2019 Scientific Conference

Benefits and Risks of Antithrombotic Therapy for Cardiovascular Disease Prevention

Friday 28th June 2019 - *8.30 am - 5.10 pm*
Donna Camilla Savelli Hotel,
Via Garibaldi, 27 - 00153 Rome

Increasing the knowledge & understanding of Aspirin

Welcome

The International Aspirin Foundation welcomes you to our 29th Scientific Conference in Rome.

These are busy and exciting times at the International Aspirin Foundation as trial results and clinical debate continue to keep aspirin activity high within scientific, medical and research communities.

As a result, our Scientific Advisory Board, chaired by Professor Carlo Patrono MD FESC, have worked hard to create a stimulating programme that delves into some of the questions we need to answer and helps achieve The Foundation's aim of facilitating discussion amongst professionals from a variety of disciplines regarding aspirin's potential in modern medicine.

Delegates will be pleased to know that this meeting has been independently accredited by The CPD Standards Office.

In 1974, Gordon Nicholson Henderson founded the International Aspirin Foundation, sadly, Nick died in December 2018 at the age of 92. At his funeral many tributes were given and David Beauchamp (formerly of Reckitt & Colman and Whitehall International) said 'the acceptance by the medical profession of Aspirin in the treatment and prevention of heart disease and cancer is surely due in large part to the work of Nick's Foundation... and the number of lives his work on Aspirin will have saved worldwide is incalculable'.

The inaugural chair of the Scientific Advisory Board, Professor Peter Elwood FRCP OBE, worked with Nick from the early days and next week in London we are launching a commemorative issue of his book; 'Aspirin yesterday, aspirin today, aspirin tomorrow: a history of prophylactic aspirin'. The foreward to this book was written by the late Nick Henderson, where he wrote;

"My hope is that this publication will also encourage medical professionals to remain passionate about this compound and continue to put effort into researching new applications for it in medicine."

The calibre of international academia speaking here today indicates this passion and we thank them for sharing their knowledge from both a basic science and clinical perspective.

We hope the conference provides each of you with an opportunity to absorb, contribute and reflect upon the lively scientific dialogue that this old but still vital medicine ignites. Thank you all for making the time to join us and take part in this event.

Pippa Hutchison MSc
Executive Director, International Aspirin Foundation

The late Nick Henderson
Founder, International Aspirin Foundation

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

Carlo Patrono
Rome, Italy

On behalf of the Scientific Advisory Board of the International Aspirin Foundation, I would like to welcome you to the 2019 Scientific Conference on "Benefits and Risks of Antithrombotic Therapy for Cardiovascular Disease Prevention ". With a wealth of new data supporting the role of antithrombotic drugs in cardiovascular disease prevention reaching publication over the last few years, the opportunity for world experts from a mix of disciplines to meet and put this evidence into clear perspective is both timely and invaluable.

The International Aspirin Foundation Conference will provide the scientific arena to enable this important discussion to take place within its two main sessions devoted to the assessment of benefits and risks of antithrombotic drugs in secondary and primary prevention settings, respectively. For each of the six main topics on the agenda, a presentation providing a mechanistic insight into the subject will be followed by a discussion of its clinical implications.

In our view, this Conference represents an exciting opportunity to review and discuss recent advances in antithrombotic therapy, from both a basic science and clinical perspective, and to revisit aspirin's role in modern medicine. I look forward to your active participation.

Programme

Session One

Benefits and risks of antithrombotic therapy in secondary prevention
Chairpersons: Andrew Chan and Peter Rothwell

9.00 - 10.00

Dropping aspirin from dual or triple antithrombotic therapy

Regulatory mechanisms of platelet activation and inhibition: Is less more? - Marco Cattaneo
Clinical trials of aspirin-free regimens - Marco Valgimigli

10.00 - 11.00

Combining antiplatelet and anticoagulant strategies in high-risk patients

The role of platelet activation and blood coagulation in atherothrombosis - Lina Badimon
Clinical trials of low-dose aspirin combined with low-dose rivaroxaban - Giancarlo Agnelli

11.30 - 12.30

Reducing upper gastrointestinal bleeding by more extensive use of gastroprotectant agents

Mechanisms of upper gastrointestinal complications induced by antithrombotic drugs - Andrew T Chan
Clinical trials of gastroprotectant agents - Angel Lanas

Session Two

Benefits and risks of antithrombotic therapy in primary prevention
Chairpersons: Michael Gaziano and John Chia

1.30 - 2.30

Optimizing the aspirin dose and dosing regimen

Interindividual variability in the extent and duration of platelet thromboxane inhibition by low-dose aspirin - Bianca Rocca
Clinical trials of different aspirin doses and dosing regimens - Peter Rothwell

2.30 - 3.30

Incorporating other benefits of low-dose aspirin in the benefit/risk equation

Mechanisms underlying the non-vascular effects of low-dose aspirin - Paola Patrignani
Clinical trial evidence supporting a cancer chemopreventive effect of low-dose aspirin - Ruth Langley

4.00 - 5.00

Targeting the right patient population for primary prevention: the case of diabetes mellitus

Mechanisms of atherothrombosis in diabetes mellitus - Gemma Vilahur
Translating clinical trial evidence into treatment recommendations for the use of aspirin in diabetes - Francesco Cosentino

Meeting concluding remarks: Professor Carlo Patrono

Speakers

Professor Giancarlo Agnelli

Professor Giancarlo Agnelli is the Dean of the School of Medicine and Surgery of the University of Perugia, Italy. Prof Giancarlo Agnelli is Professor of Internal Medicine and Director of the Department of Internal Vascular Emergency Medicine and Stroke Unit at the University Hospital in Perugia.

Professor Agnelli is the Editor-in-Chief of the European Journal of Internal Medicine.Professor Agnelli received his medical degree and specialization in Internal Medicine from the University of Perugia.

He was then a research and clinical fellow at the Department of Medicine, McMaster University, Hamilton, Ontario, Canada, and at the Academic Medical Center, University of Amsterdam, The Netherlands.

Professor Agnelli's research focuses on the clinical trials on the prevention and treatment of cardiovascular disease, including the development of new anticoagulant agents. He is also exploring the relationship between cancer and thrombosis.

Professor Agnelli has authored more than 530 publications (www. pubmed.com). He is also a reviewer for a number of journals including the New England Journal of Medicine, The Lancet, Circulation, Blood, Cardiovascular Research, Journal of Thrombosis and Haemostasis and the Journal of the American College of Cardiology.

Professor Lina Badimon

Prof. Lina Badimon is the Director of the Cardiovascular Science Program (ICCC) at the IR-Hospital Santa Creu and San Pau, Director of the Cardiovascular Research Chair of the Autonomous University of Barcelona and Director of the UNESCO Chair in Biomedical Sciences Training and Research. She is the Chair of the Advocacy Committee and Board Member 2018-2020 of the European Society of Cardiology.

Her research activities focus on cardio-metabolic diseases, thrombosis, atherosclerosis and ischemic heart disease.

She has published over 560 articles in highly qualified scientific journals with her work highly quoted in the scientific literature (Citations: 41.241; h-index 76). She has written more of 250 reviews and book chapters.

She is Member of Editorial Boards of various international scientific journals. Previous appointments include: Fellow in Cardiovascular Diseases at The Mayo Clinic, Rochester, MN, USA (1981-1983); Director of the Cardiology Basic Research Laboratory of the Division of Cardiology at the Mount Sinai Medical Center, New York, NY (1983-1991); Assistant Professor of Medicine (1983-1987) and Associate Professor of Medicine (1988-1991) at the Mount Sinai School of Medicine, NY; Lecturer in Medicine at Harvard Medical School, Boston (1991-1994); Consultant at the Cardiac Unit, at the Massachusetts General Hospital, Boston (1991-1994)

Speakers

Professor Marco Cattaneo

Professor Marco Cattaneo is Professor of Internal Medicine at Università degli Studi di Milano. He has been Post-Doctoral Fellow at McMaster University, Hamilton (Ontario), Guest or Visiting Scientist at McMaster University, Temple University, Philadelphia (PA), The Scripps Research Institute, La Jolla (CA). In 2001 he was awarded the International Society on Thrombosis and Haemostasis (ISTH) 10th Biennial Award for Contributions to Haemostasis and Thrombosis. Editor/Associate Editor/ member of Editorial Board/Advisory Board for high-tier journals, including Jornal of Thrombosis and Haemostasis, Thrombosis Research, Haematologica, Platelets, Thrombosis and Haemostasis, Arteriosclerosis, Thrombosis and Vascular Biology. Professor Marco Cattaneo is also Chair of the Working Party on Platelet Aggregation, Chair of the Scientific Subcommittee on Platelet Physiology, Scientific and Standardization Committee (ISTH). Member of the ISTH Council 2010-2016. President-Elect, President and Past-President of SISET, the Italian Society on thrombosis and hemostasis, 2002-2008. Main research interests: pathophysiology of primary haemostasis, pharmacology of antiplatelet agents, risk factors for thromboembolism.

Current affiliation: Medicina 2, ASST Santi Paolo e Carlo, Milan, Italy – Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy

Professor Andrew T Chan

Andrew T. Chan, MD, MPH, Chief, Clinical and Translational Epidemiology Unit, Vice Chair, Division of Gastroenterology, Massachusetts General Hospital, Boston, Co-leader, Cancer Epidemiology Program, Dana-Farber/Harvard Cancer Center, Boston. 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, Cancer Research UK, the American Gastroenterological Association (AGA), the Damon Runyon Cancer Research Foundation, and the Crohn's and Colitis Foundation of America. He has published over 380 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 Chair of the Gastrointestinal Oncology Section of the AGA.

Speakers

Professor Francesco Consentino

Prof. Francesco Cosentino obtained his MD degree in 1987 and specialty training in Internal Medicine and Cardiovascular Disease at the University of Rome. In 1991 moved to Mayo Clinic & Foundation, Rochester, MN, USA for a Cardiovascular Fellowship. During his stay at Mayo he fulfilled all the requirements for a PhD in Biomedical Sciences – Cardiovascular Pharmacology. In 1995, he joined the Cardiovascular Division at the University Hospital of Bern. Two years later, Francesco Cosentino moved to the Division of Cardiology of Zurich University Hospital as "lecturer" and then "titular professor" of Cardiology. In 2006, he was appointed associate professor of Cardiology at the University of Rome "Sapienza".

Since 2013 he is professor and chair of Cardiovascular Medicine, Karolinska University Hospital, Solna and Karolinska Institute in Stockholm.

Prof. Cosentino is the recipient of grants and prizes from national and international institutions, research councils and private foundations. He is the leading author of more than 150 original articles published in top-ranking, peer-reviewed journals.

Prof. Cosentino is past secretary-treasurer of the European Society of Cardiology and current chair of ESC Partnership and Policy Committee. He is ESC chairman of 2019 ESC/EASD Guidelines on diabetes, pre-diabetes and cardiovascular disease and Associate Editor of European Heart Journal.

Professor Angel Lanas

Angel Lanas is Professor of Medicine of the University of Zaragoza, Vice-Dean for Research Affairs at the Medical School of Medicine University of Zaragoza, Chairman of the Digestive Diseases Service at the University Hospital "Lozano Blesa" of Zaragoza. Spain and Scientific Director of the Aragón Health Research Institute.

Dr. Lanas was visiting professor to the Department of Gastroenterology at the University of Alabama in Birmingham, Alabama, USA since November 1989 to Dicember1991, where he worked with Professor Basil Hirschowitz.

He is or has been member of the Advisory Board of several high-impact factor Journals of the specialty, International Associate Editor of The American Journal of Gastroenterology and Editor of Frontiers in Medicine-Gastroenterology. He has also been invited as Visiting Professor to different American, Asian and European Universities. Over the years, he has held leadership positions and received numerous awards for his contributions

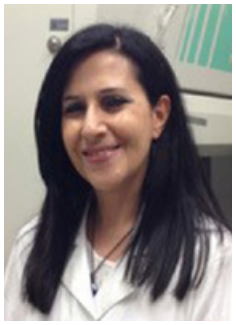
Among other associations he is member and International Fellow of the American Gastroenterological Association, member of the General Assembly of the United European Gastroenterology Federation and the Spanish Association of Gastroenterology (AEG). He was president of the AEG for 4 years and President of the AEG Foundation for another 4 years.

Dr. Lanas is actively involved in both clinical and basic investigation relating to acid peptic disorders, particularly NSAIDs, aspirin and gastrointestinal toxicity, as well as mechanisms of chemoprevention of colon cancer and Barrett's esophagus. Professor Lanas has published numerous articles pertaining to gastrointestinal damage, NSAIDs and inflammation in the most prestigious Medical Journals including the New England Journal of Medicine, The Lancet, Gastroenterology, Gut, The American Journal of Gastroenterology and American Journal of Medicine among others.

Speakers

Professor Ruth Langley

Professor Ruth Langley is a Medical Oncologist specializing in the design and management of oncology clinical trials based at the MRC Clinical Trials Unit at University College London where she leads the Cancer Group. Professor Ruth Langley has worked in a number of tumour areas including colorectal, lung and gastro-oesophageal cancer coordinating a series of trials and associated translational studies. She has a particular interest in re-purposing established medicines as cancer therapeutics, as well as cancer prevention, and is Chair of the UK Therapeutic Cancer Prevention Network. She has led the investigation of the use of transdermal oestrogen as a treatment for prostate cancer (PATCH studies). A major focus of her recent work has been the development of an international trial to assess the effect of aspirin as an adjuvant agent in several common solid tumours (the Add-Aspirin Trial) which is recruiting patients from the UK, Ireland and from several sites across India. The Add-Aspirin trial is part of a Cancer Research UK funded initiative the AsCaP collaboration to investigate the mechanisms underlying the anti-cancer effects of aspirin. She is a faculty member of the Indian CReDO (Collaboration for Research methods Development in Oncology) programme.



Professor Paola Patrignani

Professor of Pharmacology, Department of Neuroscience, Imaging and Clinical Sciences, Section of Cardiovascular and Pharmacological Sciences, "G. d'Annunzio" University, Chieti, Italy.

Paola Patrignani was graduated at the Faculty of Biological Sciences, "La Sapienza" University of Rome (Italy). Then, she followed a doctoral training in Pharmacology, at Catholic University of Rome, Italy. She worked for 2 years as Postdoctoral Research Fellow at Le Centre Hospitalier of Laval University (Quebec, Canada) and at the Department of Pharmacology of Merck Frosst (Kirkland, Quebec, Canada).

She continued her academic career at "G. d' Annunzio" University, School of Medicine, Chieti, Italy, where she is currently Professor of Pharmacology and Head of the Laboratory of Systems Pharmacology and Translational Therapeutics at the Center of Excellence on Aging and Translational Medicine (CeSI-MeT).

In 2009 she was Guest professor of Pharmacology at Goethe-Universität Frankfurt am Main (Germany). She is a member of the Italian Society of Pharmacology and she received the Upjohn Award (1981), the "Henry Christian" Award (1991) and was the winner of the 2018 International Aspirin Foundation Senior Science Award. In 2013, she received a special prize awarded by the Committee for the Promotion of Female Entrepreneurship of Abruzzo Region (Italy).

She is one of the Top Italian Women Scientists (TWIS) which includes the scientists with high impact publications. Her scientific activity is documented by 170 peer-reviewed publications in international journals ranked in the Journal Citation Reports, and 21 chapters in national-international books. Her cumulative citation index (H-index) is 56, 11831 citations.

Speakers

Professor Bianca Rocca

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

Professor Bianca Rocca, MD, PhD is Associate Professor of Pharmacology at the Catholic University School of Medicine in Rome (Italy). Professor Bianca Rocca trained as Postdoctoral Fellow at the Center for Experimental Therapeutics, University Pennsylvania of Philadelphia (USA) with Prof. Garret A. FitzGerald. She is immediate Past Chairperson of the European Society of Cardiology (ESC) Working Group on Thrombosis (2018-2020) and ex officio Member of the board of the ESC Working Group on Aorta and Peripheral Vascular Disorders. She is member of the Board of Clinical Pharmacology of the Italian Society of Pharmacology and of the Board of the Italian Group of Atherosclerosis, Thrombosis and Vascular Biology.

She has been part of several Task Forces of guidelines and position papers within the ESC. She has co-authored over 110 articles in peer-reviewed journals with over 6500 citations, 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. Her H-index is 41. Main scientific topics of interest are antithrombotic drugs, eicosanoids, primary haemostasis, platelets, non-steroidal anti-inflammatory drugs, cardiovascular diseases.

Professor Peter M Rothwell

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

Professor Peter Rothwell 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. Professor Peter Rothwell 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 500 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, and is Founding Director of a new purpose-built Centre for Prevention of Stroke and Dementia on the John Radcliffe Hospital site.

Speakers

Professor Marco Valgimigli

Marco Valgimigli is associate professor cardiology and senior interventional cardiologist at the Inselspital Universitätsspital Bern. He obtained his medical degree, summa cum laude, from the University of Bologna, and completed his training in internal medicine at the same university. He received a degree in cardiological sciences at the University of Ferrara and a PhD in interventional cardiology at Erasmus Medical Center in Rotterdam.

Prof Valgimigli's areas of research are wide ranging and include high-risk percutaneous interventions (PCI); invasive treatment of myocardial ischaemia (MI); reparative medicine with adult stem cells during MI and heart failure; antithrombotic therapy during and after PCI; and prognostic stratification during acute coronary syndromes and MI.

He serves as national coordinator on numerous clinical trials, including MULTISTRATEGY (Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study), 3T/2R (Tailoring Treatment with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel), PRODIGY (Prolonging Dual Antiplatelet Treatment after Grading Stent-induced Intimal Hyperplasia Study), EXCEL, ZEUS, MATRIX and ODYSSEY.

Prof Valgimigli is a fellow of the European Society of Cardiology, and has been widely published in international journals such as the European Heart Journal, American Heart Journal, Circulation, The Lancet, Journal of the American Medical Association, and The New England Journal of Medicine.

Dr Gemma Vilahur

Dr. Gemma Vilahur is a Senior Researcher at the Cardiovascular Program ICCC at the Research Institute of the Hospital de la Santa Creu i Sant Pau (Barcelona) where she coordinates the Translational Research Department. Her previous appointments include: Post-doctoral fellowship from the Spanish Ministry of Economy and Competitiveness at the Cardiovascular Biology Research Laboratory, Zena and Michael A. Wiener Cardiovascular Institute at the Mount Sinai School Medicine, New York, USA (2004-2006); Juan de la Cierva Researcher at the Spanish Ministry of Science and Education, (2006-2009); Ramon y Cajal Researcher from the Science and Innovation Ministry of Spain (MICINN; 2010-2015)

She has published 123 articles (Web of Science; 2.962 citations, H index = 31) and include original manuscripts, consensus and position papers, and reviews. In addition, she has contributed to 29 book chapters.She is and has been principal investigator and co-investigator of 40 research projects (National and European projects either funded by public agencies or industry) and has collaborated in two projects of the 7th Framework EU Program. Besides, she has been involved in a CENIT research program (Spanish Ministry of Science and Innovation; 2010-2015).

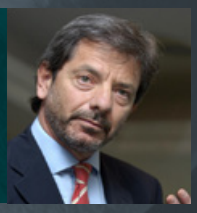
Dr. Vilahur's Awards and Honors include: European Society of Cardiology – ESC [Berlin 2002, Vienna 2003, Vienna 2007, Munich 2008 (young investigation award), London 2015]; first Prize National Congress of Cardiology (Madrid 2007; Seville 2012); first and second Prize in the National Congress of Atherosclerosis (Pamplona 2009 and Zaragoza 2013, respectively); Prize from the Northwestern Cardiovascular Young Investigator's Forum; the Arteriosclerosis, Thrombosis, and Vascular Biology Merit Award of the American Heart Association (AHA; Chicago 2006); and award by L'Oreal-UNESCO foundation - for Women in Science (2012).

Session One

Benefits and risks of antithrombotic therapy in secondary prevention
Chairpersons: Andrew Chan and Peter Rothwell

Dropping aspirin from dual or triple antithrombotic therapy

Regulatory mechanisms of platelet activation and inhibition: Is less more?
Marco Cattaneo



Clinical trials of aspirin-free regimens
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Combining antiplatelet and anticoagulant strategies in high-risk patients

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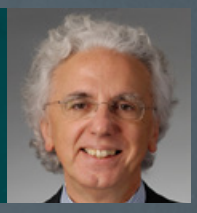

Reducing upper gastrointestinal bleeding by more extensive use of gastroprotectant agents

Mechanisms of upper gastrointestinal complications induced by antithrombotic drugs
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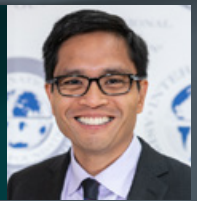
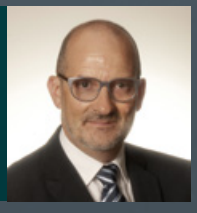


Clinical trials of gastroprotectant agents
Angel Lanas



Regulatory mechanisms of platelet activation and inhibition: Is less more?

Marco Cattaneo

Notes

Clinical trials of aspirin-free regimens

Marco Valgimigli

Notes

The role of platelet activation and blood coagulation in atherothrombosis

L. Badimon

Cardiovascular Program-ICCC, IR-Hospital de la Santa Creu I Sant Pau and CiberCV, Barcelona Spain.

Platelets are released into the circulation by bone marrow megakaryocytes, and circulate in blood for 7–10 days. They play a key role in the maintenance of the integrity of the vascular wall and in haemostasis; yet, the disruption of an atherosclerotic plaque triggers an uncontrolled platelet recruitment and thrombin production that leads to thrombus formation. The initial tethering of platelets at sites of injured vessels is mainly driven by the interaction of the collagen-anchored A3 domain of vWF with the platelet glycoprotein (GP) GPIbα receptor through the vWF A1 domain.

Platelet adhesion and further activation, in concurrence with red blood cell lysis, lead to the local release of platelet agonists (adenosine diphosphate (ADP) and thromboxane A_2 (TXA_2)) which, in combination with thrombin, generated upon atherosclerotic plaque exposure of TF, recruit additional platelets. Platelet shape change is a prerequisite for optimal granule secretion and supports platelet–platelet and platelet–matrix interactions and tethering. Platelet granule secretion leads to the local release of ADP/ATP, serotonin, Ca^{2+} adhesion proteins and coagulation factors, all of which contribute to amplify the thrombotic response.

On the other hand, activated platelets externalize phosphatidylserine, becoming a substrate for the coagulation cofactor/enzyme complexes VIIa/IXa and Va/Xa, thereby being of critical importance for driving procoagulant reactions. Regardless of the trigger, platelet aggregation is regulated in the final part of the pathway by the activation of the platelet heterodimer GPIIb/IIIa receptor (αIIbβ3), the most abundant protein receptor on the platelet surface. Fibrinogen (of plasma or platelet origin) is the main ligand for the GPIIb/IIIa receptor.

Disruption of an atherosclerotic lesion exposes thrombogenic factors that initiate platelet adhesion, activation, and aggregation, as well as thrombin generation. Platelets also participate in leucocyte and progenitor cell recruitment and are likely to mediate atherosclerosis progression. Recent data attribute to extracellular vesicles (mainly microvesicles) a role in all stages of atherosclerosis development and evidence their potential use as systemic biomarkers of thrombus growth.

Notes

Clinical trials of low-dose aspirin combined with low-dose rivaroxaban

Giancarlo Agnelli

Notes

Anti-Platelet Therapy and GI Bleeding: Overview of Mechanisms

Andrew T. Chan

Clinical and Translational Epidemiology Unit
Division of Gastroenterology
Massachusetts General Hospital and Harvard Medical School

1. Epidemiology of aspirin and GI bleeding

Regular aspirin use is associated with higher risk of gastrointestinal (GI) ulcers, major bleeding and possibly bleeding-related death.[1] Most bleeding episodes occur early, within 6 months after initiating regular use,[2] and higher dose, rather than longer duration of use is a major determinant of tissue injury.[3,4] Aspirin use appears to be associated with higher risk of bleeding when used for primary, rather than secondary cardiovascular disease (CVD) prevention. However, this difference is compensated by the lower baseline risk in the primary prevention population.[5] Age is a major factor that contributes to the risk of bleeding among regular aspirin users. In the observational Oxford Vascular Study, GI bleeding constituted half of bleeding cases and risk of major bleeding and of disabling/fatal bleeding increased steeply with age (HR for age ≥75 was 3.10, 95% CI 2.27–4.24 and 10.26, 4.37–24.13, respectively), while risk of minor bleeding was not influenced by age.[6] H. pylori infection is another risk factor associated with an increased risk of gastroduodenal ulcers/bleeding among regular aspirin users.[7] Other risk factors for upper GI complications associated with aspirin and other non-steroidal anti-inflammatory drugs (NSAID) include previous history of peptic ulcer or GI bleeding, use of two or more NSAIDs, concurrent use of corticosteroids or anticoagulants and/or presence of severe disease.[8]

2. Mechanisms of mucosal injury of aspirin

The gastric mucosa has several protective mechanisms that are stimulated by prostaglandins (PGs), such as mucin and bicarbonate secretion, increased epithelial cell proliferation and migration towards the luminal surface and enhancement of mucosal blood flow through vasodilation. Aspirin causes mucosa injury through systemic mechanisms, mostly related to PG production inhibition, and local mechanisms, non-related to PG inhibition.

Local, non-PG-related mechanisms, are mediated through incorporation of aspirin across the pH-neutral gastric mucosa and direct injury to epithelial cells. Since aspirin (and other NSAIDs) have a low pKa (3.5 to 4.85) they are not ionized at the acidic pH of the gastric lumen, and therefore are incorporated in epithelial cells since they are lipophile. Once inside the cells they are ionized, and therefore trapped. At high concentrations they inhibit mitochondrial oxidative phosphorylation, producing reduction in ATP, increases calcium permeability and release of cytochrome C, resulting in cellular apoptosis/necrosis. Further damage occurs indirectly through the damage of tight junctions and exposure of the mucosa to luminal content (acid, bile, enzymes, bacteria).[9,10] Other direct (local) mechanisms include decreased cellular hydrophobicity after NSAIDs' incorporation,[11] deacetylation of aspirin to cytotoxic salicylate,[12] and alterations in local microcirculation which result in cellular injury.[13] Topical mechanisms operate throughout the GI system. However, these mechanisms are more significant on the distal small/large bowel, rather than on the stomach/duodenum, where they exert less effect. Indeed, enteric-coated aspirin, which has little or no local effect on the stomach and duodenum, do not lower significantly the risk of gastroduodenal ulcers, suggesting that the systemic effects are more important for upper GI lesions/bleeding.[14] These effects are observed even when aspirin/NSAIDs were administered by routes ways that could have only systemic effects (I.M or I.V).[15,16]

The systemic effects of aspirin are exerted indirectly through inhibition of PG-synthesis and platelet activation. Aspirin and other NSAIDs block cyclo-oxygenase (COX) enzymes (also known as prostaglandin-endoperoxide synthase - PTGS) are responsible for PG synthesis, which, as mentioned above are responsible for gastric protective mechanisms. In addition, platelet activation is crucial for clot formation and production of growth factors responsible for tissue healing through cells growth and angiogenesis. Inhibition of both these mechanisms result in ulcer formation/bleeding, especially with higher doses.[3,15,16] These are the mechanisms that have a major impact on gastroduodenal ulcers/bleeding.

3. Other non-aspirin anti-platelet agents and GI bleeding

P2Y12 inhibitor agent

Dual antiplatelet therapy, with aspirin plus a P2Y12 (clopidogrel, ticagrelor and prasugrel) inhibitor agent is currently the cornerstone treatment after percutaneous coronary intervention. P2Y12 inhibitors have different mechanisms of action from aspirin, but achieve similar anti-platelet (and anti-neoplastic) activity.17 Clopidogrel has a similar bleeding risk profile to aspirin,[1,18,19] and when used alone has a higher risk of bleeding than aspirin + esomeprazole.[20] The new P2Y12 receptor antagonists (ticagrelor and prasugrel) are associated with increased risk of GI bleeding compared to clopidogrel,[21] but have a similar risk profile compared to each other.[22] Both clinical/environmental (age, smoking, weight, diabetes, drug interactions)[23,24] and genetic (CYP2C19*17 allele)[25] factors influence metabolism and modulate biological effects and risk of bleeding of P2Y12 inhibitors.

While P2Y12 inhibitors may not cause themselves peptic ulcers themselves (unlike aspirin), their anti -platelet activity results impaired ulcer healing and altered angiogenesis from reduced growth factor production, and increased risk of bleeding from impaired clotting mechanisms.[16]

Protease-activated receptor-1 (PAR-1) antagonist (Vorapaxar)

Effective in secondary CVD prevention, even in patients with impaired renal function.26 However, adding vorapaxar to aspirin or other anti-platelets agents has a significant increases risk of all-cause major bleeding.[27,28]

Synergic effects of combined therapy

Dual therapies (e.g. aspirin + clopidogrel) have become mainstay for CVD prevention. However, they have higher bleeding risk than monotherapy, and increase risk synergistically, since they cause bleeding through different complementary mechanisms.[29] Since combined therapy does not necessarily translate in better clinical outcomes than monotherapy,[30] and since the risk of major/fatal bleeding increases with each new agent added to the combination, there must be a careful selection of patients based on their specific risk-benefit profile.[31]

4. Prevention/reduction of GI bleeding

The risk of upper GI bleeding can be significantly reduced by adding proton pump inhibitors (PPIs) and/or histamine 2-receptor antagonists (H2RAs), which reduce gastric acid secretion and thus mucosal injury.[6] In the recent COMPASS 3-by-2 partial factorial, randomized placebo-controlled trial (RCT) of rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily, rivaroxaban 2.5 mg twice daily alone, or aspirin 100 mg once daily alone in patients with stable atherosclerotic vascular disease, patients were additionally randomized to pantoprazole 40 mg daily or placebo. There was no significant difference in upper gastrointestinal events (HR 0.88; 95%, 0.67-1.15) defined as a composite of overt bleeding, upper gastrointestinal bleeding from a gastroduodenal lesion or of unknown origin, occult bleeding, symptomatic gastroduodenal ulcer or ≥5 erosions, upper gastrointestinal obstruction, or perforation. However, pantoprazole did significantly reduce bleeding from gastroduodenal lesions (HR 0.52; 95% CI, 0.28-0.94).[32]

Some studies suggest that some types of PPI may compete with CYP enzymes that activate clopidogrel, potentially reducing its anti-platelet activity.[14] In contrast, a large RCT did not show any significant association of PPI treatment with clopidogrel activity.[33] Nonetheless, the U.S. FDA currently recommends that patients taking clopidogrel should consult with their clinician if they are also considering taking a PPI.

Other methods of reducing the risk of GI bleeding include novel platelet function tests that can be used to facilitate the choice of anti-platelet agents,[17,34,35] and timely de-escalation of anti-platelet agents after 6-12 months of dual/triple therapy,[17] in addition to carefully evaluating the risk-benefit of each single patient before initiation of combination therapy.[31]

Interruption of aspirin and/or other anti-platelet agents before non-cardiac surgery or interventional endoscopic procedures can be decided on a case-by-case basis. However, in most cases of monotherapy interruption seems to be unnecessary, and in most cases of combination therapy at least one of the anti-platelet agents can be continued.[36–38]

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Notes

Clinical trials of gastroprotective agents with antithrombotic agents

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Abstract

Anticoagulant (AC) and antiplatelet (AP) agents are worldwide used and the cornerstone for the prevention and treatment of cardiovascular (CV) diseases. Despite these beneficial effects, AP and AC therapy have been associated with a two- and a 4-fold increased risk of gastrointestinal (GI) bleeding, respectively. This risk is increased when these therapies are combined or associated with other risk factors widely studied. Of the available antiplatelet agents, low-dose aspirin (ASA) is the most widely prescribed. Low-dose aspirin inhibits COX-1 and may damage the GI tract. In endoscopic trials, proton pump inhibitors (PPIs) have been shown to be very effective both in the treatment and prevention of gastroduodenal peptic ulcers associated with low-dose ASA. Famotidine is also effective, but available studies are less consistent. In clinical trials of high-risk patients with previous ulcer bleeding, PPIs are also effective in the prevention of ulcer bleeding recurrence and more effective than thienopyridines alone. Omeprazole has been shown to be effective in the prevention of upper GI complications in patients taking dual antiplatelet therapy. The beneficial effect of antisecretory agents in the prevention of GI bleeding associated with AC, alone or combined with AP, has not been proved in clinical trials.

Peptic Ulcer and peptic ulcer complication risk with antithrombotic drugs

Cardiovascular (CV) disease is the most important cause of morbidity and mortality in the world. Low-dose aspirin (ASA) (usual dose 75-100 mg daily) alone or combined with other antiplatelet drugs such as clopidogrel, is increasingly prescribed for either primary or secondary CV prevention. ASA is effective in preventing about one-fifth of vascular complications (myocardial infarction, stroke or vascular death) in patients with previous myocardial infarction, stroke or transient cerebral ischemia. The absolute reduction of vascular mortality is 10% and a yearly absolute decrease of 1% of major coronary events (1). The benefits of ASA in primary prevention have been questioned due to the balance between CV event avoided and major bleeds (especially gastrointestinal (GI) bleeding) caused by ASA. In secondary prevention, the CV benefits substantially exceed bleeding risk. (2).

Endoscopic-controlled studies have shown that approximately 60% of patients taking ASA have upper GI erosions (erosions, unlike ulcers, do not reach the submucosa where blood vessels are and can be the cause of a major bleed). The clinical significance of these endoscopic findings is unclear, since the incidence of actual peptic ulcers and complications is much lower and their correlation with symptoms is weak. (3) In a study of 187 patient taking ASA, the ulcer prevalence was 11% (95% CI 6.3-15.1%) and the ulcer incidence, in 113 patients followed for 3 months, 7% (95% CI 2.4-11.8 %). Only 20% of patients had dyspeptic symptoms, which was not significantly different from patients without ulcer (4). The antrum and particularly the pre-pyloric area are the most frequent locations of these lesions. Most peptic ulcers are asymptomatic and small, and probably heal over a period of weeks to a few months.

Gastrointestinal (GI) bleeding due to peptic ulcers is one of the most common adverse events in patients treated with antiplatelet therapy. ASA and clopidogrel have a similar 2-fold increase risk of upper gastrointestinal complications (5). The estimated average excess risk is five cases per 1,000 aspirin users per year (6). A recent meta-analysis of 61 randomized controlled trials (RCTs) estimated the risk of major upper GI bleeding increases in ASA users (OR 1.55; 95% CI 1.27-1.90). This risk was higher when ASA was combined with clopidogrel or anticoagulants (OR, 1.86; 95% CI 1.49-2.31 and OR 1.93; 95% CI 1.42-2.61, respectively) (7).

It is unclear whether clopidogrel injures the GI mucosa, or it only induces bleeding in already damaged mucosa due to its antiplatelet effects. In an endoscopy study that included 36 healthy volunteers randomized to either clopidogrel (75mg/day) or ASA (325mg/day) for 8 days, clopidogrel did not induce macroscopic damage (8). The CAPRIE trial found that clopidogrel had a modest significant advantage over ASA for the prevention of stroke, myocardial infarction and vascular disease in 19,185 patients and was significantly associated with lower incidence of major GI bleeding than ASA (0.52% vs 0.72%, $p < 0.05$) (9). However, the dose of ASA was 325 mg/day, much higher than the 75-100 mg once daily recommended today.

There is no evidence that anticoagulants induce direct mucosal damage to the gastrointestinal tract, but however they increase the risk of gastrointestinal bleeding, presumably

from pre-exiting lesions induced by other factors. The increased risk seems higher than that found with antiplatelet agents. Combining vitamin K antagonists and non-steroidal anti-inflammatory drugs or ASA can increase the risk of upper gastrointestinal complications further (7). The new direct oral anticoagulants DOACs are also associated with an increased risk of gastrointestinal bleeding (10)

With a growing elderly population taking these compounds (alone or combined), prevention of bleeding is a clinical need. Drugs that inhibit gastric acid secretion have been shown to reduce the incidence of peptic ulcers and peptic ulcers complications. They have also been tested in the prevention and treatment of peptic ulcer and complications associated with the use of antithrombotic drugs.

Treatment and prevention of uncomplicated peptic ulcers

Misoprostol. Aspirin at low doses (75-100 mg/day), predominantly inhibits the cyclo-oxygenase isoform (COX-1) in the GI mucosa producing prostaglandin depletion and consequently favoring ulcer development. Prostaglandins have both cyto-protective properties and a moderate anti-secretory effect. An endoscopic study showed that misoprostol, a synthetic prostaglandin E1 significantly reduced the incidence of erosions in healthy volunteers taking ASA (11). Moreover, misoprostol seems to be superior to placebo for preventing recurrence of gastric ulcers among patients with prior peptic ulcer who are taking ASA and other NSAID (12). No studies have evaluated the effect of this compound in the prevention of gastrointestinal bleeding associated to ASA use.

H2-receptor antagonists. A double-blind randomized controlled trial conducted in Scotland, compared high dose famotidine (20mg /12 hours) for 12 weeks vs. placebo in ASA users without ulcers at baseline (13). Patients treated with famotidine had a significantly lower incidence of ulcers than placebo group (3, 8% vs 23, 5%, respectively). The study had however several aspects that deserve to be outlined. The rate of *H. pylori* infection was higher in the placebo group and some patients of famotidine group did not have final endoscopy evaluation. No studies have been conducted in the prevention of peptic ulcer bleeding with these drugs. In one study 160 patients with aspirin-related peptic ulcers/erosions (with or without a history of bleeding) patients were treated with famotidine (40 mg b.i.d.) or pantoprazole (20 mg once daily) in addition to aspirin (80 mg daily). The primary end point was recurrent dyspeptic or bleeding ulcers/erosions within 48 weeks. Patients in the famotidine group had recurrence of either complicated or uncomplicated peptic ulcer or erosions (20.0%; 95% one-sided confidence interval [CI] for the risk difference, 0.1184-1.0) compared with 0 of 65 patients in the pantoprazole group (P < .0001, 95% one-sided CI for the risk difference, 0.1184-1.0). Gastrointestinal bleeding was more common in the famotidine group than the pantoprazole group (7.7% [5/65] vs 0% [0/65]; 95% one-sided CI for the risk difference, 0.0226-1.0; P = .0289) (14).

Proton Pump inhibitors: PPIs are potent inhibitors of gastric acid secretion. Several studies have evaluated the effect of PPIs on reducing endoscopic damage and the risk of GI complications in both patients and healthy volunteers treated with ASA. Endoscopy studies have shown that both omeprazole and lansoprazole significantly reduced GI damage in healthy volunteers taking ASA (15, 16). The ASTERIX trial, evaluated the efficacy of esomeprazole (20mg/day) in the prevention of endoscopic peptic ulcers in patients taking ASA (17). The proportion of patients with gastric or duodenal ulcer after 26 weeks of treatment was significantly lower for esomeprazole than placebo (1.3 % vs 5.4%, respectively, p= 0.0007). Patients treated with esomeprazole had also significantly lower proportion of erosive esophagitis and dyspeptic symptoms. The OBERON trial (18) explored 2 different doses of esomeprazole in a similar setting and a large number of patients enrolled (2426 patients). Esomeprazole reduced significantly the development of peptic ulcers with both doses when compared with placebo (1.5% of patients treated with esomeprazole 40 mg, 1.1% of patients treated with esomeprazole 20 mg, and 7.4% of patients treated with placebo developed peptic ulcers).

Treatment and prevention of complicated peptic ulcers

Misoprostol: A recent double-blind, randomized, placebo-controlled trial has investigated whether misoprostol can heal small bowel ulcers in patients with a previous small bowel bleeding who require continuous aspirin therapy. The study was conducted in 84 aspirin users with small bowel bleeding who required continued aspirin therapy in Hong Kong and Japan. Patients were randomly assigned to either misoprostol (200 µg, 4 times daily; n = 42) or placebo (n = 42) for 8 weeks. All patients continued taking aspirin (100 mg, once daily). The primary end point was complete ulcer healing at follow-up capsule endoscopy. Complete healing of small bowel ulcers was observed in 12 patients in the misoprostol group (28.6%; 95% CI, 14.9%-42.2%) and 4 patients in the placebo group (9.5%; 95% CI, 0.6%-18.4%), for a difference in proportion of 19.0% (95% CI, 2.8%-35.3%; P = .026). The misoprostol group had a significantly greater mean increase in hemoglobin than the placebo group (mean difference, 0.70 mg/dL; 95% CI, 0.05-1.36; P = .035). The authors concluded that misoprostol was superior to placebo in promoting healing of small bowel ulcers among aspirin users complicated by small bowel ulcer bleeding who require continuous aspirin therapy, but that this effect was limited. Side effects with misoprostol use when compared to other effective drugs have probably prevented the widespread use of this approach (19).

H2-Receptor Antagonists: Very few studies have been conducted specifically with these compounds in

patients taking ASA to prevent bleeding. The only study compared famotidine with pantoprazole and has been commented above. The other two compared esomeprazole with famotidine in patients taking aspirin alone or dual antiplatelet therapy and it is referred in the next section.

Proton Pump inhibitors: Considerable evidence support that PPI are more effective than H2 receptor antagonist as gastroprotective agents in antiplatelet users (14). Lai et al. performed a randomized controlled trial in patients taking ASA with a history of peptic ulcer and who had already received *H. pylori* eradication therapy. The study evaluated the efficacy of lansoprazole (30 mg/ day) vs placebo to prevent recurrence of peptic ulcer bleeding for one year (20). Patients on lansoprazole had significantly less recurrence of ulcer complications than those treated with placebo (1.6% vs 14.8%). The study suggested that *H. pylori* eradication was not sufficient to prevent ulcer bleeding recurrence in high risk patients taking ASA. Combined treatment (*H. pylori* eradication plus PPI) seems the most adequate therapy for these patients. Sugano et al. conducted the LAVANDER study (21), which was a double bind, randomized, placebo-controlled and prospective trial that evaluated the efficacy of esomeprazole (20mg once daily) for 72 weeks in the prevention of recurrent peptic ulcer in ASA users. The authors concluded that esomeprazole 20 mg over 48 weeks prevented the recurrence of peptic ulcers. Ulcer free rates were consistently lower in placebo group through week 48. Interestingly 45% of patients were *H. pylori* positive, which suggests that esomeprazole protected against ulcer recurrence irrespective of *H. pylori* status. The PLANETARIUM study evaluated the efficacy, dose-response relationship (10 mg, 5 mg and control) and safety of rabeprazole for peptic ulcer recurrence over 24 weeks in Japanese patients treated with ASA. The cumulative recurrence rate of peptic ulcers was 1.4% and 2.8% in rabeprazole groups (5mg and 10mg, respectively), significantly lower that in the active control group (21.7%). In the rabeprazole groups, there were not bleeding ulcers. Rabeprazole confirmed not only the efficacy of PPIs in this population without evidence of a major dose response effect (22).

Systematic reviews and meta-analysis of randomized trials conclude that PPIs were associated with a 50-70% reduction in bleeding and symptomatic peptic ulcers related to non-steroidal anti-inflammatory drugs and also to aspirin (7, 23).

In a clinical trial, co-therapy of a proton-pump inhibitor with aspirin was compared with clopidogrel alone to evaluate the recurrence rate of upper gastrointestinal bleeding in high-risk patients. The study enrolled patients with ulcer bleeding, who were negative for Helicobacter pylori and were on aspirin to prevent vascular diseases. After the ulcers healed, they were randomized to receive either 75 mg of clopidogrel daily or 80 mg of aspirin daily plus 20 mg of esomeprazole twice daily for 12 months. The end-point was recurrent ulcer bleeding. The cumulative incidence of recurrent bleeding during the 12-month period was 8.6 percent (95 %CI: 4.1 to 13.1 percent) among patients who received clopidogrel and 0.7 percent (95 percent confidence interval, 0 to 2.0 percent) among those who received aspirin plus esomeprazole (P=0.001) (24).

The COGENT study (25), evaluated in 3873 patients taking dual antiplatelet therapy (ASA plus clopidogrel) with or without omeprazole, both the occurrence of CV and GI events. In the omeprazole group the event rate was 1.1% compared with 2.9% in placebo group (HR 0.34, 95% CI, 0.18-0.63, $p < 0.001$). The rate of upper GI bleeding was also significantly lower in the PPI group (HR 0.13, 95% CI, 0.03-0.56). No differences were observed between different doses of aspirin (26) and no differences in CV events were present at the end of the study between the 2 arms. (25).

Another double-blind, randomized, controlled trial was performed in patients with acute coronary syndrome or ST elevation myocardial infarction receiving aspirin, clopidogrel, and enoxaparin or thrombolytics to compare the efficacies of esomeprazole and famotidine in preventing gastrointestinal complications. Patients received either esomeprazole (20 mg/day) or famotidine (40 mg/day) orally for 4-52 weeks of dual antiplatelet therapy. The primary endpoint was the occurrence of upper gastrointestinal complications (bleeding, perforation, or obstruction from ulcer/erosion). One (0.6%) patient in the esomeprazole group and 9 (6.1%) in the famotidine group reached the primary end point (all had upper GIB) (log-rank test, P=0.0052) hazard ratio=0.095, 95% confidence interval: 0.005-0.504). (27). This study somehow contradicts the results of another study recently reported. The same group from Hong Kong performed a double-blind randomized trial to compare the effects of rabeprazole vs famotidine in preventing recurrent upper GI bleeding and ulcers in high-risk aspirin users. They studied patients with a history of endoscopically confirmed peptic ulcer bleeding in Honk Kong and Japan. After healing of ulcers, subjects being negative for Helicobacter pylori tests resumed aspirin (80 mg) daily and were assigned randomly to groups given a once-daily rabeprazole, 20 mg (n = 138) or famotidine, 40 mg (n = 132) for up to 12 months. The endpoints were recurrent upper GI bleeding and a composite of recurrent upper GI bleeding or recurrent endoscopic ulcers at month 12. During the 12-month study period, upper GI bleeding recurred in 1 patient receiving rabeprazole (0.7%; 95% CI, 0.1%-5.1%) and in 4 patients receiving famotidine (3.1%; 95% CI, 1.2%-8.1%) (P = .16). The composite end point of recurrent bleeding or endoscopic ulcers at month 12 was reached by 7.9% (95% CI, 4.2%-14.7%) of patients receiving rabeprazole and 12.4% (95% CI, 7.4%-20.4%) receiving famotidine (P = .26).The authors conclude that in ASA users at risk for recurrent GI bleeding, there were no differences between both therapies to prevent peptic ulcer or ulcer bleeding (28). The low frequency of events undermine the clinical significance of the results.

A recent study has assessed the effect of a PPI (pantoprazole) in the GI tract in patients taking aspirin alone, anticoagulants alone or the combination of both

aspirin and anticoagulant therapy. The study was a 3x2 partial factorial double-blind trial of 17,598 participants with stable cardiovascular disease and peripheral artery disease randomly assigned to groups given pantoprazole (40 mg daily) or placebo (n=8807). Participants were also randomly assigned to groups that received rivaroxaban (2.5 mg twice daily) with aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg) alone. Patients were followed up for a median of 3.0 years. Surprisingly, there was no significant difference in upper gastrointestinal events between the pantoprazole and the placebo groups (HR, 0.88; 95% CI, 0.67-1.15). Pantoprazole significantly reduced bleeding of gastroduodenal lesions (HR, 0.52; 95% CI, 0.28-0.94; P=.03). (29). Also there was no statistically significant difference between the pantoprazole and placebo groups in other safety events, except for enteric infections (1.4% vs 1.0% in the placebo group; odds ratio, 1.33; 95% CI, 1.01-1.75). One of the problems of the study was that the GI bleeding outcome included all types of GI bleeds, when we know that PPI should reduce only those related to acid-peptic secretion (30).

Conclusions

Proton pump inhibitors have shown efficacy in the prevention of peptic ulcer and peptic ulcer bleeding in patients taking low-dose aspirin, irrespective of the dose of aspirin or the PPI. This efficacy is superior to famotidine that has been the most frequently drug of this class (H2-receptor antagonists) tested and has shown also some efficacy in the prevention of peptic ulcers and probably peptic ulcer bleeding. Prevention of bleeding from the lower GI tract with gastroprotective drugs has only been tested with misoprostol looking at its efficacy in the healing of small bowel ulcers associated with a previous bleeding event. The efficacy was moderate. The effects of these drugs in the prevention of upper GI bleeding in patients taking anticoagulants needs further investigation.

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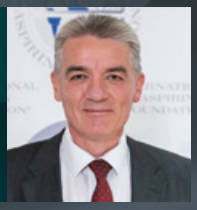
Session Two

Benefits and risks of antithrombotic therapy in primary prevention
Chairpersons: Michael Gaziano and John Chia

Optimizing the aspirin dose and dosing regimen

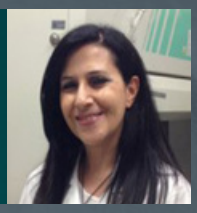
Interindividual variability in the extent & duration of platelet thromboxane inhibition by low-dose aspirin
Bianca Rocca

Clinical trials of different aspirin doses and dosing regimens
Peter Rothwell

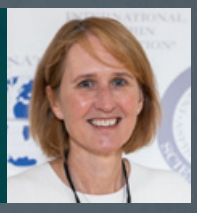


Incorporating other benefits of low-dose aspirin in the benefit/risk equation

Mechanisms underlying the non-vascular effects of low-dose aspirin
Paola Patrignani



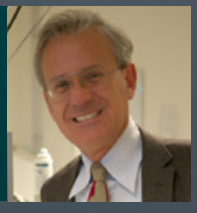
Clinical trial evidence supporting a cancer chemopreventive effect of low-dose aspirin
Ruth Langley



Targeting the right patient population for primary prevention: the case of diabetes mellitus

Mechanisms of atherothrombosis in diabetes mellitus
Gemma Vilahur

Translating clinical trial evidence into treatment recommendations for the use of aspirin in diabetes
Francesco Cosentino



Interindividual variability in the extent and duration of platelet thromboxane inhibition by low-dose aspirin

Bianca Rocca

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Understanding determinants of interindividual variability of drug responsiveness is a key step for improving drug effectiveness in the 'real world' patients and it is the main objective of precision medicine.

Aspirin is not biotransformed by the CYP450, and therefore drug-drug interaction at a pharmacokinetic level has little impact on variability in drug responsiveness, conferring to aspirin a great advantage in patients with co-morbidities and co-medications.

Patient's characteristics, including underlying diseases, can increase the variability in responsiveness to aspirin. Pre-systemic availability of aspirin, before the liver first passage, largely inhibits circulating platelets by irreversibly blocking the COX-1 enzyme. Based on systemic bioavailability, aspirin inhibits platelet precursor's that reside in the bone marrow: megakaryocytes, pro- and pre-platelets. Some chronic conditions, such as diabetes, obesity or myeloproliferative neoplasms requiring primary or secondary prevention due to high cardiovascular risk may influence the extent and/or duration of platelet's COX-1 inhibition and subsequent thromboxane (TX) A_2 generation through disease-specific, PK- or PD-based mechanisms.

In silico model of low-dose aspirin PK and PD may help designing personalized regimens to be tested in adequately sized clinical trials.

Notes

Clinical trials of different aspirin doses and dosing regimens

Peter Rothwell

Notes

Mechanisms Underlying the Non-Vascular Effects of Low-Dose Aspirin

Paola Patrignani

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Increasing evidence for a chemopreventive effect of low-dose aspirin against colorectal (and other) cancer is accumulating. The protective effects of low-dose aspirin against cancer appear to reflect prevention of early neoplastic transformation throughout the alimentary tract, as well as an anti-metastatic action. Both effects may be explained by the antiplatelet activity of low-dose aspirin which causes cyclooxygenase (COX)-1 acetylation at a critical serine residue (Ser-529) near the catalytic site of the enzyme.

Platelets sustain cancer cell invasion and metastasis formation by fostering the development of the epithelial-mesenchymal transition phenotype, cancer cell survival in the bloodstream and arrest/extravasation at the endothelium. Furthermore, platelets contribute to tumor escape from immune elimination. The drug by inhibiting platelet activation, triggered by gastrointestinal mucosal lesions, restrains the development of chronic inflammation which is considered a hallmark of cancer. Moreover, the drug can acetylate COX-1 expressed in colorectal mucosa leading to changes in mucosal phenotype.

Notes

Clinical trial evidence supporting a cancer chemoprevention effect of low-dose aspirin

Professor Ruth Langley

The evidence supporting the anti-cancer effects of aspirin is derived from pre-clinical evidence, epidemiological studies as well as randomised trials (1). The trial evidence can be considere d in 3 groups:

1. Trials originally designed to assess the cardiovascular (CVS) effects of aspirin where cancer outcomes are also available.
2. Trials focussing on whether aspirin can prevent the progression of pre-malignant lesions and primary prevention of cancer.
3. Trials assessing whether aspirin can prevent metastases and recurrence after potentially curable therapy.

Data derived from randomised vascular trials

A major part of the evidence base relating to aspirin and cancer has emerged from randomised controlled trials (RCT's) designed to evaluate the vascular effect of aspirin (2-5). In a series of papers data from over 50 randomised trials including ~77,000 participants was examined. Two major findings emerged. Firstly, those allocated to aspirin were less likely to develop cancer (hazard ratio (HR) 0.81 (95% CI 0.7-0.93). The data showed strong similarities with previous epidemiological studies with the largest protective effects seen on adenocarcinomas arising from the gastrointestinal tract, and if aspirin treatment had continued for more than 5 years. There was also an associated reduction in cancer mortality of about 15%. The second observation was an early reduction in mortality particularly non-vascular deaths. Further investigation suggested that those who had been allocated to aspirin and subsequently developed a malignancy were less likely to have metastases at presentation and less likely to develop metastases through the course of their disease. This reduction in metastases was independent of the site of metastasis and supported the hypothesis that aspirin could prevent or delay cancer progression.

Clinical trials focussed on preventing the progression of pre-malignant lesions and primary prevention of cancer

The first epidemiological evidence that aspirin could act as a chemoprevention agent was the report of a case–control study, in which aspirin use was associated with a significantly lower risk of colorectal cancer even after adjustment for other risk factors. This effect was confirmed in several other epidemiological studies and led to a series of randomised trials designed to evaluate whether aspirin could prevent the formation of colorectal adenomas, the precursor lesions of colorectal carcinoma. A meta-analysis of these trials published in 2009 (6) encompassed 4 clinical trials with 2967 participants randomly assigned a daily dose of aspirin 81-325 mg or placebo. Median follow-up was 33 months and 2698/2967 (91%) underwent colonoscopic follow-up and were included in the analysis. Adenomas were found in 424/1156 (37%) allocated to placebo and in 507/1542 (33%) allocated to any dose of aspirin. Advanced lesions (defined as tubulovillous adenomas (25% – 75% villous features), villous adenomas (≥ 75% villous features), large adenomas (≥ 1 cm in diameter), adenomas with high-grade dysplasia, or invasive cancer) were found in 12% of participants in the placebo group and in 9% of participants allocated to any dose of aspirin. The pooled risk ratio of any adenoma for any dose of aspirin vs placebo was 0.83 (95% CI = 0.72 to 0.96). This corresponded to an absolute risk reduction of 6.7% (95% CI 3.2% to 10.2%) and for any advanced lesion, the pooled risk ratio was 0.72 (95% CI 0.57 to 0.90). A more recent study (SeaFOod) (7) evaluated ~ 700 individuals recruited through UK bowel screening programme. In a 2x2 factorial design, an omega fatty acid (EPA) and aspirin 300mg daily were evaluated. Although there was no difference in the primary outcome measure (adenoma detection rate (any adenoma)), mean adenomas per patient were reduced by aspirin particularly right sided, serrated lesions supporting previous data.

The AspECT trial (8) recruited ~ 2500 participants with Barretts oesophagus, again a 2x2 factorial design evaluated aspirin (300mg) daily and 2 doses of a proton pump inhibitor (PPI) 20mg od or 40mg bd. The primary outcome measure was a composite of high-grade dysplasia, oesophageal adenocarcinoma and all-cause mortality. The analysis considered time to event in terms of a time ratio (TR) – with the greatest effects seen for high dose PPI and aspirin compared to low dose PPI/no aspirin TR 1·59, 1·14–2·23, p=0·0068.

A major study in primary prevention, the Women's Health Study (9) recruited 40,000 US female health professionals who were randomly allocated to aspirin 100mg or placebo to be taken every other day. Initial results, with a follow up of around 10 years, suggested no effect on cancer incidence but longer term follow up (~15 years) has shown a reduction in colorectal cancer incidence. A similar pattern of initial analyses recording a null result, and results in the allocated groups only diverging after longer term follow up is also seen in the CAPP2 trial (10). Patients with Lynch Syndrome were allocated to aspirin 600 mg daily or placebo with a reduction in Lynch syndrome associated cancers seen after 5 years. Results are awaited from the CAPP3 trial which has evaluated lower doses of aspirin in this group of patients.

More recently, results from the ASCEND (15,000 diabetics) and ARRIVE (12,000 at moderate risk of CVS event) trial have been published (11, 12). The trials were primarily designed to assess whether aspirin could reduce vascular events in those at medium risk. In both trials the effect on vascular effects was modest and felt to be offset by an increased risk of serious bleeding. To date neither have shown an effect on cancer outcomes and longer follow-up is required.

Results have also been released from the ASPREE trial (13) which recruited ~19,000 participants >65 years old randomly allocated to aspirin 100mg daily or placebo. The primary outcome measure was a composite of death, dementia and permanent physical disability. With a follow up 4.5 years 21.5 v's 21.2 events per 1000 person years were seen with aspirin compared to placebo (HR 1.01 (95% CI 0.92 – 1.11). In terms of the individual components of the primary outcome measure the results aspirin v's placebo were: death from any cause 1.14 (1.01-1.29), dementia 0.98 (0.83 -1.15) and permanent physical disability – 0.89 (0.7 -1.03). The increase in mortality appeared to be caused by an increase in cancer mortality and this has been reviewed in detail. After a median of 4.7 years of treatment, 981 cancer events had occurred in the aspirin arm and 952 in the placebo arm. No significant difference was observed between groups for all incident cancer (HR 1.04; 95% CI 0.95-1.14), all solid tumours (HR 1.05; 95% CI 0.95-1.15), or haematological cancer (HR 0.98; 95% CI 0.73-1.30). No significant differences between groups were observed according to specific tumour types, including colorectal cancer (HR 1.02; 95% CI 0.81-1.30). Risk of incident non-metastatic cancer was almost the same in the aspirin and placebo arms (HR 0.99; 95% CI 0.89-1.11). Risk of incident metastatic cancer, however, was elevated with aspirin (HR 1.18; 95% CI 0.96-1.46). This elevation is unexplained, it may be attributable to chance, it might also be accounted for by aspirin unmasking malignant disease through an increased risk of bleeding. The incidence and severity of bleeding with aspirin increases with age.

Trials assessing whether aspirin can prevent metastases and recurrence after potentially curable therapy

The observation that allocation to aspirin in the randomized vascular trials appeared to be associated with an early reduction in non-vascular mortality, alongside epidemiological and pre-clinical data led to the hypothesis that the effects of aspirin mediated through platelets might prevent metastases. Several large phase III trials are underway to evaluate this. The largest and most comprehensive is the Add-Aspirin study (14) which includes 4 phase III individually powered RCT's within one overarching protocol in breast, colorectal, gastro-oesophageal and prostate cancer. Approaching 7000 participants have been recruited. Following radical potentially curative standard therapy, participants enter a run-in phase of open label aspirin 100 mg daily for 8 weeks to assess tolerability and adherence and are then randomly allocated aspirin 100 mg, 300 mg or a placebo for at least 5 years.

There are a number of similar trials as summarised in the Table below.

Trial Acronym	Phase	Location	Tumour site
ASCOLT Aspirin for Dukes C and High Risk Dukes B Colorectal Cancer (200mg)	III	12 Countries, Asia and Australasia	Colorectal
ASPIRIN A Trial of Aspirin on Recurrence and Survival in Colon Cancer Patients (100mg)	III	Netherlands	Colon
US Aspirin Breast Cancer (ABC) Trial Randomized trial of aspirin as adjuvant therapy for node-positive breast cancer (325mg)	III	USA	Breast
PIK3CA based trials Adjuvant Low dose Aspirin in Colorectal Cancer – PIK3CA mutated patients only (100mg)	III	Switzerland Sweden	Colorectal
Add-Aspirin A phase III double-blind placebo-controlled randomized trial assessing the addition of aspirin after standard primary therapy in early stage common solid tumours (100 and 300mg)	III	UK and India	Breast, colorectal, gastro-oesophageal and prostate

The trials focussing on patients with PIK3CA mutations are based on epidemiological data that showed the benefits of being on aspirin after a colorectal cancer diagnosis and treatment appeared to be restricted to patients whose tumours had mutated PIK3CA (15). However, analysis of other data sets found conflicting results (16, 17).

Summary

Randomised evidence suggests aspirin can prevent malignancy though the benefits may not be seen for over a decade. Cancer chemoprevention (taking tablets to prevent cancer) is not a widely accepted concept. Even in high risk groups such as those with Lynch Syndrome and randomized evidence to support use implementation has been challenging. The evaluation of aspirin as a prolonged adjuvant or maintenance therapy after radical therapy is ongoing, recent trial data has not undermined the rationale for these trials.

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Mechanisms of Atherothrombosis in Diabetes Mellitus

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Diabetes and CVD

Diabetes mellitus (DM) is a heterogeneous metabolic disease characterized by systemic hyperglycemia. The global prevalence of diabetes has approximately doubled since 1980, being currently estimated in 422 million people worldwide, and projected to affect 10% of the world population by 2040.[1] The reasons for such exponential growth include unhealthy lifestyle habits associated with economic development and progressive population aging, rapidly becoming one of the most epidemic diseases in the 21st century.[2]

Diabetes is mainly classified into four distinctive groups: 1) Type I DM, representing 7% to 12% of all cases in developed countries, and comprises an irreversible insufficiency of insulin biosynthesis and secretion secondary to a pancreatic beta cell loss; 2) Type II DM (T2DM; 87% to 91%), encompasses an impairment in insulin secretory activity combined with peripheric insulin resistance (IR); 3) gestational DM, a transient disturbance developed during pregnancy; and 4) other specific conditions, mostly related to genetic disorders. Therefore, insulin deficiency and IR usually mark the clinical manifestations observed in diabetic patients and are often associated with other conditions such as hypertension, dyslipidemia, aging, and obesity. In fact, obesity is considered a major risk factor for T2DM and plays a key role in the development of IR because of the storage of excess lipids in metabolic organs such as liver and muscle.[3, 4] Fat may also accumulate in the pancreas and contribute to the decline in β-cell function, islet inflammation, and progressive pancreatic cell death perpetuating insulin insufficiency.[5] Nevertheless, it is important to have in mind that approximately 20% of obese patients do not have IR, while as many as 20% of thin, normal-weight people do.

During initial stages of the disease, pathophysiological changes related to hyperglycemia and IR are partially reversible, but eventually generate the development of microvascular (diabetic -retinopathy, -nephropathy, and -neuropathy) and macrovascular (stroke, cardiovascular disease, and peripheral vascular disease) complications. Around 75% of diabetic patients with diabetes will die from cardiovascular disease (CVD) [6], demonstrated by a 2-fold increase in developing coronary artery disease. Moreover, DM constitutes a coronary heart disease equivalent, sustaining the same risk level as non-diabetic patients with previous ischemic disease.[7] The complex metabolic milieu in DM promotes accelerated atherosclerosis progression and a low-grade inflammatory state associated with systemic oxidative stress that results in the enhanced pro-thrombotic environment, and the consequent development of atherothrombotic events. Preliminary studies using intracoronary angioscopy have demonstrated that patients with T2DM not only had an increased incidence of ruptured atherosclerotic plaques in their coronary circulation, but there was virtually a doubling of intravascular thrombi in these patients, suggesting an abnormal tendency towards thrombus formation or clot dissolution in these patients.[8]

Endothelial dysfunction and atherosclerosis in diabetes

The endothelium is formed by a single layer of cells in the interior of blood vessels producing a physical barrier with several bioactive properties. Its main purpose consists of maintaining vascular homeostasis regulating vascular tone and smooth muscle cell proliferation, limiting inflammatory networks, and preventing thrombosis.[9] Endothelial dysfunction portrays the initial evolutionary lesion in the development of atherosclerosis, thus emerging as a critical surrogate endpoint for cardiovascular disease.[10-12] In the setting of DM, IR and sustained hyperglycemic levels directly affect endothelial activity, inhibiting insulin-mediated protective mechanisms, and stimulating maladaptive responses. Indeed, insulin has been shown to exert significant protective actions in endothelial cells by interacting with insulin receptors leading to the synthesis of two important vasodilators and antithrombotic physiological agents, nitric oxide (NO) and prostacyclin (PGI2). [13-15] Accordingly, IR results in the diminishment of these key protective mechanisms resulting in reduced vasodilation and the loss of antiplatelet effects. On the other hand, hyperglycemia leads to an increase in systemic oxidative stress (ROS production).[16] Enhanced ROS production compromises NO synthesis and stimulates endothelial inflammation via several cellular mechanisms, including

promoting activation of PKC and NF-κB signaling. NF-κB, in turn, induces the transcription of inflammatory response-associated genes [17] and vascular adhesion molecules further stimulating leukocyte recruitment, thereby aggravating the inflammatory process.[18] In turn, ROS reduces NO levels by eNOS downregulation and induces the formation of highly oxidant peroxynitrite ion and asymmetric dimethylarginine (ADMA), an endogenous competitive inhibitor of eNOS activity. Diabetic patients, however, not only produce an excess of ROS but their antioxidant mechanisms are found to be impaired (e.g., reduced superoxide dismutase).[17, 19] The prolonged oxidative response observed in hyperglycemic states generates advanced glycation end products (AGEs) by glycosidation of proteins and fatty acids. [18] AGE activation of AGE´s receptor (RAGE) maintains endothelial dysfunction by promoting the release of pro-inflammatory cytokines and cell adhesion molecules, compromising the endothelial barrier function and leading to increased leukocyte infiltration. Finally, recent data have suggested that red blood cells also contribute to DM-related endothelial dysfunction by increasing endothelial arginase-1 activity, an eNOS competitor for L-arginine substrate.[20, 21]

Thrombotic changes in diabetes

Hyperactive Platelets and Microparticles

Multiple factors are thought to be involved in the increased platelet reactivity observed in DM patients. [22] Hyperglycemia increases Ca^{2+} mobilization from intraplatelet storage pools leading to an increased intracellular Ca^{2+} levels and the consequently enhanced sensitivity to aggregating agents. On the other hand, DM patients present insulin receptors whose function is found to be impaired.[15] The altered signaling of platelet insulin receptors promotes the expression of adhesion molecules (GpIIb/IIIa, P-selectin) and prothrombotic agonists (thrombin, ADP, thromboxane [TX]A2,). In this latter regard, platelets from patients with diabetes synthesize more TXA2 than normal platelets in response to a variety of agonists that induce deacylation of arachidonate from membrane phospholipids. Also, platelets from DM patients show hyper-responsiveness of proteinase-activated receptor 4 (PAR4) to thrombin and TXA2 and enhanced signaling of the P2Y12 receptor, the main platelet receptor for ADP. [15, 22] The hyper-reactive phenotype of diabetic platelets also results, at least in part, from enhanced platelet turnover that increases the proportion of highly-reactive, newly-formed platelets with lower platelet fluidity due to changes in membrane lipid structure or glycation of membrane proteins and with alteration in its intracellular components.[23] Particularly, we have described in an experimental animal model of crossed bone marrow transplants, that alterations in platelets produced by diabetic bone marrow megakaryocytes contribute to the enhanced thrombotic risk observed in DM.[24] Interestingly, the presence of IR was already capable of modulating bone marrow released platelets enhancing their susceptibility to form thrombi. [25, 26] Additionally, we have also proved that the bone marrow from diabetic donors induces pro-atherogenic modifications in healthy recipients, increasing their risk to develop atherosclerosis lesions.[27]

The low-grade inflammation and oxidative stress observed in DM patients also contribute to platelet reactivity through endothelial dysfunction (reduction in eNOS activity) and increased lipid peroxidation to generate F2-isoprostanes which are thought to amplify platelet activation by low concentrations of other agonists. In addition, the low-grade inflammatory state triggers IL-6, fibrinogen, and C-reactive protein (CRP) secretion. In this latter regard, elevated CRP levels constitute an independent risk factor associated with increased cardiovascular mortality in DM.[28] CRP has been shown to enhance the expression of endothelial adhesion molecules, stimulate macrophages to synthesize cytokines, and induce TF expression in monocytes. Additionally, CRP has been reported to modify the fibrinolytic balance of endothelial cells and thus promote fibrin formation, to enhance the expression of PAI-1 in human endothelial cells and inhibit tPA activity. We have reported CRP ability to contribute to thrombus progression and growth.[29, 30] Particularly, we have demonstrated that the classically analyzed serum CRP (native CRP; a pentamer formed by five non-covalently bound globular subunits) undergoes subunit dissociation in the platelet surface into a monomeric unit with pro-thrombotic potential. These monomeric subunits contribute to platelet activation, enhance platelet deposition, and increase thrombus growth under arterial flow conditions.[29, 31] Finally, it is worth mentioning the potential contribution of microparticles of platelet origin in the enhanced thrombotic risk observed in DM patients. Microparticles are small membrane vesicles with <0.1mm of diameter released from the surface or plasma membrane of cells upon activation or death. Platelet-derived microparticles, which are found to be increased in diabetic patients, [32] have shown to exert both pro-inflammatory and pro-thrombotic effects likely contributing to the progression of the atherothrombotic response.[33, 34]

Hypercoagulable blood and impaired fibrinolysis

In addition to reduced endothelial thrombo-resistance and enhanced platelet activation, diabetes mellitus is frequently associated with hypercoagulable blood, as evidenced by the quantitative and qualitative alterations observed in coagulation factors, in concurrence with depressed fibrinolysis.[35] Hyperglycaemia has shown to exert direct effects on gene transcription of coagulation

factors.[36] As such, DM is associated with increased plasma levels and activity of various coagulation factors (tissue factor, factor VII, tissue factor–coagulation factor VIIa complex activity, and factor XII) resulting in enhance thrombin production. Additionally, as mentioned above, plasma levels of fibrinogen (the soluble precursor of solid fibrin) are increased in diabetes, as part of the ongoing low- grade inflammation (particularly driven by the enhanced Il-6 levels). Changes also occur on the natural anticoagulants such as thrombomodulin, protein C, and antithrombin III, which are found to be reduced in diabetes further predisposing to the prothrombotic environment. Altogether, these changes culminate in increased thrombin generation and fibrin network formation, which is characterized by increased density and improved resistance to fibrinolysis. In this latter regard, DM contributes to thrombotic complications by altering the fibrinolytic mechanisms in charge of regulating hypercoagulable states. As such diabetic patients have decreased tissue plasminogen activator (t-PA) and enhanced anti-fibrinolytic activity explained through an increase in plasminogen activator inhibitor-1 (PAI-1) and carboxypeptidase B2 (also known as thrombin-activable fibrinolysis inhibitor), thus hampering the conversion of plasminogen to plasmin.[37] This increased level of PAI-1 is mostly associated with IR since they are predominantly observed in T2DM patients, but not in other hyperglycemic situations. At the same time, hyperglycemia can directly affect the fibrinolytic system by increasing plasminogen glycation (posttranslational modification), thereby adversely affecting protein activity and impairing its conversion to plasmin. [38]

Conclusions

DM constitutes a chronic metabolic disorder characterized by a hyperglycemic state and IR, promoting a low-grade inflammatory background and systemic oxidative stress leading to accelerated atherosclerotic progression. Cardiovascular disease is the leading cause of morbidity and mortality in this population, and DM often associates with other co-morbidities such as obesity, hypertension, and dyslipidemia that further contribute to atherothrombotic complications. The reasons for the adverse cardiovascular profile consist of several molecular and cellular pathways that combine to enhance atherosclerosis progression and thrombus formation. Endothelial dysfunction is a key factor in this setting, promoting vasoconstriction and modifying the expression and release of key protective molecules, including NO and PGI2. Increased systemic oxidative stress, in turn, contributes to fatty acid peroxidation and protein glycation generating AGE products that enhance leukocyte infiltration and the biosynthesis of pro-inflammatory molecules fostering atherosclerosis progression. On the other hand, endothelial dysfunction in concurrence with the presence of hyperreactive platelets, higher CRP and platelet-microparticle levels, and alterations in the coagulation/fibrinolytic system contribute to explain the observed higher risk of thrombotic events.

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Notes

Translating clinical trial evidence into treatment recommendations for the use of aspirin in diabetes

Francesco Cosentino

Notes

Notes

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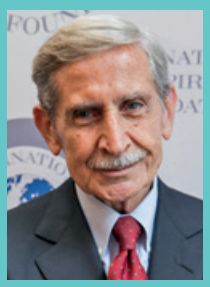

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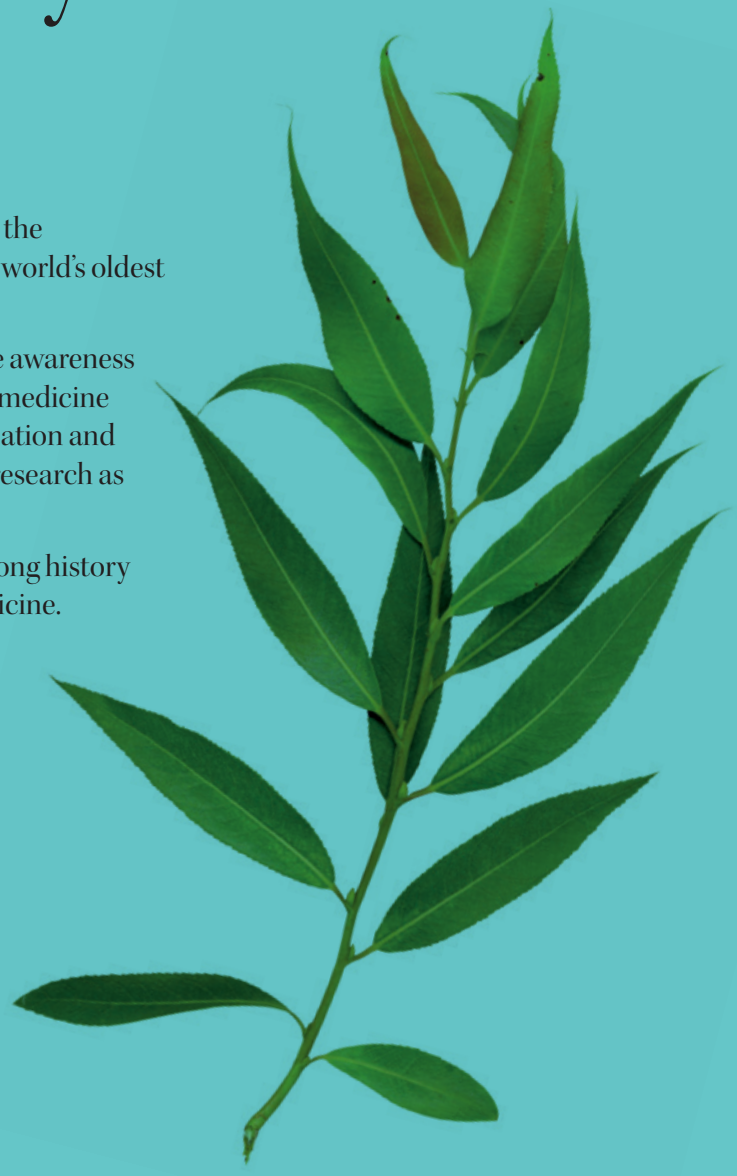

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