findings from the aspirin arm of the landmark Physicians' Health Study (PHS) indicated that prophylactic aspirin was effective in reducing the risk of a first MI. (Steering Committee of the Physicians' Health Study Research Group, 1989). Several other large-scale trials, which were either in men alone or had more men in the study population (British Doctor's Study (BDS), Peto et al, 1988; Hypertension Optimal Treatment study (HOT), Hansson et al, 1998; Thrombosis Prevention Trial (TPT), Medical Research Council's General Practice Research Framework, 1998; Primary Prevention Project (PPP), de Gaetano 2001; Aspirin for Asymptomatic Atherosclerosis Trial (AAAT), Belch et al, 2008; Prevention of Progression of Arterial Disease and Diabetes Trial (POPADAD), Fowkes et al, 2010) and one large-scale trial in women (Women's Health Study (WHS), Ridker et al, 2005) have assessed the benefits of low-dose aspirin in the prevention of CVD. It is important to note that most of those in these studies were of European descent.

The United States Preventive Services Task Force (USPSTF) conducted a systemic review of the effect of aspirin in primary prevention of cardiovascular events. (Guirguis-Blake et al, 2016). Data were synthesized from 11 good to fair quality trials most of which were in European populations. The reviewers found that aspirin provided a reduction in the risk of nonfatal MI but did not observe a reduction in the risk of stroke or all-cause or cardiovascular mortality, with the greatest reduction occurring in older adults. Regardless of whether dosages were 325 mg every other day, 100mg or less per day or 100 mg or less every other day, the findings remained the same. These benefits in MI risk reduction were greater in older individuals and the benefits appeared in the first 5 years.

The main effect of aspirin on platelet function that is responsible for the prevention of cardiovascular events in various settings is also responsible for increased bleeding risk. The two most important categories of bleeding influenced by aspirin are gastrointestinal (GI) bleeding and intracranial bleeding. When assessing the benefits of CVD reduction, GI bleeding is the main risk consideration because intracranial bleeding is usually part of the total CVD outcome and therefore it is typically accounted for in the assessment of CVD.

In 2016 the USPSTF assessed bleeding risk among large-scale prevention trials using low dose aspirin and found that GI bleeding risk increased by 58% and hemorrhagic stroke by 27% (Whitlock et al, 2016). They also found that these risks could increase depending on other factors such as a person's age, gender, medication use and CVD risk factors. It should be noted that the absolute rates of bleeding are quite small in most populations at usual risk for these events.

Given the benefit in preventing cardiovascular event and the increased risk of bleeding, the use of aspirin for lower CVD risk is dependent on the individual and the risk to benefit ratio. For those with acute MI are stroke the benefits are quite larger and risks of bleeding over the short treatment course are quite trivial. Similarly, for secondary prevention the absolute benefits clearly offset any modest risk. However, in primary prevention among those without disease the benefits and risks must be more carefully weighed.

The USPSTF recently published decision analysis on the role of aspirin in primary prevention contributed to its guidelines. (U.S. Preventive Services Task Force, 2016; Dehmer et al, 2016). Previously, the USPSTF issued guidelines on the use of aspirin in the primary prevention of vascular events. (U.S. Preventive Services Task Force, 2009). This recent publication is an evaluation of the thinking on the role of aspirin in the prevention that considers not only the cardiovascular events reduction and risk of bleeding events but also considers the benefits of aspirin in the prevention of colon cancer that is discussed elsewhere.

The decision analysis relied on, among other sources, the recent systemic reviews done on behalf of USPSTF exploring the risk and benefits of aspirin on all-cause mortality, cancer and specifically colorectal cancer (CRC) (Whitlock et al, 2016). The authors used a CVD simulation model adding CRC incidence and fatality. The model was applied separately to men and women in various age strata. The authors considered lifetime risks as the primary time horizon but also consider 10 and 20-year time windows.

They found a net benefited lifetime improvement in quality adjusted life years (QALYs) for men and women age 40 to 69 years, but no such overall benefit for those 70 to 79. The benefit was also present for total life-years among those 40 to 59 years, and for women 50 to 59 years with a 10-year CVD risk of 1% and both sexes age 60 to 69 with a 10-year CVD risk of 10%.

It is clear that aspirin is generally beneficial for patients with CVD. This decision analysis now carefully considers cancer and in particular colon cancer risk. There are subpopulations where there appears to be an overall benefit of preventive low dose aspirin. However, it still makes sense to consult a physician when considering the use of aspiring for a specific person.

While there are hundreds of trials of aspirin in acute treatment and secondary prevention, there are relatively few in primary treatment given the large size of these studies and the need for longer follow-up. There are several other primary prevention trials that are ongoing that will provide more insights into the use of aspirin in populations that have risk of CVD that is higher than the general population. These trials are: Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial that is being conducted largely in Europe and is testing daily aspirin at 100mg per day among those at moderate to high CVD risk based on CVD risk factors. Results from this trial should be forthcoming in 2018; the Aspirin in Reducing Events in the Elderly (ASPREE) trial studying those at higher CVD risk based on age being 70 years or older that is being conducted in Australia and the United States (Nelson et al, 2003); A Study of Cardiovascular Events in Diabetes (ASCEND) trial which is based in the UK and is testing low dose aspirin among those with diabetes but without known CVD (ASCEND Trial Website) ; and, the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCETP-D) is testing low dose aspirin and simvastatin among diabetics (De Berardis et al, 2007).

In summary, those with documented CVD should be on aspirin at a dose of at least 75 mg per day unless clearly contraindicated. In primary prevention in European populations, the use of aspirin for prevention must take into account the individual's long-term risk of subsequent cardiovascular disease. Currently, several guidelines recommend low dose aspirin for adults with higher risk of CVD based on risk assessment using a CVD risk calculator and who are not at high risk for bleeding as described above. Some guidelines are beginning to consider the reduction in the risk of colon cancer. These recommendations may be revised as more data become available by pooling all the primary prevention trials and from special populations that are currently under study. These guidelines consider risk and benefit in populations largely of European origin. As discussed elsewhere in this symposium the risk to benefit ratio may differ in other populations such as Asian, where the risk of MI, stroke, stroke type and bleeding may be different.

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Session Two

Oncology
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Aspirin for the Primary Prevention of Colorectal Cancer
Andrew Chan

Lynch syndrome & experience of implementing secondary prevention
John Burn

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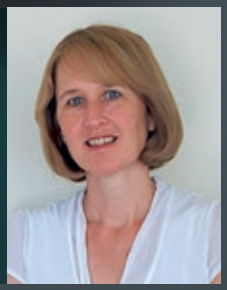
Summing up & Chairing discussion about clinical implications
Ruth Langley



Aspirin for the Primary Prevention of Colorectal Cancer

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Synopsis

Aspirin has become one of the most commonly used drugs given its role as an analgesic, anti-pyretic, and agent for cardiovascular prophylaxis. Several decades of research have yielded considerable evidence demonstrating its potential for the prevention of cancer, particularly of the colorectum. Broader clinical recommendations for aspirin-based chemoprevention strategies have recently been established; however, given the known hazards of long-term aspirin use, larger scale adoption of an aspirin chemoprevention strategy likely requires improved identification of those individuals for whom the protective benefits outweigh the harms. Such a precision medicine approach may emerge through further clarification of aspirin's mechanism of action.

Despite greater adoption of population screening and significant advances in understanding the molecular basis of colorectal neoplasia, colorectal cancer (CRC) remains a leading cause of U.S. cancer deaths.[1] Aspirin has emerged as perhaps the most promising agent for the chemoprevention of CRC.[2,3] This is due in large part to remarkably consistent data that have emerged from numerous basic, clinical, and epidemiologic studies over the past several decades. The United States Preventive Services Task Force (USPSTF) originally recommended against the use of aspirin for the prevention of CRC in 2007. However, in their updated draft recommendations for low-dose aspirin in the primary prevention of cardiovascular disease (CVD), the USPSTF acknowledged that supporting evidence[4] had become so compelling that CRC prevention warranted inclusion into their rationale for routine aspirin use among those age 50-69 with specific cardiovascular risk profiles. This move distinguishes aspirin as the first pharmacologic agent to be endorsed for cancer chemoprevention in a population not characterized as high risk for cancer. Nevertheless, the USPSTF also cautioned against the potential harms associated with regular aspirin use and highlighted the need to clarify the mechanisms by which aspirin prevents the development of colorectal neoplasia.

In this presentation, we will review the weight of the evidence supporting aspirin's chemopreventive potential and highlight advances in our understanding of aspirin's mechanisms. We will challenge the notion that aspirin prevents cancer through a single, dominant pathway, and propose an integrative multi-pathway model for its mode of action. Furthermore, we will highlight how these pathways can be leveraged to develop mechanistic biomarkers for personalized risk stratification. Such biomarkers may then be translated clinically in a precision medicine approach that is critical to the future of aspirin chemoprevention.

Weight of the evidence supporting aspirin chemoprevention

The epidemiologic evidence supporting aspirin's efficacy for the prevention of cancer, especially colorectal, is substantial.[2,3,5-9] We led a pooled-analysis of ten cohort and case-control studies that demonstrated aspirin use was associated with a 29% reduction in the incidence of CRC (odds ratio [OR]=0.71; 95% confidence interval [CI], 0.66-0.77).[10] Most recently, a study from Northern Denmark reported a 27% reduction in CRC risk (OR=0.73; 95% CI, 0.54-0.99) in those who continuously used low-dose aspirin for more than five years.[11] Beyond cohort and case-control studies, additional data have also emerged through secondary analyses of randomized clinical trials (RCTs) originally conducted to examine the role of aspirin in the prevention of CVD which have been linked to long-term cancer outcomes. A meta-analysis of four such trials found that aspirin treatment for five or more years at doses of at least 75 mg per day reduced the long-term risk of CRC by 24% (95% CI, 0.60-0.96).[8] Because aspirin treatment was randomized, these findings are less likely to be due to confounding associated with the reason for use compared to cohort or case-control studies.

Until recently, RCTs of aspirin that included cancer outcomes as pre-defined endpoints were limited in number and generated mostly discouraging findings. The Physicians' Health Study (PHS), a placebo-controlled RCT of alternate day 325-mg aspirin among 22,071 male physicians found no association between aspirin use and CRC incidence over 12 years of follow-up.[12] The Women's Health Study (WHS), the largest placebo-controlled RCT of aspirin for primary prevention, compared alternate-day 100-mg aspirin with a median

duration of treatment of 9 years. The results at completion of the originally planned follow-up of 10 years provided no evidence of an effect of aspirin on CRC.[13] Additionally, the Colorectal Adenoma/carcinoma Prevention Programme 2 (CAPP2) trial observed no reduction in the risk of colorectal neoplasia among carriers of Lynch syndrome, a hereditary CRC syndrome, after 2.5 years of planned follow-up in those assigned to 600 mg of daily aspirin. However, extended follow-up of RCTs has yielded more promising evidence. For example, in the WHS, an inverse association between those randomized to aspirin and CRC incidence emerged 10 years post-randomization (hazard ratio [HR]=0.80; 95% CI, 0.67-0.97).[14] In CAPP2, a secondary preplanned analysis, conducted after the first participant was followed for 10 years, did show a significantly reduced risk of CRC in the per protocol analysis (HR=0.41; 95% CI, 0.19-0.86) and after accounting for the multiple primary events commonly seen among patients with Lynch syndrome (incidence rate ratio [IRR]=0.56; 0.32-0.99).[15] Nonetheless, these findings may not be generalizable to sporadic, non-hereditary CRC, since Lynch tumors arise through a distinct pathway of defective DNA mismatch repair,[16,17] accounting for less than 3% of all CRC.

Thus, a definitive RCT, testing the effect of long-term daily aspirin treatment at a range of doses with sporadic CRC as a prespecified endpoint over at least 10 years of defined follow-up, remains elusive. To date, such a trial has been challenging to pursue owing to the large number of subjects and prolonged follow-up required for incident cancers to emerge. Moreover, the conduct of such an RCT would be complicated by long-term compliance with an aspirin regimen as well as the rising prevalence of aspirin use for CVD prevention, which leads to significant treatment group cross-over over time. In lieu of such studies, RCTs designed to examine the impact of aspirin on colorectal adenomas, the precursor to most CRCs,[18-21] have provided compelling evidence of causality and the efficacy of aspirin chemoprevention. Adenoma prevention trials are more feasible given the relatively short-term follow-up needed to examine the recurrence of adenomas in individuals at higher risk for colorectal neoplasia. Four trials, the Aspirin/Folate Polyp Prevention Study (AFPPS), Association pour la Prévention parl'Aspirine du Cancer Colorectal (APACC), Cancer and Leukemia Group B (CALGB) and the United Kingdom Colorectal Adenoma Prevention (ukCAP) trial, demonstrated variable reductions (4-39%) in the risk of recurrent adenoma among individuals with a high risk of sporadic CRC. Recently, the Japan Colorectal Aspirin Polyps Prevention (J-CAPP) trial showed aspirin reduced the recurrence of any adenoma or CRC (Relative Risk [RR] = 0.60; 95% CI, 0.36-0.98).[22]

Over the coming years, additional RCTs (ARRIVE, ASCOLT, ASPIRED, ASPREE, CAPP3, SeAFOod) combined with continued collection of long-term outcome data from completed trials are expected to add to the growing evidence supporting aspirin chemoprevention. All things considered, the "perfect" trial of aspirin and CRC prevention may not be feasible. However, the consistency of both epidemiological and RCT evidence thus far provides a compelling basis to more broadly consider the use of aspirin for chemoprevention, especially for CRC, a consensus opinion shared by many authorities in the field.[2,3,5,6,9] Indeed, the current level of "imperfect" evidence was considered sufficiently persuasive to lead the USPSTF to incorporate the effect of aspirin on CRC in its broader recommendation for U.S. adults between ages 50-69 with greater than 10% ten-year risk of CVD to consider chronic disease prophylaxis with low-dose aspirin.[4]

Risk-benefit associated with chronic aspirin use

Several studies have estimated the magnitude of potential side effects associated with regular aspirin use, particularly gastrointestinal bleeding, through assessment of the severe adverse events reported during RCTs. A recent meta-analysis of 35 RCTs of daily aspirin doses of 75-325 mg estimated a HR for major gastrointestinal bleeding of 1.42 (95% CI, 1.27-1.58).[23] For average risk individuals, this translates into 1-2 gastrointestinal bleeding events per 1,000 person years. Most,[24] but not all,[25,26] studies find that such toxicities are largely dose-related, with the hazards for bleeding generally higher with 300-325 mg than 75-162.5 mg.[27-30] However, in 2012, a meta-analysis of RCTs by Rothwell and colleagues concluded that long-term (≥3 years), low-dose (<300 mg) aspirin use was not significantly associated with a persistently increased risk of major extracranial bleeding (mainly gastrointestinal) events.[7] Therefore, consideration of such risks highlights the importance of developing a precision medicine strategy to identify those individuals who are most likely to benefit from a prophylactic aspirin regimen.

Molecular risk stratification for aspirin chemoprevention

A precision medicine approach to aspirin chemoprevention may emerge through advances in our understanding of the potential anti-cancer mechanisms associated with aspirin. These biological pathways may be exploited as molecular biomarkers for risk stratification. In this section, we will review the progress made thus far in elucidating aspirin's mode of action, which has been facilitated by advances in biobanking, genomics, and integrative molecular epidemiology over the last decade.

Prostaglandin synthesis and catabolism

The capacity of aspirin to irreversibly bind and acetylate, and therefore inhibit prostaglandin-endoperoxide synthase (PTGS or cyclooxygenase [COX])-1/2 has been widely considered to be central to its chemopreventive mechanisms.[31-39] These enzymes perpetuate pro-inflammatory signals leading to promotion of cellular proliferation, angiogenesis, and apoptotic resistance. PTGS enzymes are responsible for the conversion of arachidonic acid into downstream effectors

that are further metabolized into prostaglandins (PG) and related eicosanoids (i.e. PGE_2, PGD_2, PGF_2, thromboxane $[TX]A_2$, and prostacyclin). PGs then can bind to several downstream targets, including transmembrane and nuclear receptors. Increased synthesis of PGE2, directly attributable to PTGS-2 activity, has been consistently observed within colorectal neoplasia and promotes colorectal carcinogenesis.[40,41] Genetic deletion of PTGS2 or any of several PGE2 receptors results in decreased intestinal tumor incidence and burden in mouse models of CRC.[42-46] The relevance of this chemopreventive mechanism in humans is further supported by our molecular epidemiology studies. Within the Nurses' Health Study (NHS) and Health Professionals' Follow-up Study (HPFS), we showed that regular aspirin use conferred a significant reduction of risk of cancers that overexpress PTGS-2 (RR=0.64; 95% CI, 0.52-0.78) as measured by immunohistochemical staining of the tumor.[39] However, aspirin use was not associated with the risk of cancers with low or negative PTGS-2 expression (RR=0.96; 95% CI 0.73-1.26, $P_{heterogeneity}$=0.02).

Hydroxyprostaglandin dehydrogenase 15-(NAD) (HPGD, 15-PGDH), the primary enzyme that catabolizes PGs, functionally acts as a metabolic antagonist, or "brake" for PTGS-2. In vivo experiments have demonstrated that HPGD-null mice are more susceptible to colon tumorigenesis[47] and are insensitive to non-steroidal anti-inflammatory drug (NSAID)-based chemoprevention.[48] The Adenoma Prevention with Celecoxib RCT provided human evidence supporting the role of HPGD as a critical mediator of NSAID-based chemoprevention.[48] Celecoxib, a selective PTGS-2 inhibitor, only prevented adenoma recurrence in patients with concomitant expression of HPGD transcripts within normal colonic mucosa, suggesting a cooperative role for HPGD and PTGS-2 inhibition in reducing risk of neoplasia. These provocative findings were extended to aspirin in our study of HPGD expression in the adjacent normal mucosa of CRC tumors in the NHS/HPFS.[38] We demonstrated that aspirin use was associated with a reduced risk of CRC in those individuals with high expression of HPGD in normal colon tissue (HR=0.49; 95% CI, 0.34-0.71). Conversely, in individuals with low colonic expression of HPGD there was no protection associated with aspirin use (HR=0.90; 95% CI, 0.63-1.27, $P_{heterogeneity}$=0.02). These results highlight the potential importance of HPGD in conferring sensitivity to aspirin and suggest that normal tissue markers such as HPGD mRNA may serve as predictive biomarkers for chemoprevention. If validated further in other populations, a clinical strategy could include additional biopsies of normal mucosa among individuals who undergo resection of an adenoma during endoscopy. Assessment of the level of expression of HPGD in these biopsies could then be used to predict the likelihood of response to aspirin treatment in the prevention of recurrent neoplasia.

Additional evidence of the relevance of PG balance in colorectal neoplasia has been assembled through the application of methods to quantify the major urinary metabolite of PGE_2, 11alpha-hydroxy-9,15-dioxo-2,3,4,5-tetranor-prostane-1,20-dioic acid (PGE-M),[49] in the urine. Urinary PGE-M is widely accepted as the most accurate quantification of in vivo systemic PGE_2.[50] Multiple studies have demonstrated an increased risk of CRC and adenoma associated with higher pre-diagnostic urinary PGE-M levels.[51-53] In addition to supporting the importance of PGs in carcinogenesis, urinary PGE-M may also have potential for molecular risk stratification. Within the NHS, we found that regular use of aspirin and/or NSAIDs was associated with a 39% reduction (95% CI, 0.43-0.87) in adenoma risk among women with high baseline PGE-M, but not low PGE-M (OR=1.05; 0.50-2.19).[54] Further studies are needed to determine the potential use of urinary PGE-M as a biomarker for chemoprevention.

The advent of gene x environment (GxE) interaction analyses within the context of genome wide association studies (GWAS) has facilitated the discovery of novel genome-wide significant interactions between germline variants and the risk of CRC in the context of regular aspirin use. We led a study of 8,634 CRC cases and 8,553 controls from 10 studies that identified a single nucleotide polymorphism (SNP) rs2965667 that appears to predict a differential response to aspirin use with putative, albeit somewhat distant, relevance to PG synthesis.[10] For rs2965667, aspirin and/or NSAID use was associated with a lower risk of CRC among individuals with the TT genotype (OR=0.66; 95% CI, 0.61-0.70, $p=7.7 \times 10^{-33}$). In contrast, aspirin use among those with rare (4%) TA or AA genotypes was associated with an increased risk of CRC (OR=1.89; 95% CI, 1.27-2.81, p=0.002). This SNP lies proximate to a number of candidate genes associated with aspirin's putative mechanisms: microsomal glutathione S-transferase 1 (MGST1), a member of membrane-associated proteins in eicosanoid and glutathione metabolism (MAPEG) family, which is upregulated in a number of cancers, including CRC, and has high sequence homology with PGE_2 (MGST1L1);[55-57]

Taken together, these studies demonstrate multiple associations implicating PTGS-2 inhibition as a major mode of action for aspirin chemoprevention and the potential of tissue, urinary, and genomic biomarkers associated with PG synthesis for personalized risk stratification.

Wnt/ß-catenin signaling

Given the critical importance of Wnt dysregulation in the development of most CRC,[17,19] the possible effects of aspirin on this signaling pathway have become a focus of mechanistic investigation. Briefly, this pathway is activated through extracellular Wnt ligand binding to surface receptors resulting in cytosolic stabilization of ß-catenin and, ultimately, translocation of ß-catenin to the nucleus.[58] Within the nucleus, ß-catenin binds to transcription factor 7 like-2 (TCF7L2) to form a transcriptional activation complex and results in the expression of genes affecting cell proliferation and migration. In the absence of ligand, ß-catenin becomes ubiquitinated and targeted for degradation through the formation of the

Axin-APC-ß-catenin-GSK3ß complex. Aberrant activation of Wnt signaling resulting in nuclear accumulation of ß-catenin is observed in the majority of CRCs. Aspirin treatment of human CRC cell lines reduces the cytoplasmic pool of ß-catenin through inactivation of protein phosphatase 2A (PP2A), the phosphatase responsible for dephosphorylating the ß-catenin amino acid residues (T41 and S45) that target ß-catenin for ubiquitination.[59]

Mechanistic investigation as to the potential for interaction of PGE_2 and Wnt signaling has further highlighted the relevance of Wnt modulation for aspirin chemoprevention that has been previously reviewed in detail.[60] In brief, PGE_2 appears to enhance Wnt signaling via multiple downstream effectors. In vitro and in vivo models demonstrate that PGE_2 stabilizes ß-catenin and inhibits the destruction complex through activation of cyclic AMP (cAMP) and protein kinase A (PKA) during development. PGE_2 increases transcription of proliferator-activated receptor-∂ (PPAR-∂), whose gene is a direct transcriptional target of Wnt signaling via the ß-catenin/TCF7L2 transcriptional complex. PPAR-∂ is upregulated in some CRCs[61] and has been associated with proliferation and apoptotic resistance within CRC cell lines. Moreover, genetic deletion of PPAR-∂ in $APC^{Min/+}$ mouse models of CRC tumorigenesis abrogates the pro-tumorigeneic effects of PGE_2.[62]

Beyond experimental models, mechanistically-based candidate gene studies have provided proof-of-principle that aspirin may influence Wnt signaling in humans. GWAS of CRC susceptibility has consistently identified a SNP, rs6983267, on chromosome 8q24 as an important CRC risk locus,[63,64] with the T-allele associated with an approximate 20% reduction in CRC risk. This SNP appears to play a role in Wnt signaling by modulating the binding of TCF7L2, which leads to lowers expression of the MYC proto-oncogene.[65] Since experimental studies have demonstrated an effect of aspirin on Wnt signaling, it follows that aspirin may interact with genetic variation at this locus. Among a nested case-control cohort within the NHS and HPFS, we showed that the association of regular aspirin use with CRC differed significantly according to the presence of this SNP,[66] with the benefit of aspirin predominantly evident among individuals with at least one T allele ($P_{interaction}$=.01). Compared with nonuse, aspirin use was associated with ORs of 0.61 (95% CI, 0.47 to 0.79) among those with GT genotypes and 0.52 (95% CI, 0.35 to 0.78) among those with the TT genotypes. In contrast, regular aspirin use was not associated with lower risk among individuals with GG genotypes (OR = 0.99; 95% CI, 0.70 to 1.40). Importantly, the T allele was also associated with decreased MYC expression in CRC tissue, (P_{trend}=0.03) and among those with at least one protective T allele aspirin use was specifically associated with lower risk of CRCs positive for nuclear accumulation of ß-catenin (OR=0.44; 95% CI, 0.26-0.75, $P_{interaction}$=0.04). Taken together, these data support a mechanistic connection between aspirin chemoprevention and the Wnt/ß-catenin signaling axis, the functional relevance of 8q24 genetic variation in carcinogenesis, and the potential utility of rs6983267 as a mechanistic biomarker.

Inflammatory / immune response

Aspirin's anti-inflammatory properties and the establishment of chronic inflammation as a risk factor for CRC has elicited possible mechanistic connections between aspirin chemoprevention, chronic inflammation, and modulation of the host immune response.[36] PTGS-2 can be induced at sites of inflammation in response to cytokines produced by inflammatory cells, such as interleukin-1α/ß, interferon-γ and tumor necrosis factor-α (TNF-α). Additionally, PGE_2 seems to mediate inflammation-associated tumorigenesis in $APC^{Min/+}$ mouse models of CRC.[67] During inflammation-associated tumorigenesis, infiltrating neutrophils and tumor-associated fibroblasts were found to express the transmembrane receptor of PGE_2 (EP2), TNF-α, interleukin (IL)-6, CXCL2 (a prostaglandin producing enzyme), PTGS-2, and Wnt5a.[68]

Multiple studies have examined the association of CRC risk and circulating inflammatory markers in context of aspirin use within human populations. In a nested-case control within the NHS, we found that plasma soluble tumor necrosis factor receptor-2 (sTNFR-2), but not IL-6, or C-reactive protein (CRP), were associated with risk of CRC (RR=1.67; 95% CI, 1.05-2.68).[69] Among women with high baseline sTNFR-2, aspirin/NSAID use was associated with lower risk of CRC (RR=0.39; 95% CI, 0.18-0.86). In contrast, women with low baseline sTNFR-2 did not experience a preventive benefit associated with initiation of regular aspirin/NSAID use (RR=0.86; 95% CI, 0.41-1.79). These results, however, were not observed in men.[70] The circulating inflammatory cytokine macrophage inhibitory cytokine-1 (MIC-1, also known as growth differentiation factor 15 [GDF-15]) may be an important mediator in systemic inflammatory response and, as a member of the human transforming growth factor-ß (TGFß1) superfamily, play a specific role in colorectal carcinogenesis.[71,72] In a study within the NHS and HPFS, we examined plasma levels of MIC-1 in the context of CRC risk.[73] Comparing extreme quintiles, higher MIC-1 was associated with a 93% increased risk of CRC (95% CI, 1.27-2.94, P_{trend}=0.004). Furthermore, in exploratory analyses, among individuals with high MIC-1, aspirin and NSAIDs were associated with a lower risk of PTGS-2 positive (RR=0.60; 95% CI, 0.41-0.88) but not PTGS-2 negative CRC (RR=1.21; 95% CI, 0.71-2.07).

GWAS have further implicated a potential role for aspirin in modulation of inflammation as a mechanism for cancer prevention. Within a genome-wide GxE case-only interaction analysis,[10] we identified the SNP rs16973225 using a case-only interaction analysis. This SNP resides at chromosome 15q25.2, approximately 625 kb upstream of the interleukin (IL)-16 gene, a multifunctional cytokine with critical functions in pro-inflammatory processes such as inflammatory bowel disease and CRC. This SNP showed a genome-wide

significant interaction with use of aspirin and/or NSAIDs ($P_{interaction} = 8.2 \times 10^{-9}$). Regular use was associated with a lower risk of CRC among individuals with the AA genotype (OR=0.66; 95% CI, 0.62-0.71, $p = 1.9 \times 10^{-30}$). However, the reduced risk associated with regular aspirin use was nullified among those with AC or CC genotypes (OR, 0.97; 95% CI, 0.78-1.20;).

We have also shown that aspirin may have an influence on the immune compartment of CRC. We recently showed that aspirin use was linked with a reduced risk of CRC with low-level tumor infiltrating lymphocytes (TILs), but not CRC with high-level TIL.[74] These results provided the first population-based evidence for the role of host immunity in mediating the effect of aspirin in CRC chemoprevention. More recently, we advanced these findings by observing a stronger association of aspirin use with CRC survival in tumors with low-level CD274 (PD-L1) expression than in tumors with high-level CD274 (PD-L1) expression.[75] Taken together, these data suggest that aspirin's anti-cancer effect may operate at least partially through modulation of chronic inflammation and the immune system.

Platelet-mediated effects

Unlike epithelial cells, which express both PTGS-1 and PTGS-2,[9] platelets express only PTGS-1 and, as non-nucleated cells, lack the ability to resynthesize the enzyme. Thus, low-dose aspirin leads to permanent inhibition of platelet-mediated production of the prostanoid TXA_2. This action has been hypothesized to largely explain the vascular benefits of aspirin since TXA_2 is the major metabolite that promotes activation and aggregation of platelets, vasoconstriction, and vascular smooth muscle cell proliferation. Recently, the anti-cancer effects of aspirin has been proposed to also be mediated by platelets rather than through a direct effect on epithelial cells.[9] Such a hypothesis would explain why aspirin, at least in secondary analyses of CVD RCTs, appears to be effective in preventing cancer even at low doses, which would be rapidly metabolized and generate systemic concentrations not expected to be high enough to directly inhibit epithelial PTGS-2 and subsequent production of systemic PGE_2. To reconcile this with the highly consistent evidence implicating the importance of PTGS-2 in colorectal carcinogenesis, it has been hypothesized that activated platelets recruited to the mucosa in response to inflammatory events or mucosal injury leads to paracrine upregulation of PTGS-2 expression in epithelial cells. Thus, even low doses of aspirin, typically considered enough only to inhibit platelets, may eventually lead to significant downstream inhibition of PTGS-2 in epithelial and tumor cells.

Additional mechanisms

Beyond its effect on cancer initiation, aspirin may also influence cancer progression. Several studies have shown that aspirin use, particularly after diagnosis, is associated with a lower risk of colorectal cancer-specific mortality among patients with established CRC.[7,8,76-81] These associations may also be explained by the effect of aspirin on pathways such as PG synthesis or Wnt signaling. For example, in the NHS, we showed that aspirin was associated with improved survival, particularly among individuals with index primary tumors that overexpressed PTGS-2 compared to those with tumors without PTGS-2 overexpression. However, there may be additional distinct pathways by which aspirin influences cancer progression or metastasis but not initiation.[82,83] For example, aspirin use does not appear to be differentially associated with developing cancer with activating mutations in PI3K, catalytic subunit alpha polypeptide gene (PIK3CA),[84] a pathway that appears to share significant cross-talk with PTGS-2.[85] However, after diagnosis, we have shown that aspirin use was associated with dramatically improved survival among individuals with PIK3CA mutant CRC (HR=0.18; 95% CI, 0.06-0.61).[86] In a separate analysis within a clinical trial of adjuvant rofecoxib, others have also shown that aspirin use is associated with a HR of 0.11 (95% CI, 0.001-0.83) for PIK3CA mutant CRC.[87] Two additional observational studies did not individually support these findings.[88,89] However, a recent meta-analysis, which included one of these null studies,[88] concluded that the association of aspirin with CRC-specific survival does appear to differ according to PIK3CA mutation status.[90] Additional RCTs (ASCOLT, ADD-ASPIRIN) designed to assess the effect of aspirin in patients who have undergone potentially curative surgery for CRC are currently underway and will provide additional opportunities to determine if PIK3CA or other molecular biomarkers of cancer-specific pathways may be leveraged to predict responsiveness to therapy.

Conclusions

In conclusion, the recent USPSTF recommendation that recognizes the weight of the evidence supporting aspirin for CRC prevention is a critical first step in realizing a potential broader population-wide impact of aspirin use for chemoprevention. However, the future of aspirin chemoprevention will still benefit from molecularly-inspired human research aimed at clarifying aspirin's interrelated anti-cancer mechanisms. Such studies will be critical for fulfilling the promise of precision medicine for cancer prevention.

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Lynch syndrome & experience of implementing secondary prevention

John Burn

When the first participants in the CAPP2 trial of aspirin and/or resistant starch as chemopreventives in Lynch syndrome reached the tenth anniversary of their recruitment, an analysis of cancer rates revealed a significant protective effect of aspirin (Burn et al 2011) but not of starch (Mathers et al 2012). A secondary analysis of the impact of obesity revealed a significant interaction with the genetic predisposition such that those who were overweight were more than twice as likely to develop a colorectal cancer. This effect was partially abrogated in the aspirin limb compared to the placebo limb (p=0.02) supporting the possible anti-inflammatory role of the 600mg dose used in CAPP2.

The last recruit into CAPP2 reached her 10th anniversary in 2016. Analysis of the complete ten year blinded follow up data confirms the protective effect of aspirin and demonstrates that this is a true preventive effect rather than suppression of tumours which might emerge later (Burn et al paper in preparation). With rare exceptions the aspirin was discontinued in CAPP2 prior to the impact on cancer incidence, arguing against a direct effect on malignant cells as the primary mechanism and in favour of an impact on precancerous lesions, possibly by enhanced apoptosis or enhanced immune clearance of defective stem cells.

CaPP3 is a randomised dose non-inferiority trial comparing the 600mg dose shown to be effective in CAPP2 with 300mg or 100mg daily. This is an efficacy trial as the difference in adverse events between these three sub-analgesic doses is insufficient to be detected with the target 2000 recruits followed for 5 years. As cancer is the "hard" endpoint rather than polyps and the majority of recruits are from the UK where there is national cancer registration, the randomised groups will be blinded for 2 years and continue on the same doses for a further three years until their first census point. To date over 1,000 MMR gene defect carriers have been recruited in the UK with a rapidly expanding recruitment in Finland and Australia. Israel will begin to recruit in 2017. The target completion date for recruitment is late 2018 with an assessment of adverse events scheduled for 2020 and the efficacy analysis scheduled for 2023. A biobank will assess Frame Shift peptide antibody titres as a possible biological surrogate of cancer development.

Aspirin for Cancer Prevention and Cure – Is the Time Now?

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Asia with its burgeoning populations, will in the coming decades face twin challenges of rising cardiovascular disease and cancer – where the estimated economic impact exceeds a trillion dollars[1]. Aspirin has been shown in randomised controlled trials, to reduce cancer incidence, however it's adoption in the community has been hampered by concerns over toxicity - principally gastrointestinal and cerebral haemorrhage.

Recently the USPSTFA has reversed its stance and guidance, to recommend aspirin for prevention of cancer and cardiovascular disease - in individuals with a 10-year cardiovascular risk of 20% or less[2]. The recommendation draws from Markov and Micro-simulation models of bleeding, cardiovascular events and cancer - undertaken by the Kaiser Permanente Researchers on behalf of the Agency for Healthcare Research and Quality[3], showing net benefit. Here we review past and ongoing trials of aspirin in cancer, and ask if widespread adoption of aspirin as a chemoprevention agent in Asia, is an idea whose "time has come".

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2017 Scientific Conference
Aspirin: 120 years of innovation

Session Three

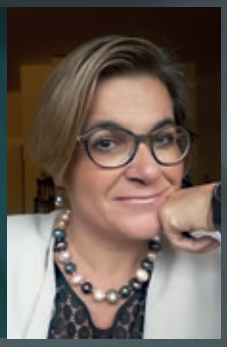
Mechanism of Action
Chair: Professor Carlo Patrono

The aspirin-sensitive platelet lipidome: beyond thromboxane A2

Valerie O'Donnell

PK/PD determinants of the interindividual variability in the antiplatelet response: aspirin "resistance" revisited

Bianca Rocca



Defining the aspirin-sensitive platelet lipidome.

Valerie O'Donnell

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Synopsis

Aspirin exerts its cardioprotective actions through blocking cyclooxygenase-1 (COX-1) dependent generation of the pro-thrombotic lipid, thromboxane A2 (TXA2). New generation mass spectrometry approaches are now enabling the characterisation of cellular lipidomes in unprecedented ways. High resolution methods that allow profiling of thousands of species combined with informatics can generate significant insight into how this class of molecules behave in health and disease. In this presentation, the use of lipidomic MS to profile platelet lipids and how they change with aspirin treatment will be presented. New informatics tools and how they can be applied to define signaling lipids will be highlighted.

Lecture notes

Although aspirin is considered highly specific for COX-1 in platelets when administered at low doses to humans, we became interested in its potential to have wider effects on the platelet lipidome, as part of a project that aimed to determine the total number and diversity of lipids in these cells. Furthermore, activation of blood cells leads to major changes in membrane structure and function, however up to now, what this translates to in terms of global changes in lipids was not known. To undertake this study, we needed to apply new analytical and informatics approaches. High resolution LC/MS was chosen since (i) long chromatography analyses enabled wide coverage of the total lipidome including separating isobaric species (typically 50 minute reverse phase runs), (ii) high resolution MS enabled lipids with similar m/z values to be distinguished. An Orbitrap Elite platform, generating full scans in negative or positive ion mode, at approximately 3 scans per second was used to profile platelet global lipids basally, following thrombin activation and before/after aspirin supplementation in 3 genetically unrelated human volunteers.

While many families of lipids are well characterized, the total diversity and number of individual lipids in cells, how they alter during activation of cells, and differ between individuals is unknown. This gap in our knowledge hampers integration of lipidomics with systems biology, and addressing it will improve our understanding of lipid biochemistry, (ii) help find new drug targets for therapy and (iii) improve identification of lipid biomarkers in cohort samples. This is especially relevant for finding bioactive lipids that are generally present in very small amounts and thus not detected routinely.

Previous estimates for the number of lipids in mammalian cells have been placed around 2,000-100,000, with theoretical numbers around 100,000-500,000, but until recently, esperimental attempts to define a typical amount were not undertaken (1,2). To this end, we used a workflow that tries to maximize, including writing our own in house software in Excel, then translating into Python (now available as LipidArrays) that undertakes extensive cleanup of the data and using painstaking manual verification of data(3). Aspirin at low/platelet specific doses may prevent cancer metastasis (4-6), and this may involve lipid bioactivity. Also, COX-1- eicosanoids can mediate of pain, fever, vasoconstriction and thrombosis. Due to this, we began to characterize the platelet aspirin-sensitive lipidome, and to use this to uncover lipidomic networks (7). Our data indicated that the human platelet lipidome is complex, with major changes on activation and following aspirin injestion. Large numbers of lipids appeared on activation with over 70% being sensitive to aspirin. Of interest, 192 fatty acids (FA) and oxidized phospholipids (oxPL) were identified. FA release required cytosolic phospholipaseA2 (cPLA2), and many of these then fed into mitochondrial ß-oxidation. The activation of cPLA2 by thrombin was found to require energy. Last, FA oxidation was required for maintaining membrane asymmetry. Acute lipidomic flux was thus linked with metabolism during innate immunity. Last, the large numbers of unknown lipids represent a discovery opportunity for the future. At this time, we still have no information on the diversity of aspirin responses over time in the same and different groups of healthy individuals. A British Heart Foundation funded project is now following 30 volunteers over a six month window of time with repeat aspirin supplementation and we expect to report on our findings shortly. This work was funded by the European Research Council and Wellcome Trust.

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PK/PD determinants of the interindividual variability in the antiplatelet response: aspirin "resistance" revisited

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Abstract

Aspirin exerts its antithrombotic activity through a permanent acetylation of a Serine 529 residue of the cyclooxygenase (COX)-1 isoenzyme, causing an irreversible inhibition of thromboxane (TX)A_2 generation from activated platelets. Apirin pharmacokinetics involves esterases and phase II enzymes, without contribution of the cytochrome P450 system. Inter- and intra-individual variability in the degree of platelet COX-1 inhibition largely depends on aspirin pharmacodynamics.

The renewal rate of COX-1 in platelets and its precursors, the competition at a COX-1 docking site common to aspirin and traditional non-steroidal anti-inflammatory drugs may explain most of the variability in responsiveness, and can be corrected. A pharmacokinetic-based variability can occur in obese subjects and it is predicted by in silico models, although further mechanistic studies are needed in severely-obese subjects.

In conclusion, as for most of the drugs, variable response is hooked on aspirin characteristics, and understanding the determinants influencing drug response is crucial for personalizing therapy.

Aspirin irreversibly inhibits thromboxane (TX) A_2 generation from activated platelets through a permanent acetylation of a Serine 529 residue located in proximity of the catalytic pocket of the cyclooxygenase (COX)-1 isoenzyme. The inhibition by low-dose aspirin administered once-daily is cumulative upon repeated daily dosing, and virtually complete (97-100%) (1). Upon aspirin withdrawal, the re-appearance of TXA_2 biosynthesis displays a 24- to 48-hour delay with full recovery after 7-10 days (1). These pharmacodynamic features reflect the permanent blockade of a short-lived drug (20-min half-life in plasma) of a molecular target, i.e. the COX-1 expressed in two key compartments: peripheral platelets which survive 7-10 days and bone marrow megakaryocytes which releases ~10% of new platelets in the peripheral blood every day (2) (Figure).

In silico physiologically-based pharmacokinetic modeling was able to reproduce these pharmacodynamic features, in the presence of physiological lifespans of platelets and of their immature precursors resident in the bone marrow (megakaryocytes, pre- and pro-platelets) (3). The pharmacokinetics of aspirin is relatively simple (Figure) as it does not involve the cytochrome P450 (CYP450) system, but rather other biotransformative reactions which are less exposed to clinically-relevant pharmacokinetic drug-drug interactions. In addition, mutagenesis studies have shown that Arginine 120 residue of the COX-1 is a docking site shared by aspirin and traditional non-steroidal anti-inflammatory drugs (NSAIDs) containing a carboxylic acid moiety (4,5), that may displace aspirin, preventing subsequent acetylation of Serine 529 (2).

At variance with drug resistance, inter-individual variability in drug response is largely dependent on the mechanism(s) of drug absorption and biotransformation, and/or on patient's characteristics. Differently from drug resistance, which makes drug useless as in the case of the antibiotics, variability in drug responsiveness can be potentially restrained and corrected by understanding the underlying mechanisms and adjusting drug dosing regimens, tailoring treatment to patient's characteristics, comorbidities and comedications.

Under conditions of primary or secondary increase of platelet generation rate, COX-1 activity recovers faster resulting in a shorter (less than 24 hours) duration of the full COX-1 antiplatelet effect of the once-daily aspirin regimen (6). Importantly, the relationship between platelet COX-1 suppression and the inhibition of TXA_2-dependent platelet activation in vivo is strikingly non-linear, which implies that a modest in vivo platelet inhibition can occur whenever COX-1 activity is suppressed by <97% (7). Clinical conditions permanently or temporarily associated with increased platelet generation rate as well as reduced responsiveness to standard low-dose aspirin include essential thrombocythemia (8), inflammatory conditions including post-coronary artery bypass grafting surgery (9), diabetes (10), obesity (11). A different pharma-

codynamics of aspirin in essential thrombocythemia and obesity could be also described and predicted by in silico pharmacokinetic modeling (3). Some of these conditions such as diabetes, essential thrombocythemia and coronary artery bypass grafting surgery are also associated with evidence of sub-optimal antithrombotic preventive effect of standard low-dose aspirin once daily. More frequent dosing (twice-daily) has been shown to enhance platelet TXA_2 inhibition, thereby reducing variability of pharmacodynamics response in these disorders. However, the efficacy and safety of more intense aspirin regimens awaits the clinical validation of randomized trials.

Another source of acquired and temporary intra-individual variability in aspirin responsiveness can derive from the co-administration of tNSAIDs: most tNSAIDs, especially when chronically used, hamper the virtually complete and long-lasting inhibition of platelet COX-1. The pharmacodynamic interaction between some tNSAIDs and low-dose aspirin, by reducing the degree of platelet COX-1 inhibition, might further increase the cardiovascular risk associated with the use of tNSAIDs (12).

In conclusion, the misplaced paradigm of aspirin 'resistance' is shifting toward the understanding of the determinants of a variable drug responsiveness, mostly based on pharmacodynamics-related features. Understanding diseases-dependent variables widening drug responsiveness and having in silico tools for predicting pharmacological response are both crucial to design and test alternative regimens to ensure a favorable benefit/risk profile not only of aspirin, but also of other irreversibly-acting antiplatelet drugs.

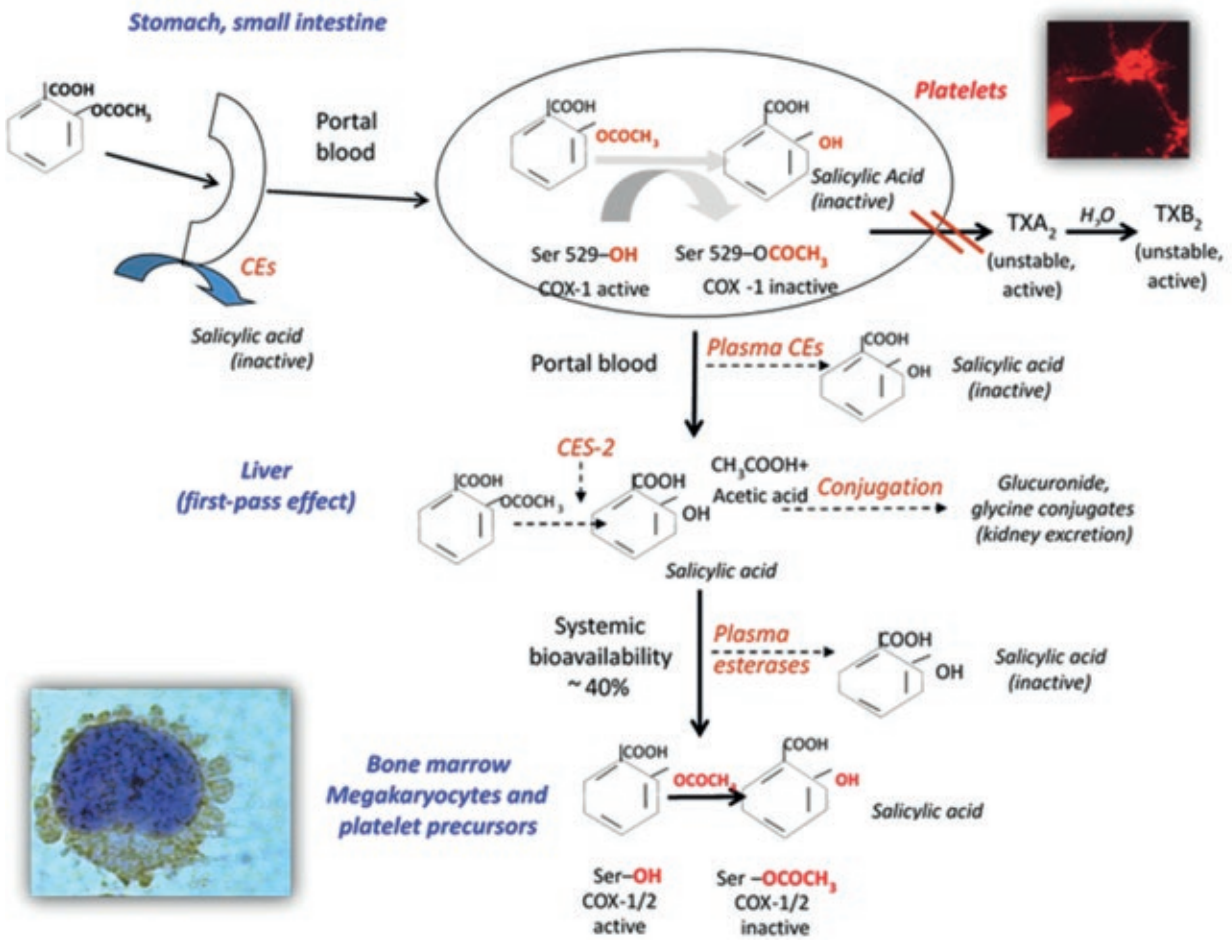

Figure:

Aspirin pharmacodynamics and pharmacokinetics. Aspirin is absorbed in the stomach and small intestine, permanently acetylates the Ser-529 residue of cyclooxygenase (COX)-1, already in the portal blood, and is biotransformed to inactive salicylic acid by intestine, plasma and liver carboxylesterases (CE), mainly the isoenzyme 2. Its systemic bioavailability is approx. 50%. Aspirin entering the systemic circulation reaches bone marrow megakaryocytes and platelet precursors inhibiting COX-1 and -2. COX-1-dependent arachidonic acid path in platelets generates mainly thromboxane (TX)A_2 which amplifies platelet activation. TXA_2 is quickly and non-enzymatically hydrolysed to TXB_2, biologically inactive. Abbreviations: CE: carboxylesterase; MK: megakaryocytes. Modified from Rocca et al., Exp Rev Cardiovasc Ther 2013;11:365-79.

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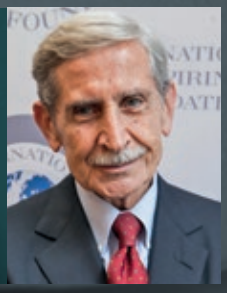
Session Four

Bleeding on aspirin
Chair: Professor Lina Badimon

What is the risk of bleeding?
Peter Rothwell

Causes of bleeding and strategies for prevention
Chris Hawkey

Meeting concluding remarks
Carlo Patrono



Risks, severity, time-course and outcome of bleeding on long-term antiplatelet treatment

Peter M Rothwell

Aspirin and other antiplatelet drugs increase the risk of major bleeding, particularly upper-gastrointestinal (GI) bleeds,[1] but this risk is reduced by 70-90% by proton pump inhibitors (PPI).[2] However, co-prescription of PPI with aspirin is not routine due to concerns about adverse effects,[3-6] and perhaps because upper-GI bleeds had low case-fatality on aspirin in previous trials[7] and are not generally thought to cause permanent disability. Clinical guidelines on secondary prevention of vascular events make no recommendations on PPI use, and although some consensus statements advocate them in "high-risk" patients,[8] definitions of "high-risk" vary and uptake in practice remains low. Since the likely absolute benefit of routine PPI use will depend on the risk of upper-GI bleeding on long-term follow-up, and about half of patients taking antiplatelet drugs for secondary prevention are now aged ≥75 years, we need reliable estimates of age-specific risks and consequences of bleeding in a real-world setting.

The risk of upper-GI bleeding on antiplatelet treatment increases with age,[9-11] but it is uncertain whether older age alone is a sufficient indicator of "high risk" to justify routine co-prescription of PPI. Published estimates of age-specific risks of bleeding vary by more than 10-fold, particularly at older ages, and derive mainly from primary prevention settings, with relatively short follow-up. Completeness of ascertainment of bleeding events is also uncertain in many studies due to reliance on only administrative coding data. Previous trials of antiplatelet drugs with face-to-face follow-up will probably have better ascertainment, but recruited few patients aged ≥75 years, tended to exclude high-risk patients, and had relatively short follow-up. Although the excess risk of bleeding attributable to aspirin was shown to decline after several years of follow-up in trials in primary prevention,[7] the time-course of bleeding risk in older patients in secondary prevention is uncertain and data on the functional outcome of upper-GI bleeds are lacking.

A recent population-based cohort study of patients with a recent transient ischaemic attack (TIA), ischaemic stroke or myocardial infarction (MI) treated with antiplatelet agents without routine use of PPI (Oxford Vascular Study) therefore attempted to determine the age-specific risks, site, severity, outcomes, time-course and predictors of bleeding complications, to compare the risks with those of recurrent ischaemic events and with the risks reported in previous randomised trials, and to estimate the potential impact of routine PPI use on reducing bleeding in secondary prevention of vascular events.[12]

In 3166 patients (1582 aged≥75 years) with a first TIA, ischaemic stroke or myocardial infarction from 2002-2012 treated with antiplatelet drugs (mainly aspirin-based, without routine PPI use), all bleeds requiring medical attention was identified from multiple overlapping sources, including face-to-face follow-up for 10 years.[12] A total of 405 first bleeding events (218 GI; 45 intracranial; 142 other) occurred during 13,509 patient-years of follow-up. Of 314 (77.5%) patients with bleeds admitted to hospital, 117 (37.3%) were missed by administrative coding. Risk of non-major bleeding was unrelated to age, but major bleeding increased steeply with age (≥75 years HR=3.10, 2.27-4.24, p<0.0001), particularly for fatal bleeds (HR=5.53, 2.65-11.54, p<0.0001), and was sustained during long-term follow-up. The same was true of major upper-GI bleeds (≥75 years HR=4.13, 2.60-6.57, p<0.0001), particularly if disabling/fatal (HR=10.26, 4.37-24.13, p<0.0001). At age ≥75 years most major upper-GI bleeds were disabling/fatal (61.6% vs 47.4% for ischaemic stroke), outnumbering disabling/fatal intracerebral haemorrhage (45 vs.18), with an absolute risk of 9.15 (6.67-12.24) per 1000 patient-years. The estimated number-needed-to-treat (NNT) for routine PPI use to prevent one disabling/fatal upper-GI bleed over 5-years fell from 338 at age<65 to 25 at ≥85 years.

Thus, this large prospective population-based study of long-term antiplatelet treatment in secondary prevention of vascular disease showed that the severity, case-fatality and poor functional outcome of bleeds increase steeply with age.[12] Moreover, in contrast to the general impression that upper-GI bleeds are mostly non-disabling with low case-fatality, it showed that in patients aged ≥75 years, most major upper-GI bleeds were disabling or fatal, substantially outnumbering disabling or fatal intracerebral haemorrhage. Given that half of the major bleeds in patients aged ≥75 years were upper-GI, the estimated NNT for routine PPI use to prevent major upper-GI bleed are low and should be considered in future secondary prevention guidelines.

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Aspirin: protective strategies

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Initial concerns that aspirin would weaken the heart were unfounded but in 1937 it was shown by endoscopy to cause gastric ulceration. Evidence gathered to implicate aspirin (used at high anti-inflammatory and ulcerogenic doses) in the development of peptic ulcer and its serious complications of bleeding and perforation.In the last 40 years use of aspirin as an anti-inflammatory drug has been supplanted by non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase (COX)-2 inhibitors and aspirin became used for cardiovascular (CV) prophylaxis, based upon its ability to inhibit platelet aggregation. However at these doses aspirin is still associated with gastrointestinal bleeding, and risk rises with age [1,2].

In contrast to NSAIDs (where results ranging from harm to protection have been reported), there is clear clinical and epidemiological evidence that the bacteria Helicobacter pylori increases the risk of ulcer development and bleeding with aspirin [1]. One explanation of these differences could be that aspirin main action is to abrogate haemostasis and promote bleeding in lesions caused by another agent (main known upper GI ulcerogen H.pylori) whilst the drugs' intrinsic ulcerogenic activity is more important with NSAIDs.

Thus, there are 2 main strategies to protect against aspirin-associated ulceration and ulcer bleeding: use of an ulcer healing agent or H. pylori eradication

Ulcer healing agents. Ten randomised controlled trials (RCTs) involving 8780 participants have evaluated the ability of proton pump inhibitors (PPIs) to reduce the development of gastrointestinal bleeding and/or endoscopic ulceration [3]. In 5 studies a PPI was compared to placebo comparisons, in 2 to gefarnate (proposed to be cytoprotective) and in 3 an H2 receptor antagonist (H2RA). Compared to placebo PPIs decrease the risk of endoscopically detected ulcers in patients taking low-dose aspirin by approximately six fold (OR 0.16, 95% CI 0.12–0.23). There was in approximately four fold reduction in bleeding (OR 0.27, 95% CI 0.16–0.43). In 4 studies (2 vs placebo, 2 vs H2RA) patients were also taking clopidogrel. In these patients there was an approximately three fold reduction in GI bleeding (OR 0.36, 95% CI 0.15–0.87) without an increase in the risk of major adverse cardiovascular events (OR 1.00, 95% CI 0.76 –1.31.) [4]

In this meta-analysis, PPIs were superior to both H2 receptor antagonists and gefarnate in preventing ulceration or bleeding. These data support PPIs as the most effective strategy for prevention of clinically significant GI endpoints. However a recent paper finds famotidine to be as effective as a PPI [5]

However, there are concerns that long-term PPIs do or may have important deleterious effects [6] , including bacterial gastroenteritis, small bowel bleeding [7], malabsorption, osteoporosis and risk of hip fracture. These are real concerns although most evidence is descriptive and weak [4].

H. pylori eradication. The association between H. pylori and ulcer bleeding on low dose aspirin raises the mechanistic possibility that the main effect of aspirin is to enhance bleeding from ulcers caused by H. pylori) and the pragmatic hypothesis that H. pylori eradication would reduce or eliminate the risk of peptic ulcer bleeding on aspirin.

In endoscopic studies of patients on low dose aspirin there is a fivefold increase in ulcer prevalence and incidence in H. pylori positive compared to negative patients [2]. H. pylori eradication has been associated with low recurrence rates in patients presenting with bleeding peptic ulcer on aspirin, but these studies have lacked a placebo control group [8]. This led us to set up the Helicobacter Eradication Aspirin Trial (HEAT) to test directly whether H. pylori eradication would specifically reduce the incidence of bleeding peptic ulcer in aspirin users. [9] HEAT is an ongoing study with approximately 1300 general practices participating, over 27,000 subjects enrolled and over 5,000 infected with H. pylori randomised to eradication treatment (lansoprazole, clarithromycin, metronidazole) that was associated with high (92%) success. The primary endpoint is admission to hospital or death due to bleeding peptic ulcer. Events are tracked by patient contact, review of National Hospital Episode Statistics, ONS Data and by regular upload of accumulating information in the GP database. The study uses a number of innovative methods, including:

- Recruitment in general practice using the MIQUEST search tool that enables electronic scrutiny of records supported by any of the clinical systems used in UK general practice
- Use of an automated Docmail postal system that ensures invitations are received within 48 hours of patient identification, whilst maintaining record confidentiality

- Use of nurses available through the National Institute for Health Research (NIHR) Clinical Research Network (CRN) for the purposes of recruitment
- Using the recruitment visit opportunistically to obtain health check data to patient and GP benefit, including blood pressure, BMI, alcohol consumption and smoking status
- A dedicated central facility for H. pylori analysis
- Despatch of treatment by post (validated in pilot study)
- Replacement of conventional follow up visits by multiple methods for endpoint ascertainment: patient report, automated scrutiny of GP records, regular download of hospital episode statistics (HES) and mortality data, using the secure NHS N3 spine
- Validation of endpoints by the adjudication process used in the TARGET study [9]
- The trial is expected to finish in 2020

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To the Aspirin Advisory Board and all attending the 2017 Conference

I am a part of all that I have met;
Yet all experience is an arch wherethro'
Gleams that untravell'd world whose margin fades
For ever and forever when I move.
Alfred Lord Tennyson in Ulysses

Research on aspirin, much of it encouraged and supported by Nick Henderson and the Foundation, has helped uncover some of the science and a few of the mysteries of aspirin. One marvels that such a simple molecule could have such a profound, and such a variety of effects on biological mechanisms, leading ultimately to reductions in human, animal and botanical disease – though perhaps these last should perhaps be listed in the opposite, chronological, order!

The successes of aspirin so far have been in the reduction of vascular disease and cancer, but evidence is now growing of benefits in the treatment of disease, and treatment of no less a disease than cancer. To date, well over sixty published papers describe an overall reduction by low-dose aspirin in the mortality and the metastatic spread of cancer. But there are problems and much further work is needed. Almost all the evidence on aspirin in the treatment of cancer comes at present from observational studies, and aspirin now faces the difficulty that because of its vascular benefits, withholding it from some of the patients in randomised trials raises serious ethical issues. Furthermore, most of the evidence of benefit is limited to a few of the most common cancers.

A research approach which was first used brilliantly in following up participants in early vascular disease trials for evidence on cancer prevention, could be used to test effects on other disease outcomes. A host of diseases could of course be tested in such studies.... but dementia springs to mind. Why should a drug which is anti-inflammatory and reduces cerebral thrombosis and infarction not help reduce cognitive impairment?

It is important that research work is entertaining. If satisfaction and pleasure is not generated by tireless searching, pondering, discussing and arguing, motivation can be lost and standards can fall. The Foundation has not only provided a forum for stimulating and helpful interactions between scientists in different disciplines, but it has also contributed to entertainment. Collaborations between colleagues have been facilitated and discussions have been stimulated by the meetings and conferences organised by the Foundation, and occasionally by money granted by the Foundation! In all this, Nick Henderson has contributed - enriching the meetings of the Foundation with his warm friendship and encouragement, and occasionally with Scottish hospitality at his Caledonian Club.

As one of the few Fellows, I wish the Foundation further successes and continuing entertainment!

Life piled on life
Were all too little, and of one to me
Little remains: but every hour is saved...
To follow knowledge like a sinking star,
Beyond the utmost bound of human thought.

Peter Elwood
with great memories, and with even greater expectations!

16th August 2017

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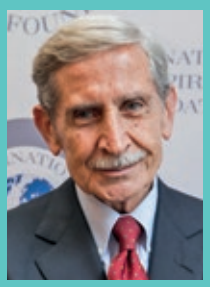

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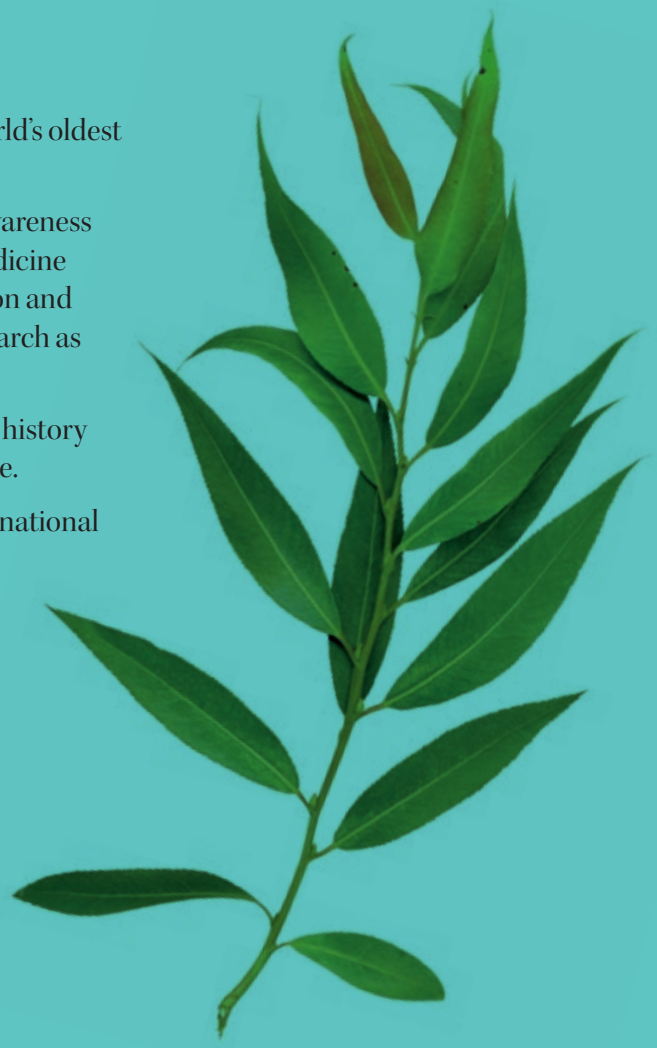

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