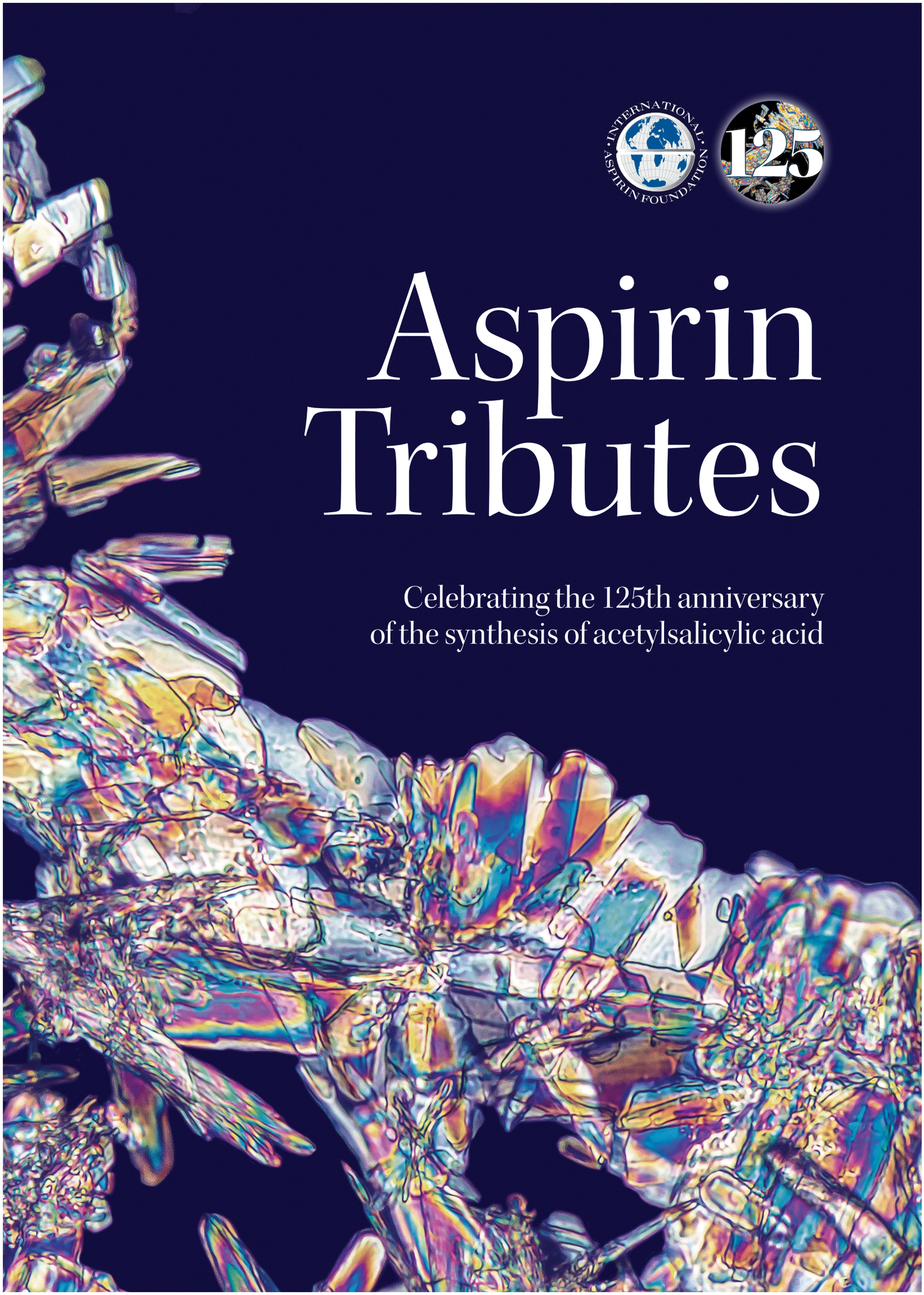
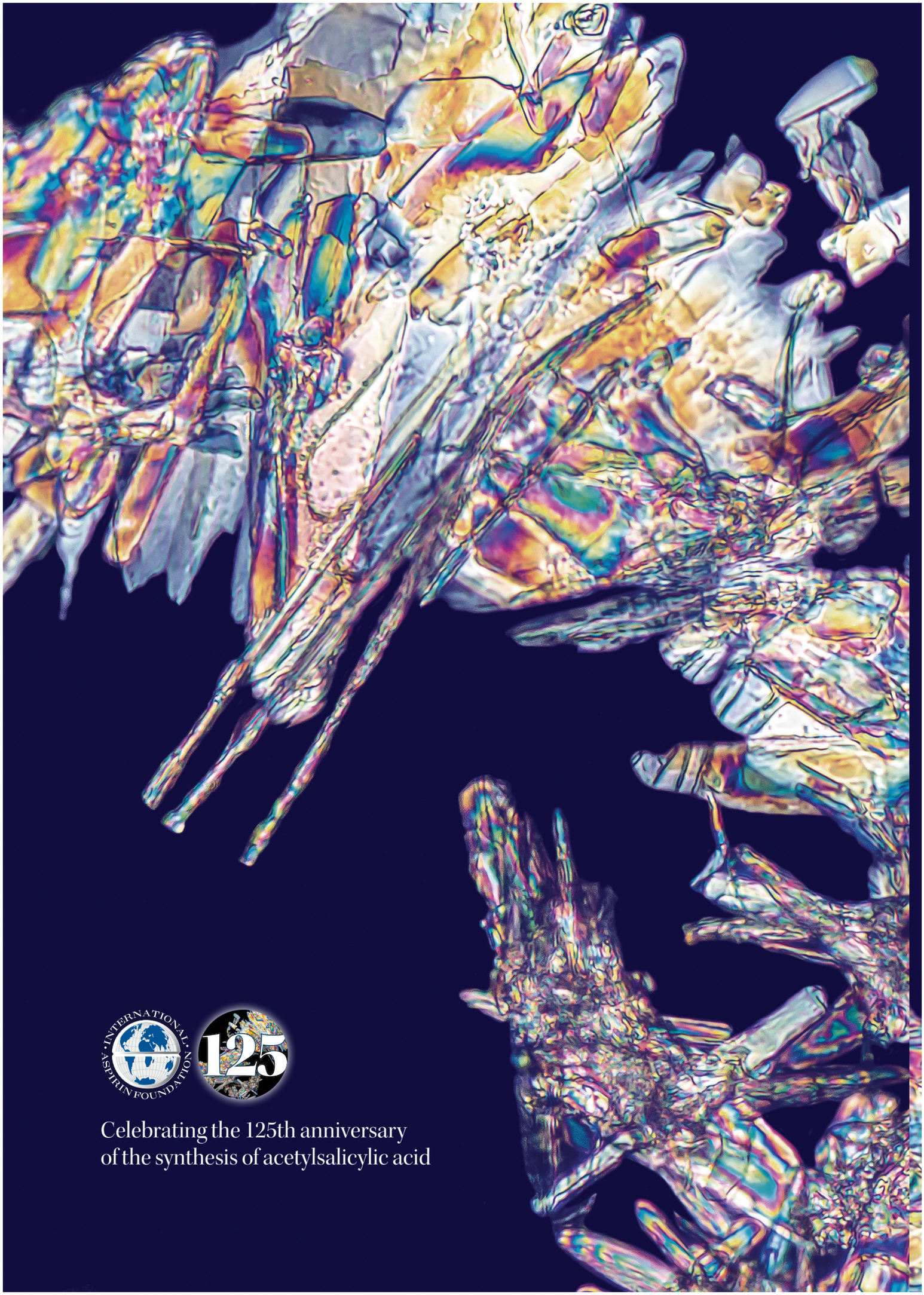


Aspirin Tributes

Celebrating the 125th anniversary
of the synthesis of acetylsalicylic acid



Celebrating the 125th anniversary
of the synthesis of acetylsalicylic acid

Dr Luis A. Garcia Rodriguez

Aspirin Tributes

Luis A. Garcia Rodriguez is a Spanish pharmacoepidemiologist, who directs the Centro Español de Investigación Farmacoepidemiológica (CEIFE), in Madrid. The CEIFE, established in 1994, has pioneered use of automated computer-based data-bases to perform large-scale pharmacoepidemiologic research.

Pharmacoepidemiology, explains Garcia Rodriguez, explores utilization and effects of drugs in large populations, estimating probabilities of both beneficial and adverse effects.

In pharmacoepidemiology aspirin, says Garcia Rodriguez, represents one of the most widely studied drugs.

"*Aspirin has been off-patent for many years, with the result pharmaceutical companies no longer have any major economic interest in studying it. Therefore, much of the new clinical information derives from pharmacoepidemiology,*" explains Garcia Rodriguez. This, he adds, directly contrasts with new oral anticoagulants, such as apixaban and rivaroxaban, where much of the information has been derived from clinical trials.

Who is your aspirin hero?

"Over the years many scientists have contributed to knowledge about aspirin in the cardiovascular (CV) field, with notables including Felix Hoffman, Harvey Weiss and John Vane. But for me, Carlo Patrono, from the Catholic University of Medicine, Rome, represents the scientist who has made the greatest contribution to disentangling the molecular mechanisms behind the antiplatelet effects of low-dose aspirin.

Carlo conducted studies on the human pharmacology of platelet thromboxane inhibition by aspirin. In 1980, he published the first paper on the methodology of measuring serum thromboxane B2 (TXB_2), which in 1982 opened the way for his second paper describing the cumulative nature and biochemical selectivity of platelet TXB_2 inhibition by low dose aspirin.[1] Ultimately, it was this work that laid the foundations for establishing low-dose aspirin as a potential therapeutic strategy to prevent and treat CV disease (CVD).

Carlo, who chairs the Scientific Advisory Board of the International Aspirin Foundation, provides an example of a true Renaissance scientist who has mastered a whole range of disciplines from basic biology to clinical epidemiology. His work shows that once you understand the mechanisms involved you can achieve a far greater understanding of potential adverse effects, helping to identify relevant endpoints in clinical trials and observational research. Throughout his career, Carlo has been incredibly good at making complicated things simple."

What's the biggest difference aspirin has made in cardiology?

"Undoubtedly becoming one of the main pillars in secondary cardiovascular prevention for people who have already suffered a previous myocardial infarction (MI) or ischaemic heart disease. The first main study was The International Study of Infarct Survival-2 (ISIS 2), which between 1981 and 1985 randomised intravenous streptokinase, oral aspirin, both or neither to 17,187 patients with suspected acute MI.2 Results showed that low-dose aspirin once daily was effective and safe in reducing vascular mortality at five weeks by approximately one quarter.

For the last 20/ 30 years virtually everyone being discharged from hospital after an MI has been put on low dose aspirin. This strategy has undoubtedly resulted in saving a huge number of lives, although it would be difficult to tease out the exact contribution of aspirin since patients are also prescribed a multitude of other drugs."

What is the main research currently taking place with aspirin?

"Looking to see whether low dose aspirin might play a role in primary and secondary prevention of certain cancers. So far a primary prevention study of aspirin in cancer hasn't proved feasible due to the fact cancers aren't so common in the general population making it necessary to recruit an enormous number of patients over an extended period of time to show any difference between the arms.

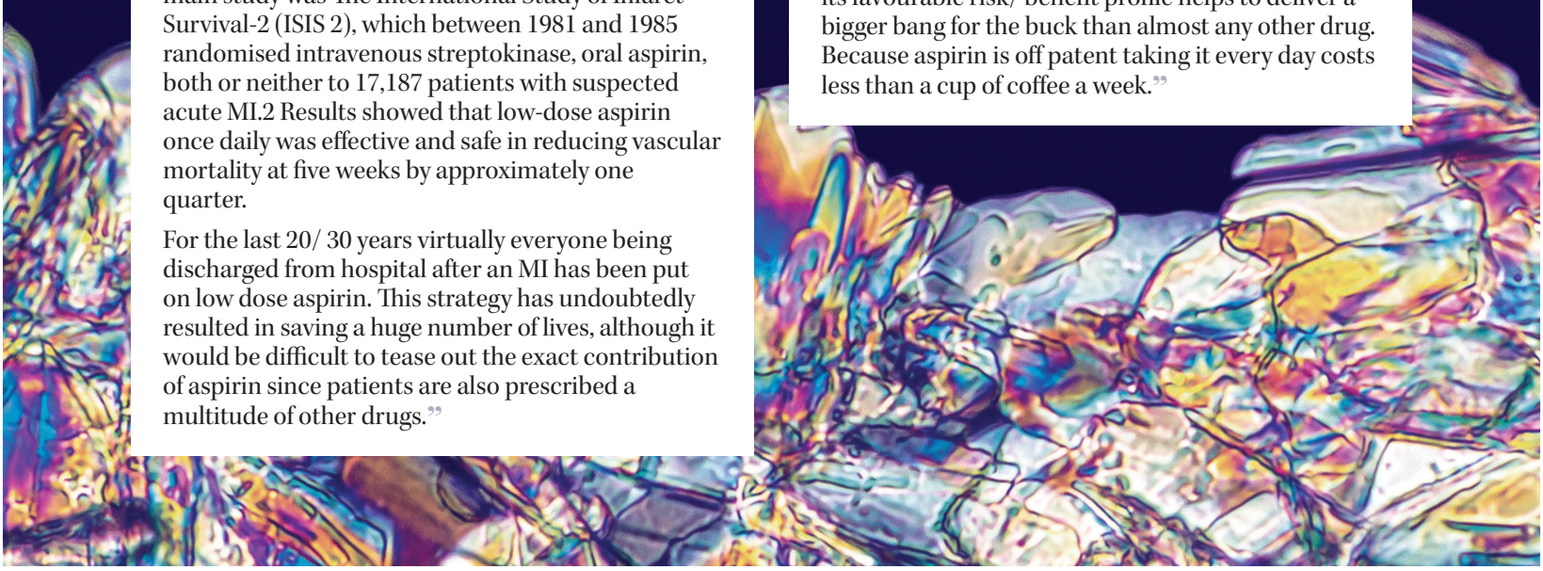
However, epidemiological studies have shown that individuals who chronically use aspirin (for both primary and secondary CVD prevention) reduce their risk of GI tract cancers (colon, stomach and oesophageal cancers) by around one third.

Carlo Patrono and colleagues developed a theory that aspirin worked in cancer prevention through a mechanism analogous to CVD prevention, through inhibiting platelet activation and downregulating participation of platelets in tissue repair, angiogenesis and immune response.

Currently, Ruth Langley (University College London) is running the secondary prevention Add-Aspirin trial to see whether after initial treatment for early-stage cancer taking aspirin every day for five years could help to prevent the cancer from coming back. Over 11,000 people who have been successfully treated for cancers of the breast, bowel, stomach/ oesophagus or prostate, are being recruited. If aspirin works in cancer prevention it would be marvellous because this would represent an additional benefit on top of CVD."

Why are you such a big aspirin fan?

"To my mind the low cost of aspirin together with its favourable risk/ benefit profile helps to deliver a bigger bang for the buck than almost any other drug. Because aspirin is off patent taking it every day costs less than a cup of coffee a week."



If you could do just one aspirin study what would it be?

"My ultimate aspirin experiment would be to perform a long-term observational study exploring all the major benefits and risks of low dose aspirin in the very same population. The usual approach is to say that in study A the benefit was X, while in study B the risk was Y and then combining the effects coming from different studies. The problem here is that we make the assumption that populations in study A and study B are the same, which is unlikely to be the case. If we looked at everything in the same population we'd be able to add and subtract all the different outcomes because they have the same denominator. To evaluate consistency of the findings the same study would need to be performed in different countries. Ultimately, this approach would provide us with an accurate risks/ benefits analysis for aspirin and the net impact of aspirin use in the general population.

For me this is the ultimate study because the overarching theme of my aspirin research has been to explore the different pieces that go into the overall risk benefit of aspirin in the general population.

Studies that I've undertaken with aspirin include looking at the role of aspirin in the primary prevention of MI in post-menopausal women[3], the effect of aspirin discontinuation, the bleeding risk of aspirin at different sites and looking to see whether low dose aspirin reduces progression of colorectal cancer as well as other cancer.[4]"

Tell us a surprising fact about aspirin?

"Virtually all worldwide production of acetylsalicylic acid, the main active ingredient of aspirin, comes from a factory in a town called La Felguera in Asturias, Northern Spain. The area was first selected to manufacture acetylsalicylic acid in 1942 because the nearby coal mines and iron and steel works provided carbon to make acetic anhydride and salicyclic acid. Even though the key ingredients have changed (to petroleum and acetic anhydride) production has remained at the same factory. From here Bayer transfers the powdered form acetylsalicylic acid to nearby Gijón, where it is shipped to centres around the world to be processed into pill form. For me personally, what's the biggest coincidence it that the acetylsalicylic factory happens to be just about 20 km south of Oviedo where I was born."

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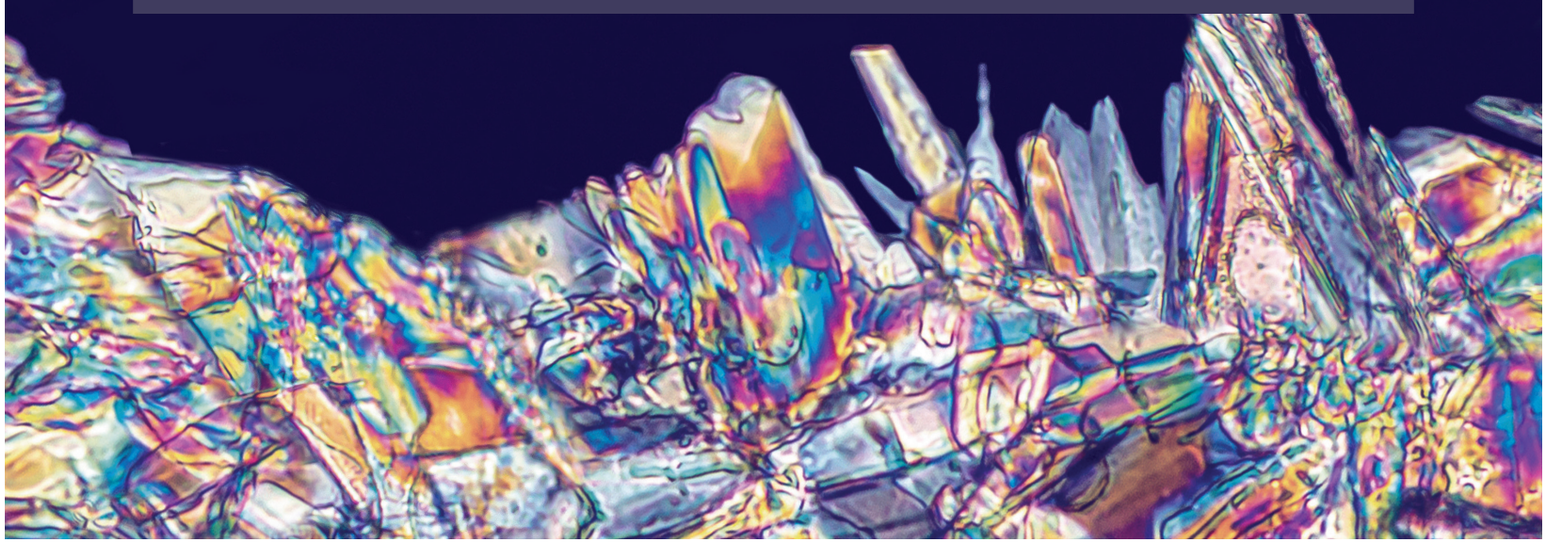
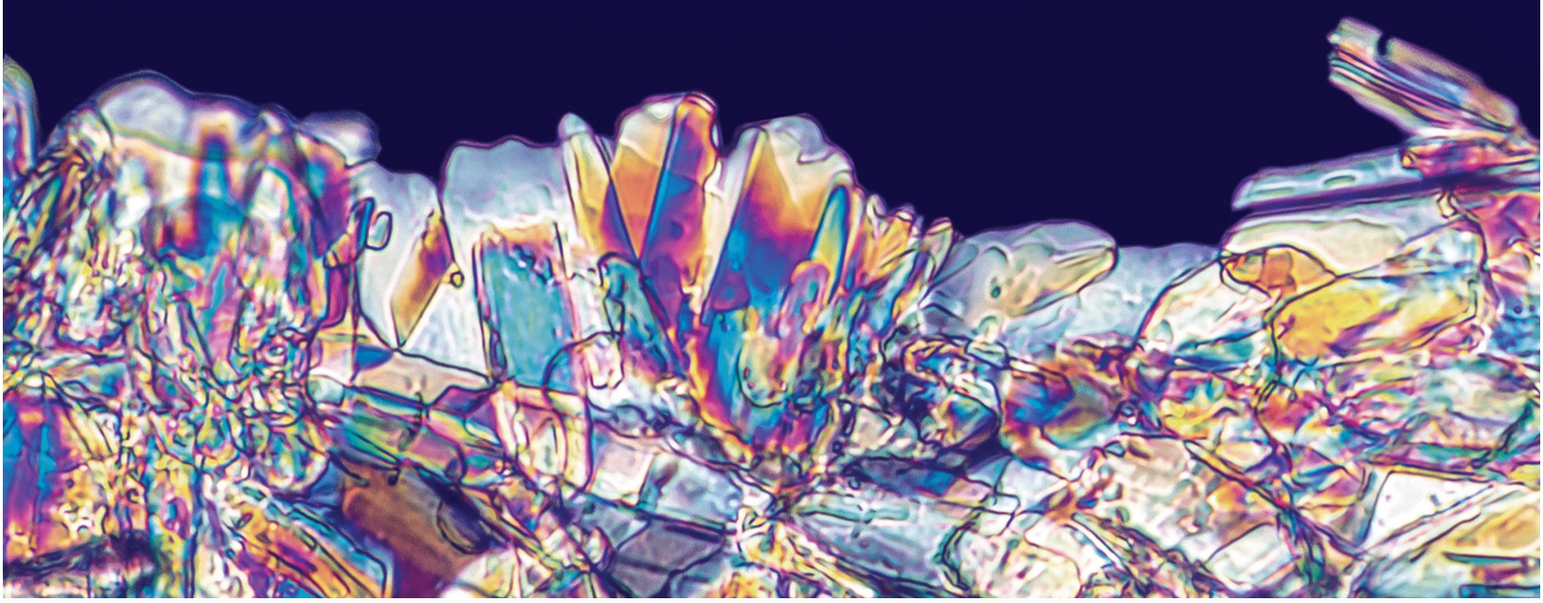


Professor Gemma Vilahur

Aspirin Tributes

Gemma Vilahur is the current chair of the Working Group of Thrombosis of the European Society of Cardiology (ESC). Gemma is a basic/translational science researcher in the cardiovascular (CV) field working at the Research Institute of the Hospital de la Santa Creu I Sant Pau, Barcelona.

Gemma specialises in ischemic heart disease, where she is involved in discovery and assessment of new cardioprotective strategies, including antiplatelet agents, with particular emphasis on understanding cardiac structural and functional benefits and the molecular mechanisms of action. In diabetes Gemma has explored the role of aspirin in the setting of primary CVD prevention.



Who is your aspirin heroine?

If I had to pick a heroine from the world of aspirin and CVD, it would be Julie Buring, Professor of Medicine at Harvard Medical School and Brigham and Women's Hospital and Professor of Epidemiology at Harvard School of Public Health. Julie's primary focus has been the epidemiology of chronic diseases in women, in particular CVD and cancer. Her landmark Women's Health Study (WHS), initiated in April 1993, explored risks and benefits of low-dose aspirin and vitamin E in primary prevention of CVD and cancer in nearly 40,000 US women aged ≥ 45 years.

The WHS study concluded that aspirin lowered the risk of stroke but did not affect the risk of myocardial infarction (MI) or death from CVD.[1] However, a subgroup analysis showed that aspirin significantly reduced risk of major CV events, ischemic stroke, and MI in women ≥ 65 years. In this group, aspirin use, compared to placebo, led to 44 fewer MIs, strokes or deaths from CV causes (P=0.008), but to 16 more gastrointestinal haemorrhages requiring transfusion (P=0.05). Such data emphasizes the importance of balancing risks and benefits.

At the time, Julie and her all female team of investigators showed amazing foresight in just focusing on women. Even today, despite guidelines and legal requirements, women remain underrepresented in CVD clinical trials.

Although the WHS trial ended in March 2004, the team persuaded 89% of the original participants to continue in an observational study, which involved no pill-taking, just completing yearly follow-up questionnaires. As a result, the WHS has evolved into one of the largest observational studies of women's health, directly resulting in more than 600 publications. The publications have included important findings that have added to our understanding of aspirin, such as a follow-up at 18 years revealing that women randomised to the active aspirin group had risk of colorectal cancer reduced by 20%, with the difference between the aspirin and placebo arms only starting to emerge after the first 10 years.[2]

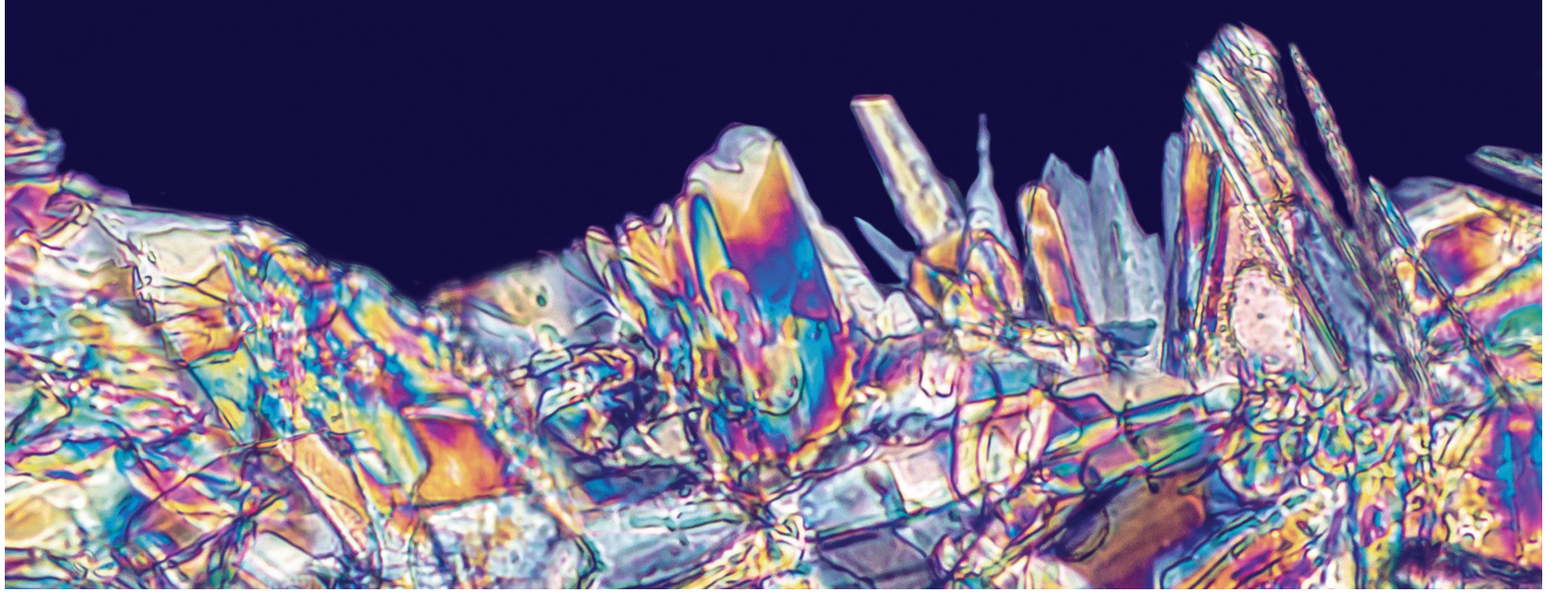
What role does aspirin have to play in the primary prevention of CVD?

Currently, using aspirin in primary prevention continues to be the subject of debate. The use of aspirin for the primary prevention of CV outcomes in patients with diabetes mellitus (DM), who are established to be at CVD risk, illustrates the need to explore individual levels of patient risk.

Although routine use of aspirin for all patients with DM is not recommended there's now growing evidence that low dose aspirin may prove beneficial for primary prevention in high risk DM patients (defined as DM and ≥ organ damage or ≥ 3 major risk factors, or any risk factor and ≥ 10 years disease duration without organ damage) in the absence of contraindications.

The ASCEND study, randomizing 15, 480 people with DM but no evident CVD to aspirin 100mg or placebo, found after a mean follow-up of 7.4 years 8.5% of people in the aspirin group experienced serious vascular events versus 9.0% in the placebo group (P=0.01).[3] However, major bleeding events occurred in 4.1% of people in the aspirin group versus 3.2% in the placebo group (P=0.003). Such statistics clearly illustrate how aspirin benefits can come at the expense of higher rates of bleeding.

On this balance of risks, aspirin may be indicated on an individualized basis for some very high risk DM patients. However, both European and US guidelines have yet to include mention of aspirin in this patient population.



Why might aspirin be beneficial in patients with DM?

Diabetes mellitus (DM), representing a group of metabolic disorders characterized by systemic hyperglycaemia, is estimated to affect almost 9% of the global population. The gravity of the condition is underlined by estimates suggesting around two thirds of patients with DM will ultimately die from CVD.[4]

DM is characterized by multiple pathological processes, including, insulin resistance, chronic inflammation, oxidative stress, and associated metabolic conditions that damage the endothelium, and increase platelet reactivity, resulting in the development of prothrombotic environments.[5]

Insulin, besides well-known protective effects in the endothelial layer (where it stimulates nitric oxide synthesis) also displays direct anti-platelet activity by attenuating signalling pathways and expression of platelet receptors involved in platelet activation.

In patients with DM, besides the deleterious effects associated with insulin resistance, an array of mechanisms exist to enhance platelet reactivity including increased synthesis of Thromboxane A2 (TXA2), a potent platelet activator. With this in mind, low-dose aspirin can be used to inhibit platelet cyclooxygenase-1 (COX-1) enzyme, preventing the formation of prostaglandin H2, from which TXA2 is generated through the enzyme thromboxane-A synthase.

Platelets are enucleated, and therefore unable to resynthesize COX-1, rendering the action of aspirin irreversible. However, it's important to bear in mind aspirin has a short half-life and in cases of increased platelet turnover, as occurs in DM, newly generated platelets may escape inhibitory effects of aspirin, resulting in need for more frequent dosing (twice-daily).

What studies have you undertaken in aspirin and DM?

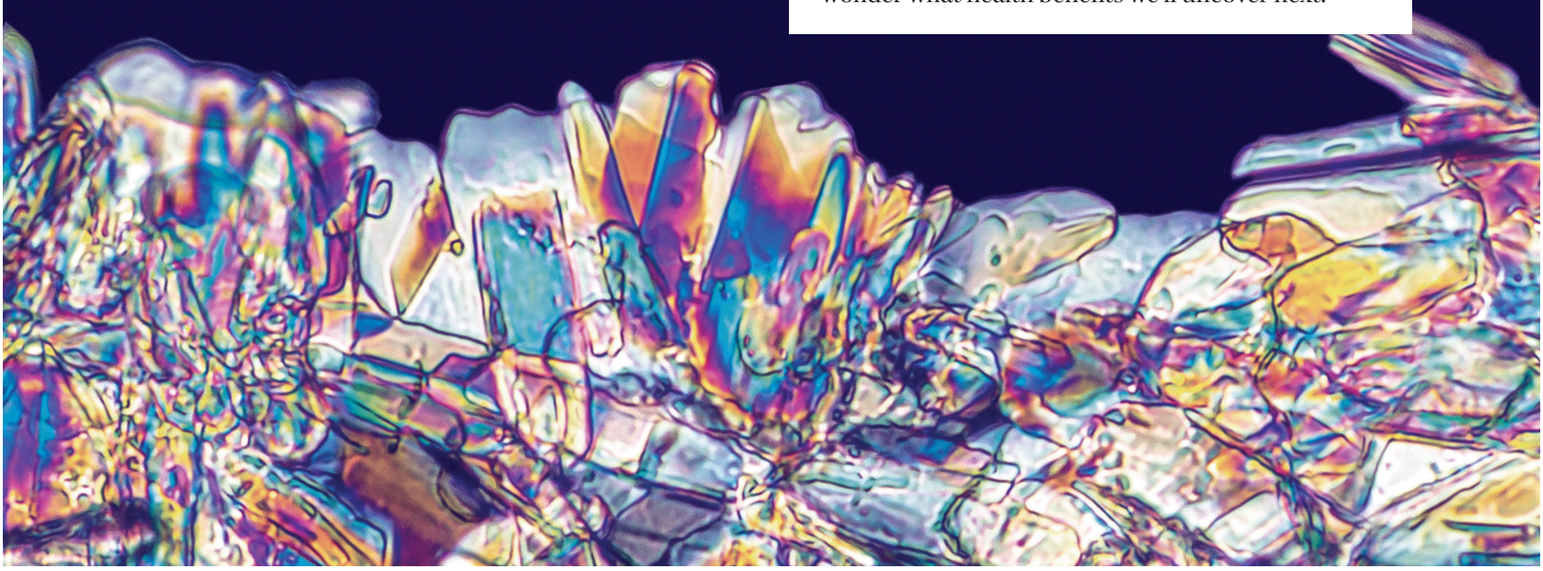
As mentioned earlier, use of aspirin in primary prevention for DM patients remains controversial. We wondered whether aspirin might have pleiotropic effects going beyond thromboxane inhibition in diabetes patients with no previous CV event. With this in mind, we investigated the effects of low-dose aspirin on activation of cells from the vascular compartment in type 1 and 2 diabetic patients. Activation was assessed by microparticle shedding, a process where fragments of the parent cells (microvesicles) are shed to the blood stream when exposed to stressful conditions.

We observed that aspirin treatment resulted in decreased microparticle shedding from erythrocytes, monocytes and smooth muscle cells.[6] The effects were similar in type 1 and type 2 patients. Hence, we showed in diabetic patients without previous vascular events aspirin therapy resulted in reduced vascular wall cell activation suggesting the potential of low-dose aspirin to ameliorate the pro-atherothrombotic milieu characterizing DM.

Why are you such a big aspirin fan?

Because of aspirin's low cost together with its favourable risk/ benefit profile. Although, there are newer antiplatelet agents on the market, which may be 5 to 10 % more effective than aspirin, their high price means not all health systems can afford them. Aspirin's cost means there is universal access throughout the world. Additionally, I love aspirin's versatility, the fact that one pill can help prevent CVD, diabetes and cancer.

Despite aspirin having been around for 125 years, we're finding there's still so much more to discover about it. First aspirin was found to have anti-inflammatory effects, then antiplatelet and now we're looking at anti-cancer effects. It makes you wonder what health benefits we'll uncover next.



If you could do one aspirin study what would it be?

I'm a basic science/translational researcher and would like to increase understanding of links between aspirin and arachidonic acid. We know that aspirin blocks the enzyme cyclooxygenase, involved in converting arachidonic acid to prostaglandins. So, the question arises - what are the multiple down-stream effects on signalling pathways that occur when you interfere with prostaglandin synthesis and how does this change between different aspirin dosages? I'd also like to understand whether there's variance between different conditions, i.e. what happens in patients with CVD, thrombosis, inflammation or cancer?

Ultimately, such information would enable personalised treatment where we could administer the right dose of aspirin to the right patient population.

Tell us a surprising fact about aspirin.

In the CVD field aspirin works in everything apart from peripheral artery disease (PAD). The lack of aspirin on PAD has been shown in a number of studies and meta-analyses. [7,8,9]

We don't understand why, but it may be that PAD, which affects return of blood from the legs, is associated with venous thrombosis rather than arterial thrombosis. In venous thrombosis fibrin plays a key role, as opposed to platelets in arterial disease, with the result that aspirin exerts little benefit.

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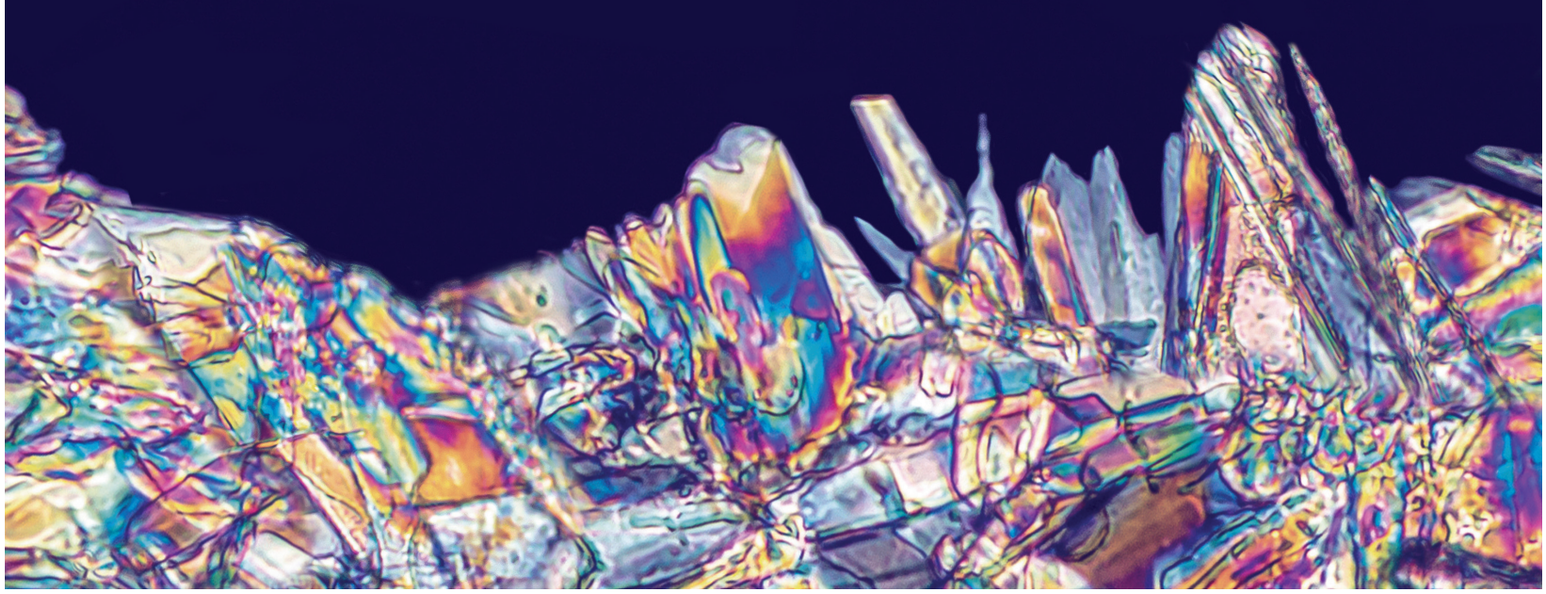
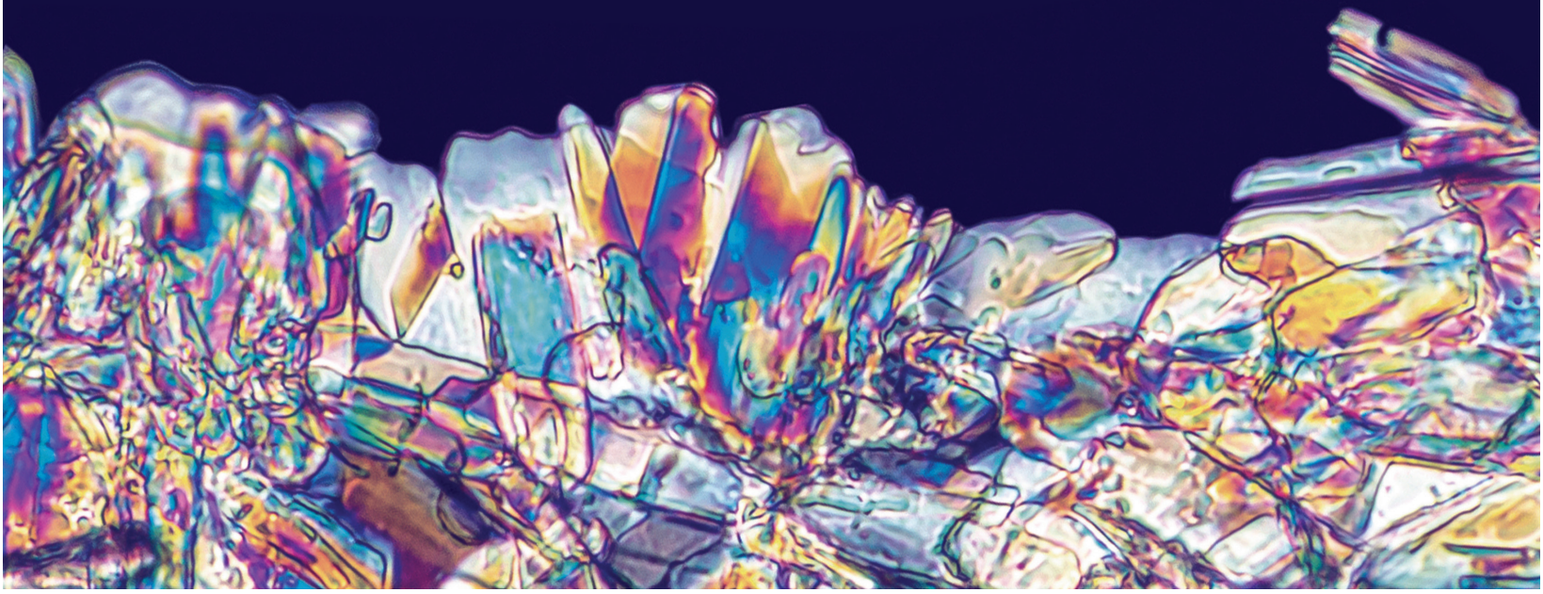


Professor Bianca Rocca

Aspirin Tributes

Bianca Rocca, a haematologist and clinical pharmacologist, from the Catholic University of Medicine, Rome, says that platelets and aspirin have been the 'leitmotif' recurring throughout her career. In her PhD thesis on platelet activation and inhibition in Essential Thrombocythemia (ET), submitted in 1998, Bianca first worked with aspirin. Since then, she has been involved in many investigator-initiated trials on aspirin and cardiovascular (CV) diseases including diabetes, patients undergoing coronary artery bypass surgery, atherothrombosis as well as ET, including the Aspirin Regimens in Essential Thrombocythemia (ARES) trial. Bianca, who chaired the European Society of Cardiology (ESC) Working Group on Thrombosis from 2018 to 2020, has also participated in writing ESC position papers and guidelines and was recently elected to the ESC Nominating Committee for the years 2022-2024. A particular research interest, says Bianca, is exploring individual patient variability in the effectiveness of aspirin, and helping to re-purpose an 'old, cheap and highly effective antiplatelet drug for the modern age'.



Who is your aspirin hero?

In the aspirin story there are many heroes, making it difficult for me to choose just one.

There's Bengt Samuelsson, who was awarded the 1982 Nobel Prize in Medicine for showing anti-inflammatory drugs (including aspirin) prevent prostaglandins forming through inhibiting the cyclooxygenase (COX) enzyme.

Then there's Garrett Fitzgerald (Vanderbilt University, Tennessee) and Carlo Patrono (Catholic University, Rome) who established that lower doses of aspirin than used for pain relief could effectively block platelets. For this discovery in 2013 they were awarded the Grand Prix Scientifique of the French Academy of Sciences.

Finally, there's the ISIS-2 trial investigators, who showed that the combination of streptokinase and aspirin first used at low doses in a large phase 3 trial on patients with myocardial infarction (MI), was better than either agent alone in avoiding vascular deaths.[1] The group, led by Sir Richard Peto and Sir Rory Collins, from the University of Oxford, first tested 160 mg/ day aspirin (as opposed to much higher doses used in the 1970s), providing an approach to hit acute atherothrombosis while avoiding damage to the gastric mucosa, thus improving the efficacy/safety balance.

What research are you undertaking with aspirin?

Around 10 years ago it was observed that aspirin works less well in patients who have increased platelet turnover.[2] In our research group, we always opposed using the term resistance because if you say a patient is 'resistant' to a drug this means that the drug is no longer usable, even at higher dosages (as in the case of antibiotics). We had evidence that these patients were only less responsive to standard aspirin dosing regimens, being outliers in the Gaussian distribution of drug response, as happens when a number of drugs are used in 'real world' settings. We are trying to understand the pharmacological causes of 'differences' and how to correct them, rather than concluding that aspirin is useless. Thinking back, we were ahead of our time, reasoning in terms of personalized medicine and precision drug dosing, well before this therapeutic approach was officially classified.

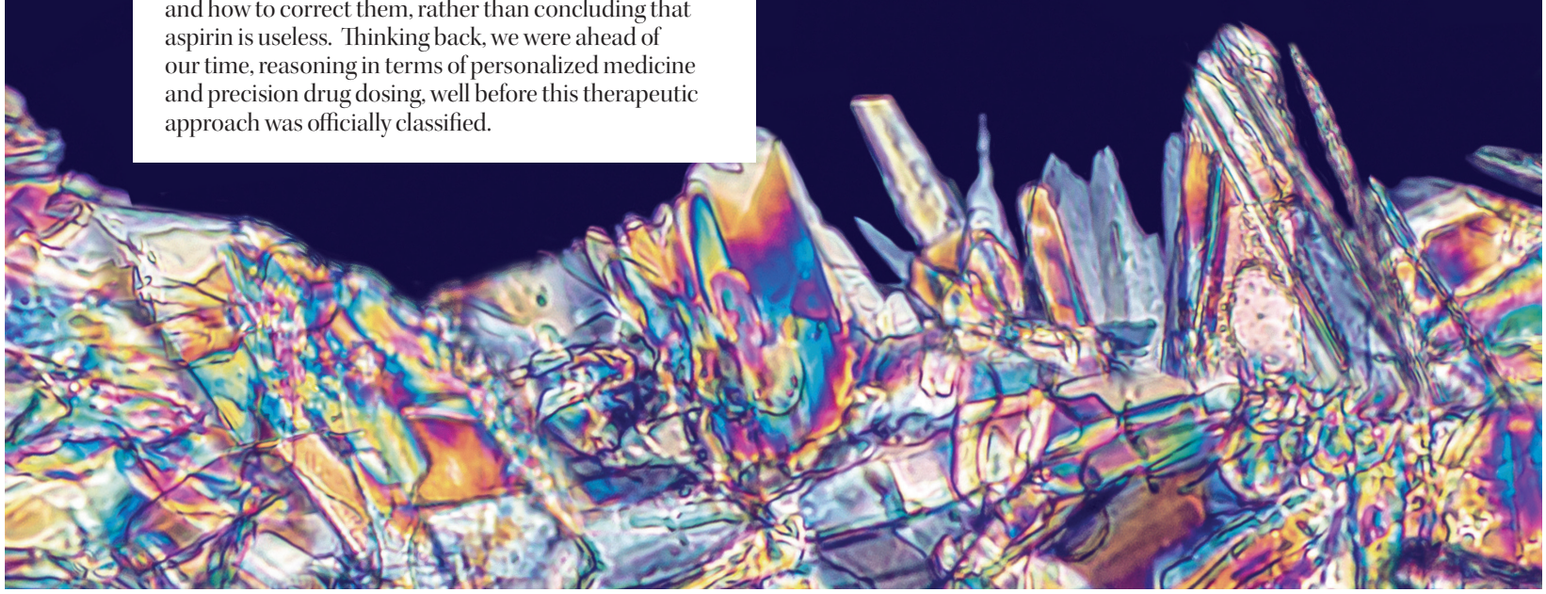
I've been interested in Essential Thrombocythemia (ET), a myeloproliferative neoplasm, as a paradigm to study how platelet turnover impacts aspirin responsiveness. Estimates suggested that up to 50% of ET patients experience a thrombotic events (including MI, ischemic stroke, transient ischemic attack or venous thromboembolism) despite taking antiplatelet drugs.[3]

In spite of aspirin's short half-life (~ 20 minutes in the human circulation), blockade of platelet COX-1 activity lasts for the entire platelet life span due to limited platelet capacity for new COX-1 synthesis, thus allowing once daily dosing. However, in ET accelerated platelet generation and turnover is associated with higher-than-normal daily release rates of new platelets with the result that when you prescribe aspirin in this situation you need to consider both the drug and lifespan of its target.

Low-dose aspirin (75–100 mg once daily) is currently recommended for both secondary and primary CV prevention in the majority of ET patients. To explore whether there's an optimal dosing regimen for aspirin that would correct to normal in ET we designed the ARES (Aspirin Regimens in Essential Thrombocythemia) trial, where we exposed patients to different frequencies of aspirin intakes, once daily, twice daily and three times daily to select the optimal dosing regimen for a phase 3 ET trial.[4]

Results showed that patients assigned to twice-daily and thrice-daily regimens displayed substantially reduced inter individual variability and improved response to aspirin compared to patients assigned to the once daily arm. However, the thrice daily arm reported higher abdominal discomfort scores, leading us to recommend that antiplatelet responses to low-dose aspirin can be improved by shortening the dosing interval to once every 12 hours.[5]

The long-term superiority, compliance and tolerability of this optimized aspirin regimen is currently being investigated in the ongoing phase 2 ARES trial.



What tools have you found most useful in your aspirin work?

When you find good tools in science, they can be used to unlock many doors. In 1980 Carlo Patrono, my mentor at the Catholic University, Rome, discovered that levels of Serum thromboxane B2 (TxB2), a stable metabolic product of TxA2, could be used as a specific biomarker for platelet inhibition by aspirin.[6] TXB2 could be used to predict the efficacy of aspirin and hence became an important way of understanding the causes of reduced response to aspirin and guiding strategies to correct them.[7]

I have used serum TxB2 as a biomarker to explore the effectiveness of aspirin in different settings, such as obesity and diabetes, which has enabled me to start to understand more about individual patient variability. We used TxB2 in the ARES trial to understand the effect platelet turnover has on effectiveness of aspirin.[4,5]

If you could do one aspirin study, what would it be?

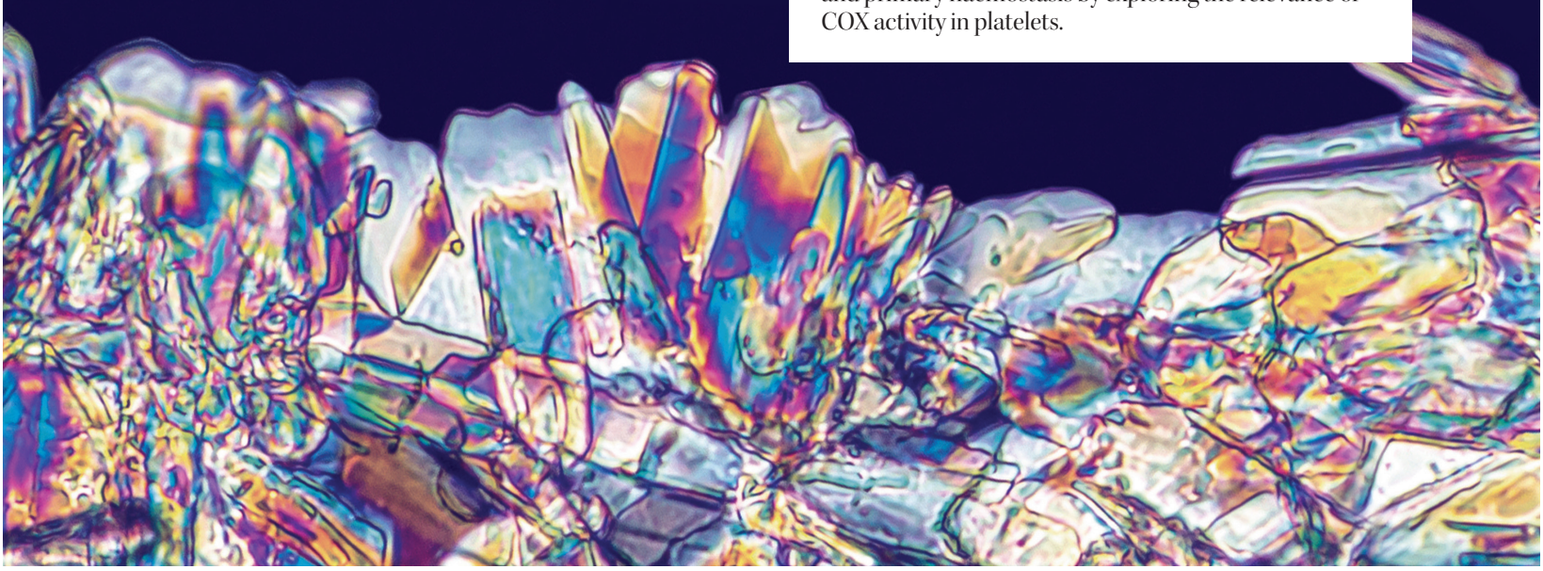
In 2018 three randomized trials explored whether to pursue aspirin for primary cardiovascular disease (CVD) prevention: the ASCEND trial (in diabetics)[8], ARRIVE trial (in patients with moderate CV risk)[9] and the ASPREE trial (in patients aged ≥70 years).[10] While the ASCEND trial showed that the absolute benefits outweighed the risks, the ARRIVE and ASPREE trials drew neutral conclusions.

However, both ARRIVE and ASPREE have major limitations. ARRIVE recruited low risk subjects in spite of its initial prediction, for whom it was already known there was no benefit for primary prevention. The ASPREE trial used the primary endpoint of 'disability free survival' making it possibly the only example of an antiplatelet trial having a non-CV primary end point.

Moreover, there has been observational data suggesting aspirin can be useful in primary prevention in patients who have a lot of calcium in their coronary arteries, [11] and in patients who have a documented atherosclerotic lesion in their arteries, even if they have not yet developed stroke or MI. Therefore, I'd like to undertake a phase 3 primary prevention trial including imaging to stratify the CV risks of individual patients according to coronary artery calcium scores or ultrasound in addition to medical history, cholesterol and blood pressure. In doing this, we might find that there are specific groups of patients where primary prevention benefits of aspirin outweigh the risks.

Why are you such a big aspirin fan?

The fact that aspirin offers a never ending scientific and pharmacological story that is continually evolving. It's an ancient drug that has progressed from being used in pain control to having a role in secondary and primary prevention of CVD and now is being explored in cancer chemoprevention. Aspirin can also be used as a research tool that helps us to understand more about platelets and primary haemostasis by exploring the relevance of COX activity in platelets.



Tell us a surprising fact about aspirin

When speaking to patients taking part in trials what's really struck me is the enormous difference that aspirin can make to their quality of life. In the ARES trial some patients who had been randomized to take aspirin two times a day told me that they didn't want to go back to taking aspirin once a day. They reported that activities of daily living using their hands, like washing dishes and preparing meals, could be performed so much better when they took aspirin twice a day. This was due to a subjective reduction in micro-vascular symptoms which cause pain in the hands and feet of patients and make their daily life complex. What really struck me is that aspirin, a drug that we have been using for years, still has the ability to surprise us.

What does the future hold for aspirin?

In future, I think that we'll be doing more in-silico modelling to define 'precision dosing', i.e., the optimum aspirin doses for individual patients who haven't proved suitable for phase 3 trials, in the context of personalized medicine.

In-silico models acquire real world data, using measurements of serum TxB2 as a proxy for Cox-1 activity in peripheral platelets, and combine this information with mathematical equations to simulate special disease conditions.[12] They allow you to explore drugs in patients who are clearly outliers and who are usually excluded from trials due to factors, such as being severely obese or having high or even low platelet counts. The approach also lets you to combine rare conditions and model aspirin doses for real world situations. Achieving the optimum aspirin dose for an individual patient is vitally important because it both makes drugs more effective and reduces dangerous side effects, like the risk of bleeding.

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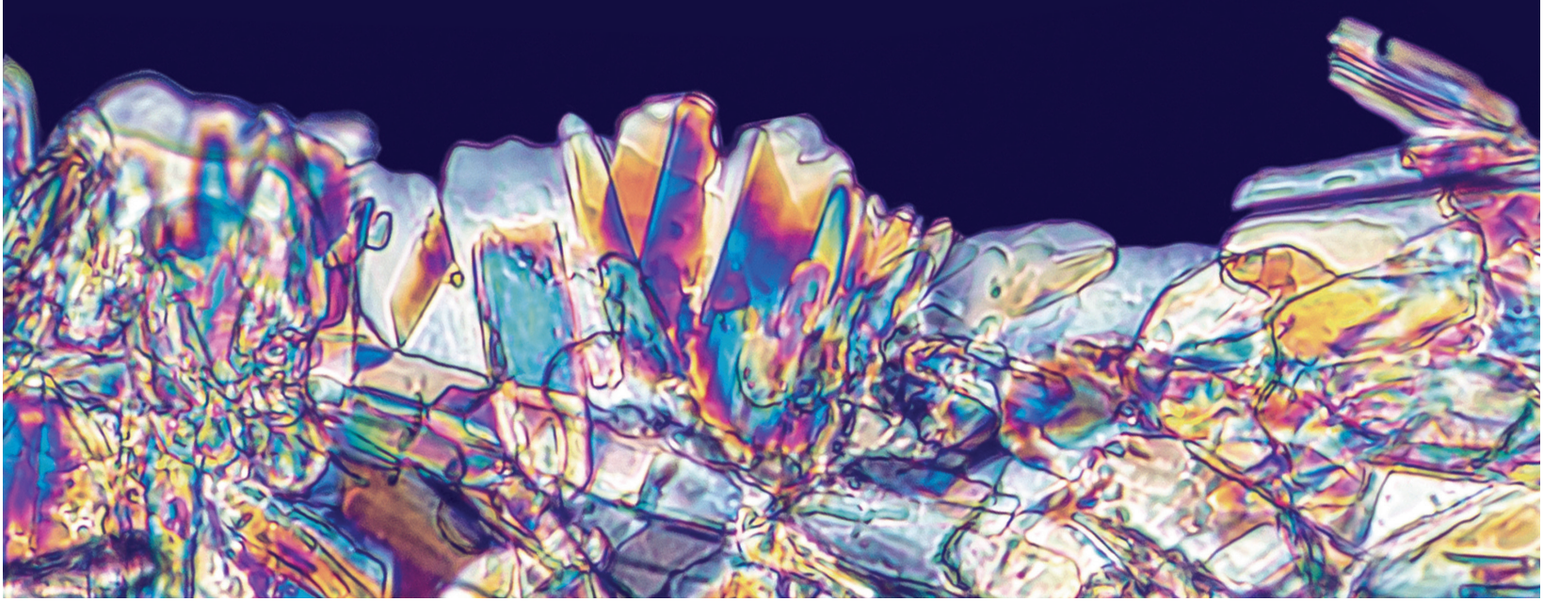
Professor Ruth Langley

Aspirin Tributes

Professor Ruth Langley is chief investigator of the Add-Aspirin trial, which is being coordinated by the MRC Clinical Trials Unit at University College London. The phase 3 Add-Aspirin trial is evaluating whether regular aspirin use can delay or stop cancer coming back in patients treated for early breast, colorectal, gastro-oesophageal or prostate cancer.[1]

Ruth, a medical oncologist, has a particular interest in drug repurposing and improving trial design. She is also involved in the STAMPEDE prostate cancer trial which helped pioneer the concept of Multi-Arm Multi-Stage (MAMS) trials.[2] The MAMS approach was subsequently used to accelerate the assessment of antiviral agents against COVID-19.[3]



Who is your aspirin hero?

My inspiration is Carlo Patrono, from the Catholic University School of Medicine, Rome, who has been working on aspirin for the last 40 or 50 years. He has a unique in-depth knowledge of aspirin pharmacology and associated clinical studies. Carlo's work, has laid the foundations for much of the current research into aspirin. When I was new to the aspirin field Carlo was enormously generous with his time, helping us to design the Add-Aspirin trial. He is my 'go to person' for any complex issues to do with aspirin.

I would also like to pay tribute to the work of a husband-and-wife team, Gabriel J Gasic (1912- 2003) and Tatiana B Gasic (1924- 2014).[4] While working at the Department of Pathology at the University of Pennsylvania School of Medicine in Philadelphia, they wrote a seminal paper published in the Lancet in 1972 providing one of the earliest indications that aspirin might play a role in cancer therapy.[5] They performed a simple experiment where they injected sarcoma cells into mice and studied the effect of aspirin. They found fewer lung metastases in the mice who had received aspirin. These findings led to a series of epidemiological studies and ultimately to the clinical trials being performed today.

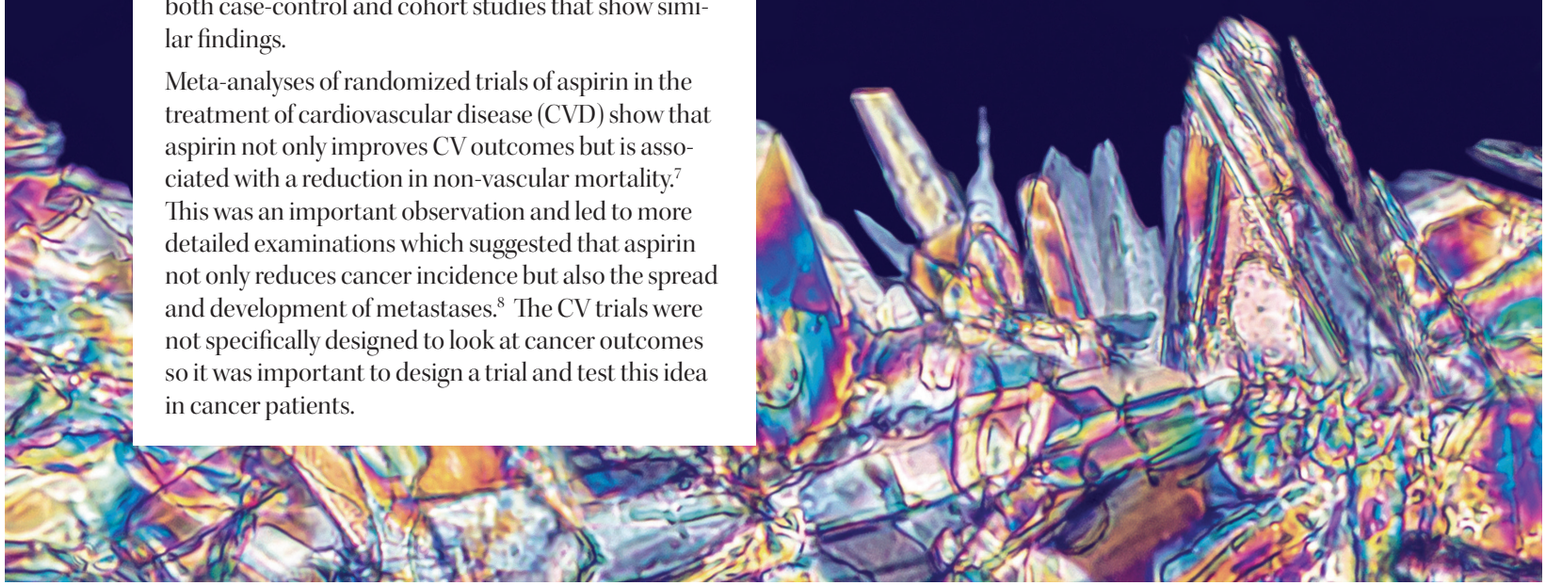
What other evidence suggests aspirin might play a role in cancer?

The evidence that aspirin might play a role in preventing and treating cancer comes from several sources. The first epidemiological evidence that aspirin could act as a chemoprevention agent was an Australian case-control study where aspirin use was associated with a significantly lower risk of colorectal cancer (CRC) even after adjustment for other risk factors.[6] There have been many epidemiological studies since both case-control and cohort studies that show similar findings.

Meta-analyses of randomized trials of aspirin in the treatment of cardiovascular disease (CVD) show that aspirin not only improves CV outcomes but is associated with a reduction in non-vascular mortality.[7] This was an important observation and led to more detailed examinations which suggested that aspirin not only reduces cancer incidence but also the spread and development of metastases.[8] The CV trials were not specifically designed to look at cancer outcomes so it was important to design a trial and test this idea in cancer patients.

What first triggered your interest in aspirin?

It was serendipitous. At the time, around 2005, the STAMPEDE trial was evaluating the drug celecoxib with or without zoledronic acid in men with prostate cancer.[2] Celecoxib is similar in some ways to aspirin. We were approached by a retired doctor, Dr Geoffrey Venning who had previously worked in the pharmaceutical industry. He questioned why we were exploring the newer cyclo-oxygenase inhibitors as potential anti-cancer agents when aspirin had not been fully investigated in this arena? He pointed to the original Gasic and Gasic publication.[5] Ultimately Geoff's insights led us to establish the Add-Aspirin trial.



Tell us about the Add-Aspirin trial

The aim of the Add-Aspirin study, which is funded by Cancer Research UK (CRUK) and the National Institute of Health Research (NIHR), is to see if aspirin can reduce or delay the number of people who have a cancer recurrence after a previous diagnosis. Patients who have undergone potentially curative treatment for an early breast (n=3600), colorectal (n=2270), gastro-oesophageal (n=840) or prostate cancer (n=1890) are registered into four tumour specific cohorts. Eligible participants first undertake an active run-in period where they receive 100mg aspirin daily for approximately eight weeks. Participants who are able to tolerate aspirin then undergo a double-blind randomisation and are allocated in a 1:1:1 ratio to either 100mg aspirin, 300mg aspirin, or a matched placebo to be taken daily for at least five years. The exception is participants aged ≥75 years who are randomised between 100mg aspirin and placebo.

The primary outcomes of the trial, which started in October 2015 and is anticipated to take 10 to 15 years to report, are disease recurrence for each of the tumour groups and overall survival for the whole cohort. The study is being run at 187 sites in UK, India and the Republic of Ireland. The lead investigator in India is Professor CS Pramesh, from the Tata Memorial Hospital, Mumbai. The reason for partnering with India is that aspirin is a low-cost generic drug and the incidence of cancer is increasing in low- and middle-income countries therefore testing global applicability is important.

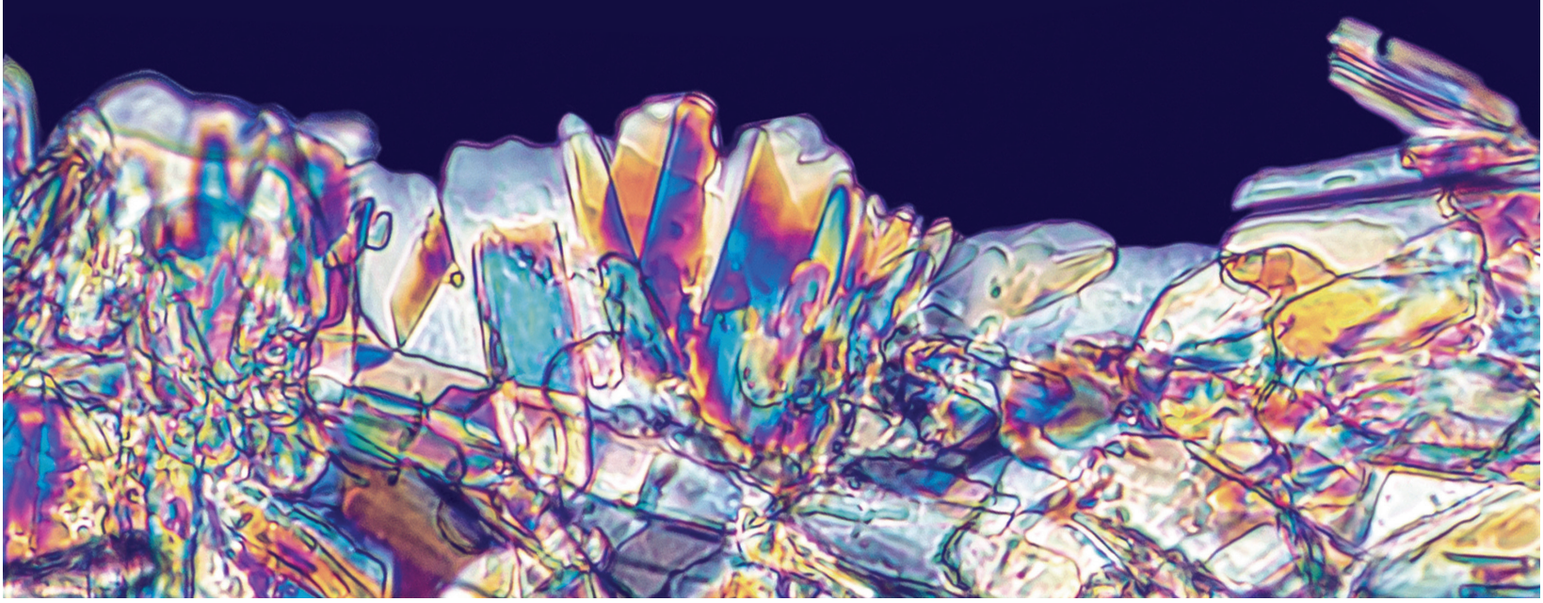
We now have ~10,000 patients registered, the breast and colorectal cancer cohorts have completed recruitment in the UK, prostate will finish early next year with the gastro-oesophageal cohort scheduled to finish recruitment in 2025.

What other studies are taking place in secondary prevention?

In addition to Add-Aspirin, there are several other world-wide studies evaluating aspirin as an adjuvant cancer therapy. Most of these are focussed on CRC. These include:

- The ASCOLT (Aspirin for Dukes C and high-risk B COLorecTal cancer) study which is investigating the utility of low dose aspirin on improving disease free and overall survival in patients with resected Stage III (Dukes C) and high-risk Stage II (Dukes B) CRC. The phase 3 trial, which started in 2008 and is being coordinated by the National Cancer Centre Singapore, has recruited 1587 participants from 60 sites across 11 countries.
- The Aspirin Trial Belgium, which started in 2018 (and also involves patients from the Netherlands) is determining the effect of 80mg aspirin (given orally once daily for five years) on five-year overall survival for stage II and III colon cancer patients ≥ 45 years of age.
- Adjuvant Low Dose Aspirin in Colorectal Cancer (ALASCCA), which is exploring aspirin after surgery in patients with stage II and III CRC who have PIK3 CA mutations, which are known to be present in 10 to 20 % of CRCs. This follows from a 2012 paper suggesting that CRC patients who derived benefit from aspirin had PIK3CA mutations.[9]

  In collaboration with the meta-analysis group of the MRC Clinical Trials Unit, we are co-ordinating a prospective collaboration which will ultimately bring the data from all of these trials (and others) together. This will allow a more detailed analysis of the potential benefits of aspirin in the prevention of metastases.



Does aspirin have a role in primary prevention of cancer?

For primary cancer prevention with aspirin the jury is still out. In their latest guidelines, published April 2022, the U.S. Preventive Services Task Force (USPSTF), modified its advice saying that there was currently insufficient evidence to recommend aspirin to reduce CRC incidence or mortality.[10]

This is a departure from the 2016 USPSTF guidelines, which recommended low-dose aspirin for primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year risk of CVD, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.[11]

However, in the UK The National Institute for Health and Care Excellence (NICE) now recommends that people with the inherited genetic condition Lynch Syndrome should consider taking daily aspirin for more than two years to prevent CRC.[12]

The NICE advice is based on the CAPP2 study, led by Professor Sir John Burn from Newcastle University, which showed that patients with Lynch Syndrome who received aspirin had a significant decrease in CRC compared with those who took a placebo. This benefit took more than five years to become detectable but persisted for up to 20 years.[13]

While there's little doubt aspirin benefits people with Lynch Syndrome, the challenge remains of identifying Lynch Syndrome carriers from within the general population and relaying the message that they should be on aspirin providing they have been assessed by a medical professional. In the future the use of aspirin for primary prevention is likely to be focussed on people considered at high risk of developing cancer based on genetic, clinical and life-style factors.

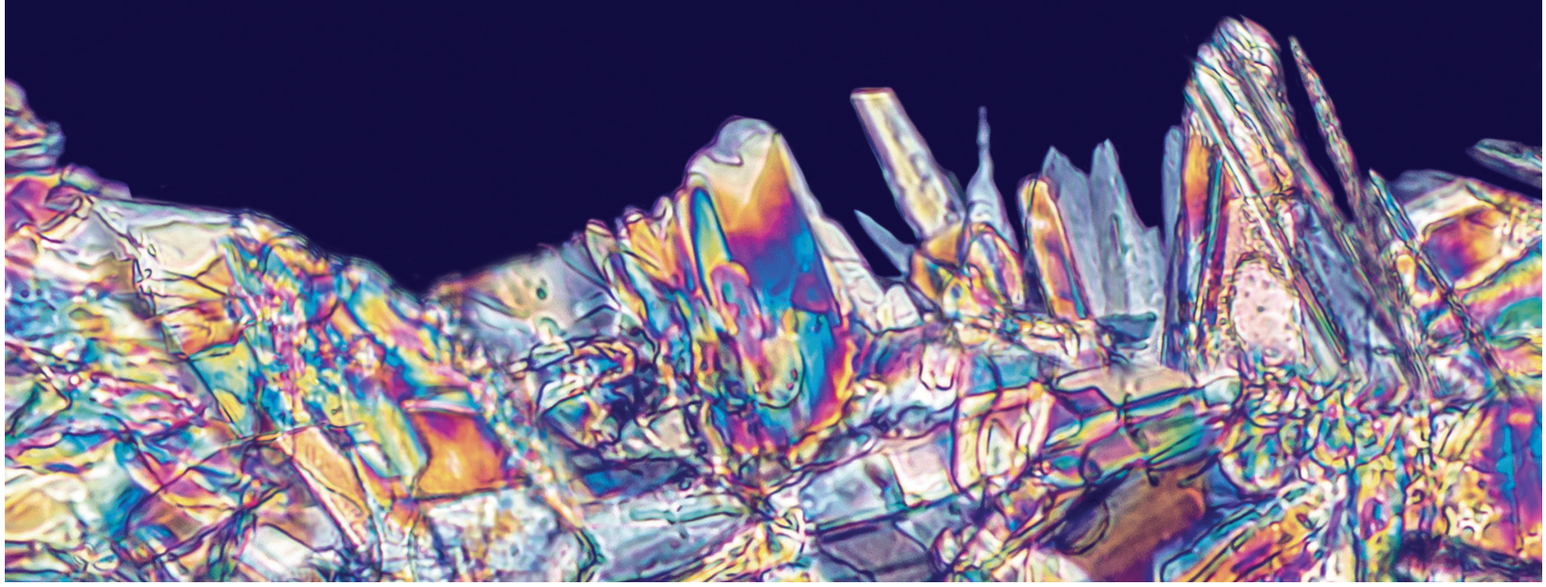
What are the potential mechanisms of action for aspirin in cancer?

Of particular importance to both its CVD and cancer indications is aspirin's ability to irreversibly inhibit platelet COX-1 preventing platelet activation during the remaining lifespan of the platelet. Platelets play a role in inducing epithelial-mesenchymal transition (EMT), the process that allows circulating tumour cells to invade local tissues distant from their original site. From the Add-Aspirin trial we have some interesting data showing that platelet activation is higher than expected in individuals who have recently had a cancer diagnosis and treatment. It's a plausible hypothesis that inhibition of platelet activation explains (or at least partly explains) aspirin's anti-cancer effects.

Why are you such an aspirin fan?

I'm interested in drug repurposing i.e. investigating whether medicines that have been developed and used for one clinical indication might also be useful in other disease areas. Aspirin is a very good example of a repurposed drug. It was first developed as a painkiller but has been used widely for over 30 years as a CV drug, and we're now investigating whether it might be useful as a treatment for cancer.

The case for repurposing is that new drugs are very expensive and hence have limited global impact, at least initially. The biggest rise in cancer is in low- and middle-income countries, so if we have an affordable repurposed drug that can be used across the globe there is potential for a large impact.



What's happening next with Aspirin and cancer?

We're involved in The Aspirin for Cancer Prevention (AsCaP) collaboration, again funded by Cancer Research UK, which has been set up to better understand the role aspirin can play in preventing cancer. The collaboration, which is led by Professor Jack Cuzick from Queen Mary University, London, involves a range of international researchers undertaking complementary research.

All of us are looking at the mechanisms by which aspirin could exert its anti-cancer effects so we can identify which patients will be most likely to benefit from aspirin.

Tell us a surprising fact about aspirin?

There is a rose named 'Aspirin', developed to mark the occasion of the 100th anniversary of the invention of aspirin. Again, quite fortuitously I spotted it in a garden centre and it grows very well in my garden. At first it blooms white, and as the weather cools the centre of the flower changes to a subtle pink.

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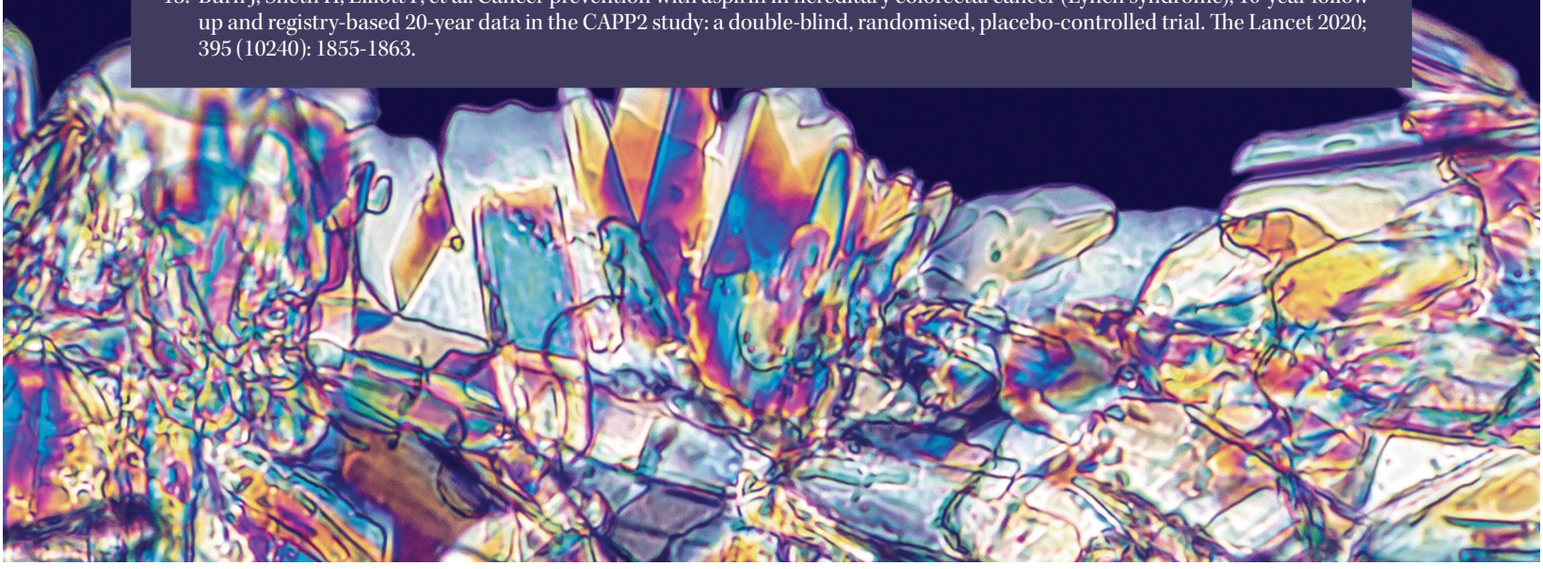
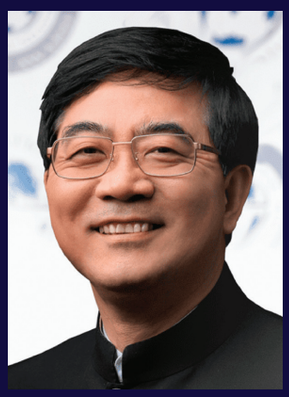




Professor Junbo Ge

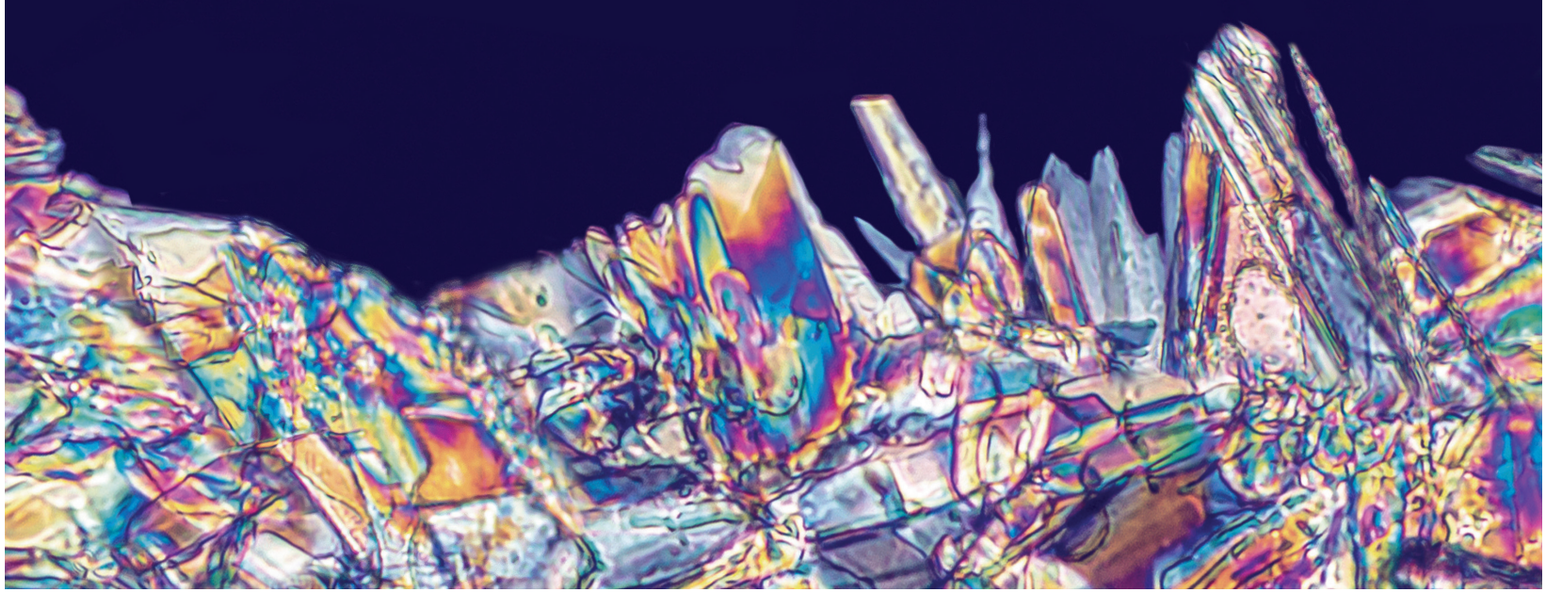
Aspirin Tributes

Junbo Ge, received his doctorate from University Mainz, Germany, in 1993. In 1995, he was appointed Director of the Intravascular Ultrasound lab at the Department of Cardiology, University Essen, Germany. In 1999, Prof. Ge returned to China where he was appointed Co-Director of the Department of Cardiology at Zhongshan Hospital, Fudan University, Shanghai.

Prof. Ge is a member of the Chinese Academy of Sciences; Director of the Department of Cardiology, Zhongshan Hospital, Fudan University; Chairman of Shanghai Cardiovascular Clinical Centre ;Chairman of Shanghai Institute of Cardiovascular Diseases; Dean of Institutes of Biomedical Sciences, Fudan University; and Chairman of National Clinical Research Centre for Interventional Medicine.

He is also President of Chinese College of Cardiovascular Physicians; President of The Chinese Cardiovascular Association; Past President of Chinese Society of Cardiology (2015-2018); International Governor of American College of Cardiology; Board Member of World Heart Federation; and Daniel L. Macken Visiting Professor at Columbia University, New York.

Prof. Ge has not only achieved great success in clinical and scientific research,

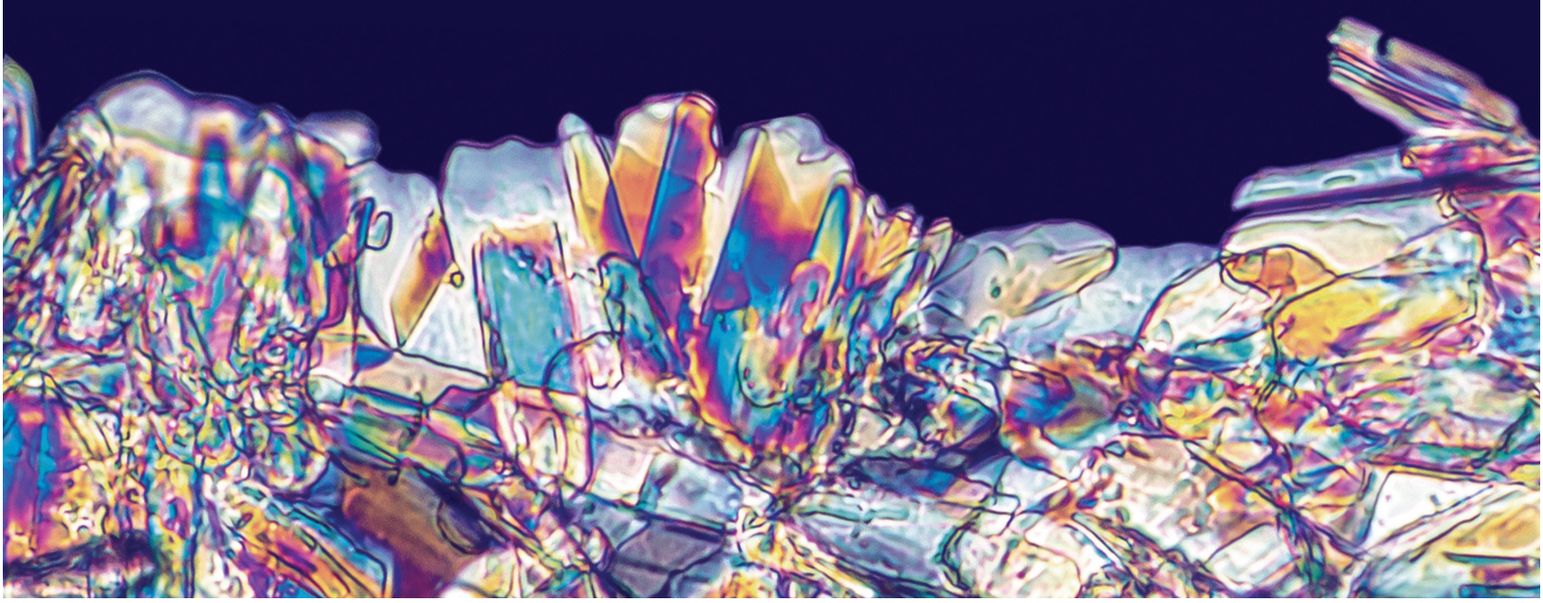


but also had wide experience in writing textbooks and editing journals. He has been responsible for over 120 international and national scientific research projects, published more than 500 papers in international peer reviewed journals, edited 22 books (one published abroad) and co-edited more than 20 monographs and textbooks.

He is also the Deputy Editor of International Journal of Cardiology; Deputy Editor of Herz; , Editor-in-Chief of Cardiology Plus; Chief Editor of Textbook of Internal Medicine (8th and 9th editions); Chief Editor of Practical Internal Medicine (15th edition); and on the editorial board of many international academic journals.

Prof. Ge has long been involved in cardiovascular disease (CVD) research and interventional cardiology. In 2005, he created the retrograde wire technique (which has since become the routine approach for coronary total occlusion) and undertook the first live demonstration of the retrograde wire technique in the world. Later he modified the retrograde wire technique with AGT(Active Greeting Technique) which made the procedure easier and faster. Together these techniques have greatly improved the success rate of coronary total occlusion procedures. Furthermore, he has developed and patented many innovative devices including biodegradable polymer (DES), As2O3 drug coated stent, and Valve Clamp (a transapical mitral valve repair device). In 1999, he implemented the 'green channel' treatment concept for acute myocardial infarction (MI) which has been incorporated into China's chest pain treatment system, organised by China Chest Pain Center, which covers around 4000 hospitals in China. Implementation of this system has been responsible for saving the lives of millions of cardiac MI patients throughout China.

He has undertaken hundreds of coronary intervention live transmissions to international meetings (such as TCT, Euro-PCR, CCT), and national meetings, and been invited to more than 20 countries including Indonesia, Kazakhstan, Kyrgyzstan, Bangladesh, India, Japan, Korean, Singapore, South Africa, India, and the Philippines. to perform live interventions. Under Prof. Ge's leadership, CCA has established close relationships with most of the international cardiovascular societies and 38 well-known medical centres.



Who is your aspirin hero?

I propose two names. The first is Chen Haozhu (1924-2020), who was my mentor and encouraged me to study cardiology in Germany. Chen, who worked at the Shanghai Medical University, is credited with pioneering modern cardiology in China. As Editor in Chief of 'The Practice of Internal Medicine', the textbook for Chinese medical students, he was able to spread the word about the antiplatelet effects of aspirin in secondary coronary artery disease (CAD) prevention.

The second is Xiaoying Li, who retired last year from her post as Chief of Cardiology at The People's Liberation Army General Hospital, Beijing. After finding some patients experienced bleeding from aspirin, Xiaoying embarked on a quest to find the best aspirin dose for different types of patients. To decide on the optimum dose for individuals she took into account factors such as age, gender, body weight and comorbidities (e.g., heart and renal failure). To extend her reach to local doctors, who don't often get the opportunity to attend academic meetings, she published a brochure explaining how to adapt aspirin doses for different patients.[2]

Tell us a surprising fact about aspirin.

In China and Japan, where people tend to have much lower body weights than in the West, aspirin is manufactured in tablets of 25 milligrams (as opposed to 75 milligrams in the West). We took the decision to make smaller tablets to avoid complications like bleeding . If people need higher doses, we just increase the number of tablets prescribed to suit individual patient requirements.

How is aspirin used in China?

Before 1978 virtually no one suffered myocardial infarction (MI) in China, due to the fact that the population was poor and ate peasant style diets that were high in fibre and low in fat. However, since then we have seen an explosion of heart attacks caused by atherosclerosis due to people adopting Western diets that are high in fat. In 1990, ischemic heart disease was the seventh leading cause of life lost, but by 2010 it had jumped to number two.[3]

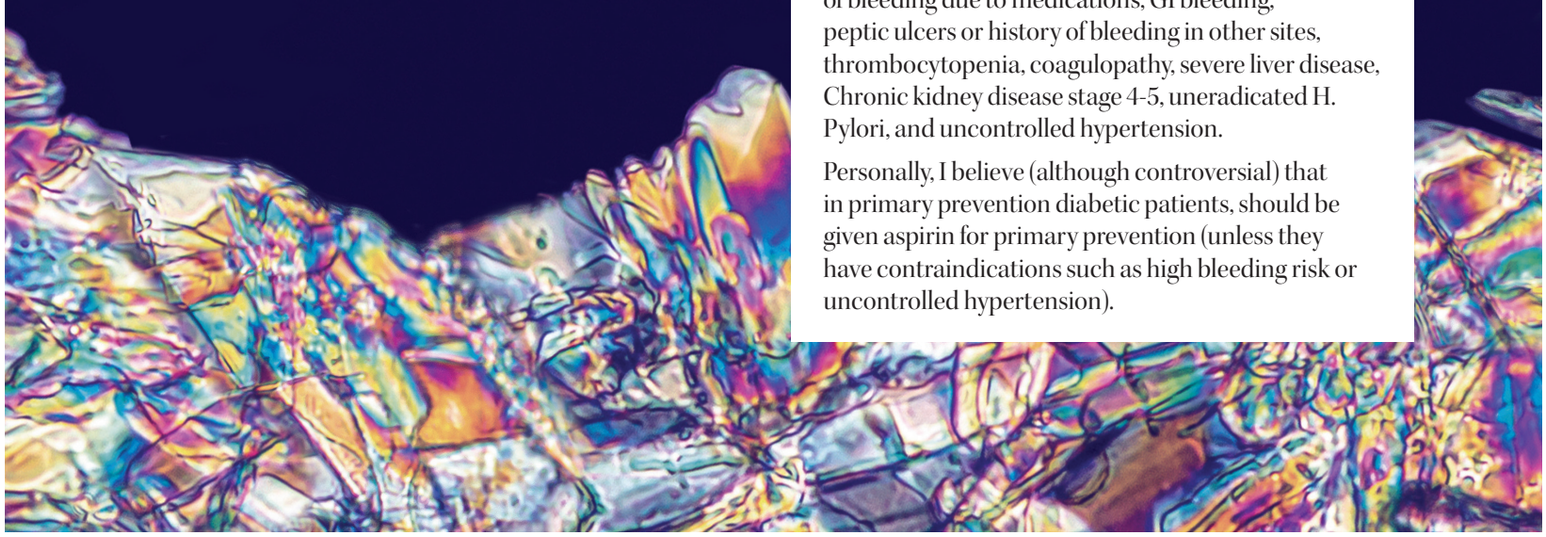
Risk scores suggest that among Chinese adults 33% of men and 28% of women have a 10-year risk of fatal cardiovascular disease (CVD) ≥ 10%, a figure considered among the highest in the world.[4]

In the 1990s we came to the idea that aspirin could be used as an antiplatelet to eliminate thrombus formation. In China, guidelines advocate using aspirin for both primary and secondary prevention. The 2019 Chinese expert consensus recommends that high risk people use aspirin for primary prevention in clearly defined patient populations. The consensus states that people who should consider taking low-dose aspirin (75-100 mg/day) for primary CVD prevention are adults aged 40-69 years if 10-year expected risk of ASCVD is ≥10 % for in initial risk assessment and with three or more major risk factors that remain poorly controlled or difficult to change after treatment interventions (e.g., family history of early onset CVD).[5]

The Chinese consensus places great emphasis on risk assessment, identifying measures to take before prescribing low-dose aspirin in primary CVD prevention. These incude assessing the risk/ benefit ratio and excluding those with a high risk of bleeding, reducing risk by identifying and treating H. pylori and considering use of prophylatic PPI or H2 receptor antagonists.

Populations not recommended low-dose aspirin for primary CVD prevention are those < 40 years or ≥ 70 years, and people whose bleeding risk is assessed greater than their thombosis risk. Additional categories excluded include those at higher risk of bleeding due to medications, GI bleeding, peptic ulcers or history of bleeding in other sites, thrombocytopenia, coagulopathy, severe liver disease, Chronic kidney disease stage 4-5, uneradicated H. Pylori, and uncontrolled hypertension.

Personally, I believe (although controversial) that in primary prevention diabetic patients, should be given aspirin for primary prevention (unless they have contraindications such as high bleeding risk or uncontrolled hypertension).



If you could do one study with aspirin, what would it be?

In China, family meals often involve each person using chopsticks to select food from a common dish. The downside of this traditional way of eating is the spread of Helicobacter pylori (H. pylori), an infection initiating local inflammation that can result in higher risks of bleeding if people take aspirin. I'd like to do an endoscopic study of patients who have suffered stomach bleeds after undergoing coronary artery stenting to explore whether they've been infected with H.pylori. If we can establish a link, patients could be tested for H.pylori prior to undergoing percutaneous coronary interventions (PCIs), and if an infection is found be prescribed a proton pump inhibitor (PPI). A meta-analysis, involving 10 trials, demonstrated that GI bleeding was reduced in patients taking aspirin by prescribing a PPI in comparison to placebo (OR 0.27).[6]

With emergency procedures like PCI, PPIs offer a more pragmatic approach than eradicating H.pylori with antibiotics. Although the two methods prevent aspirin associated GI bleeding by approximately the same amount, antibiotics take two to four weeks to work. Such time frames obviously aren't feasible when patients have suffered an MI and require emergency PCI.

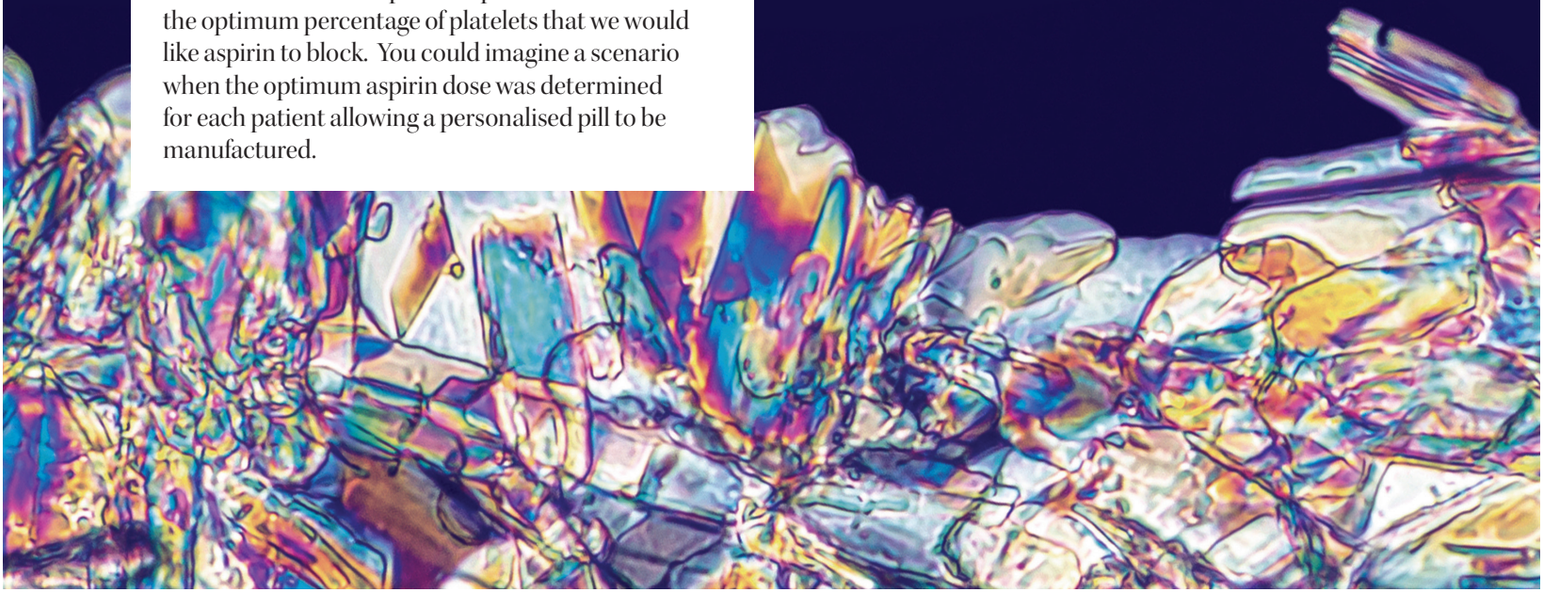
What does the future hold for aspirin in cardiology?

Personalised dosing. We need to consider why some patients experience bleeding and others don't. We should take a big data 'approach to identify which dose is most appropriate for individual patients. The information that needs to be analysed relates to genetics, but also to other factors such as the patient's renal function. Ultimately, we might be able to test the function of individual patient's platelets to determine the optimum percentage of platelets that we would like aspirin to block. You could imagine a scenario when the optimum aspirin dose was determined for each patient allowing a personalised pill to be manufactured.

Why are you such a big aspirin fan?

In the last few years, the contribution made by aspirin, one of our oldest pharmaceutical agents, to CV medicine has been nothing short of extraordinary. It has prevented literally millions of deaths worldwide. I see aspirin as absolutely fundamental to the secondary prevention of MI, following an MI. Benefits are seen not only with MI, but also with stroke and peripheral artery disease (PAD).

Benefits were clearly demonstrated in the ISIS 2 study involving 17,187 patients from 417 hospitals enrolled within 24 hours after onset of suspected acute MI and randomized to receive: (i) a 1-hour intravenous infusion of 1.5 MU of streptokinase; (ii) one month of 160 mg/day enteric-coated aspirin; (iii) both treatments; or (iv) neither. ISIS II showed that one month of low-dose aspirin started immediately after MI in 1000 patients would prevent 25 deaths and 10 to 15 nonfatal infarcts and strokes.[7]



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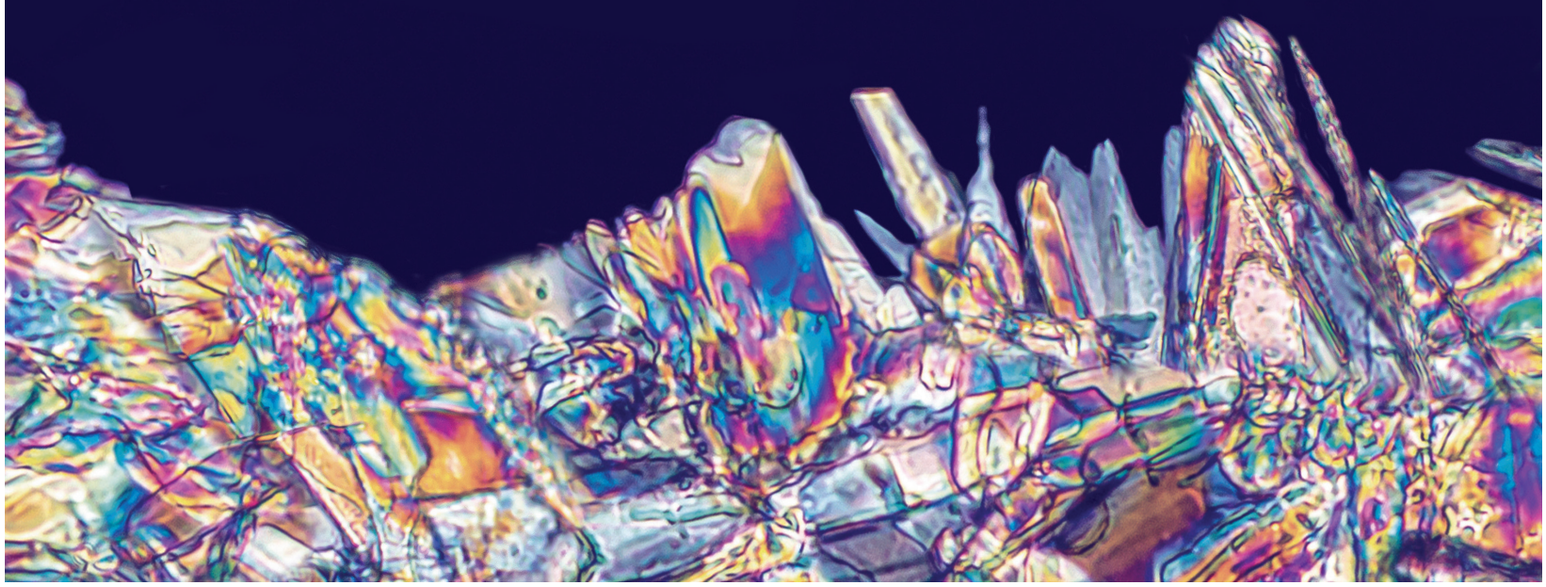


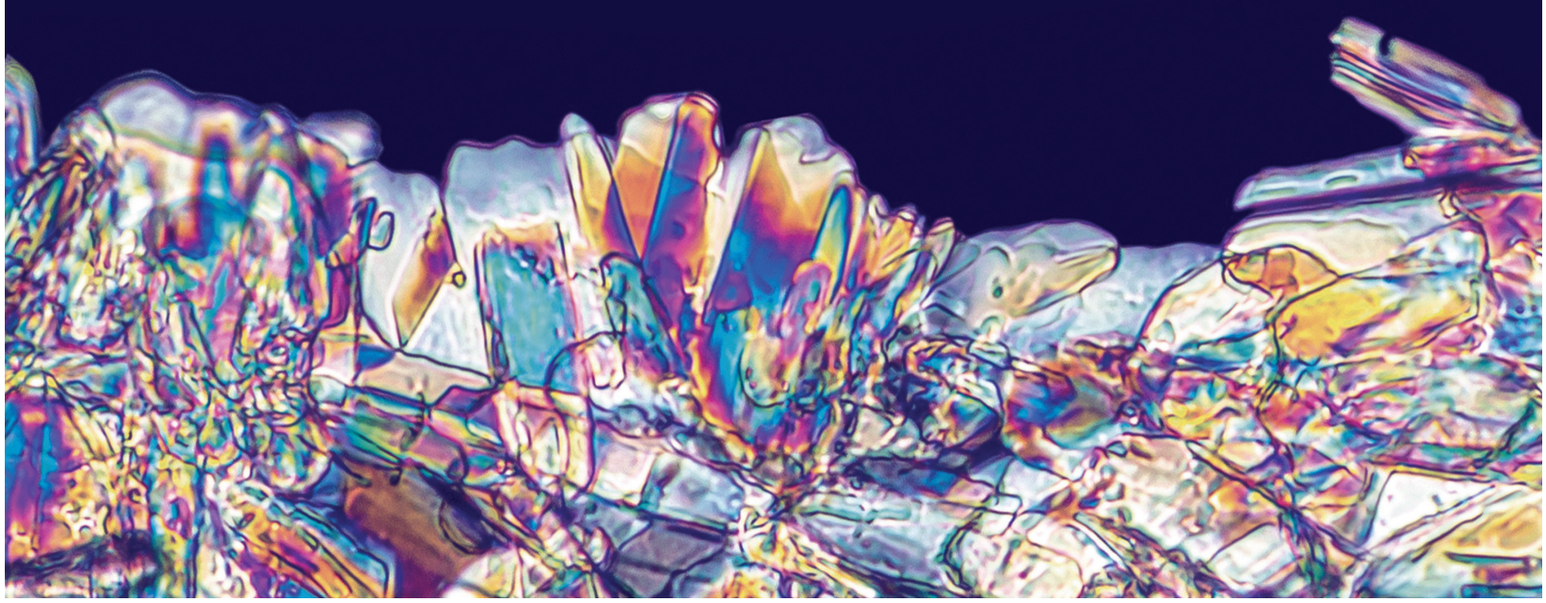
Dr Elisa Llurba

Aspirin Tributes

Elisa Llurba is a maternal and foetal medicine specialist at University hospital Sant Pau, Barcelona, with an interest in preeclampsia, intrauterine growth restriction and foetal loss. After a PhD exploring oxidative stress as a mechanism behind endothelial damage in preeclampsia, Elisa became interested in prediction and using aspirin as a preventive strategy to manage development of preeclampsia.

Elisa has undertaken studies exploring use of biomarkers to identify women at risk of developing preeclampsia and a meta-analysis showing the combination of aspirin with low molecular weight heparin is more effective than aspirin alone for preventing preeclampsia in high-risk women.

She is now involved in a range of studies exploring aspirin, including giving it to women undergoing Invitro Fertilization (IVF) prior to implantation and to women who suffered preeclampsia to see if it benefits their long-term cardiovascular (CV) health.



What is preeclampsia?

Preeclampsia, affecting 2 to 8% of all pregnancies, represents one of the world's leading causes of maternal and perinatal morbidity and mortality.[1] Statistics from the World Health Organization (WHO) for 2014 showed that globally preeclampsia was associated with 76 000 maternal and 500 000 infant deaths.[2]

Preeclampsia is a multisystem disorder of pregnancy, usually defined as hypertension and proteinuria diagnosed after 20 weeks of gestation, occurring in women whose blood pressure was previously in the normal range. We still don't really understand why preeclampsia occurs. Current theories include pathogenesis being due to release of anti-angiogenic factors into the maternal circulation, causing systemic inflammation and oxidative stress. This in turn affects the endothelium throughout the mother's body, ultimately resulting in preeclampsia. We now know that the problem starts early in pregnancy when there is an impairment in remodelling of the spiral arteries in the uterus and placental dysfunction. Overall, these changes, lead to higher resistance to placental blood flow, and ultimately reduced blood flow to the foetus.

For mothers complications include seizures (eclampsia), cerebral ischemia, kidney and/or liver failure, pulmonary oedema, and low levels of platelets leading to disseminated intravascular coagulation. For babies, the disorder can lead to intrauterine growth restriction, hypoxia, and being born early with all the complications that prematurity entails. Additionally, we're now becoming aware how preeclampsia can increase the risk of both mother and baby developing cardiovascular disease (CVD) in later life.[3]

Preeclampsia can have devastating consequences. Overnight pregnant women go from a 'happy place' anticipating the birth of their baby to being in ICU fearing for the life of their unborn child. The best scenario is that they have a preterm baby, the worst is that they lose the pregnancy or even die themselves. After such harrowing experiences, many women are often too traumatised to consider subsequent pregnancies.

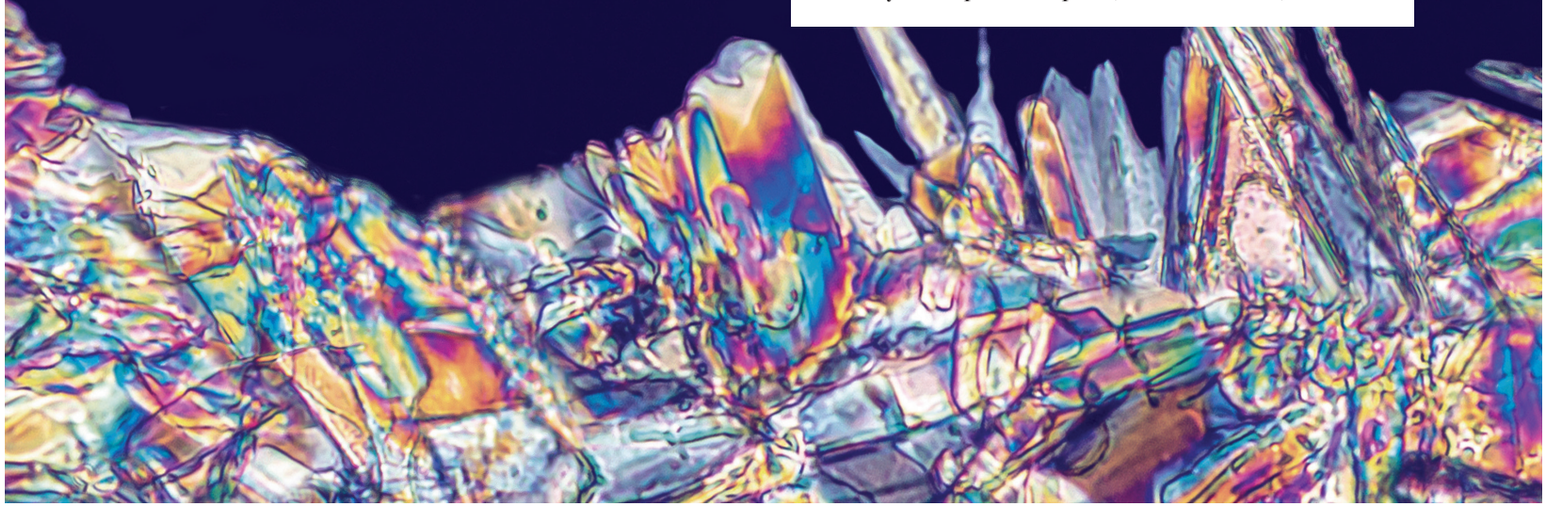
How has management of preeclampsia evolved?

The only cure for preeclampsia is for women to give birth as soon as possible because once the placenta is removed symptoms clear. However, a recent advance has been our ability in the first trimester to predict which women are likely to develop preeclampsia later in their pregnancy. Algorithms have been developed using combinations of maternal characteristics, biophysical markers (mean arterial blood pressure and mean uterine artery pulsatility index) and biochemical markers which can identify 80%–90% of pregnant women who would go on to develop preeclampsia without treatment.[4,5]

The PROGNOSIS study,[6] which I was involved with, established that the ratio of soluble fms-like tyrosine kinase 1 to placental growth factor levels was an effective biomarker for predicting preeclampsia. Using ratios above 38 as our cut-off, we were able to demonstrate a positive predictive value for preeclampsia development within four weeks of 36.7% and more importantly, the negative predictive value was 98% at week one and 95% at week four. The result is that we're now able to distinguish with a high sensitivity and specificity which women need to be admitted to hospital (or have close follow-up) to avoid maternal and foetal complications from those who can be reassured about the condition and sent home.

What role can aspirin play in preeclampsia?

For women found to be at high-risk of developing preeclampsia we now give 150 mg aspirin daily from 12 weeks to 36 weeks gestation. This practice is based on the ASPRE trial,[7] by Kypros Nicolaides, from King's College, London. ASPRE, which randomised 1776 women at high-risk for preeclampsia to 150 mg of aspirin (from 11-13 weeks' gestation until 36 weeks) or placebo, showed that in the aspirin arm there was a 62% reduction in incidence of preterm eclampsia (before 37 weeks) and 82% reduction in the incidence of early onset preeclampsia (before 34 weeks).



Who is your aspirin hero?

Emmanuel Bujold, from Université Laval, Quebec, Canada, is my hero because he created order from the chaos of the early preeclampsia and aspirin studies. Without Emmanuel's visionary work it's doubtful that anyone would still be using aspirin to prevent preeclampsia.

In 1979 an observational study had first shown that women who took aspirin regularly during pregnancy were less likely to develop preeclampsia than women who did not.[8] In the subsequent decades, studies investigated low dose aspirin (50 to 150 mg per day) for preventing preeclampsia. However, the difficulty here was lack of unity between the studies – they used different criteria for diagnosing preeclampsia, involved heterogenous groups of patients with hypertension as well as preeclampsia, and made no distinction between women starting treatment before and after 16 weeks gestation. The result was that in a meta-analysis there was only found to be a marginal benefit (10% reduction),[9] leading to the dismissal of aspirin as being of limited use in preeclampsia.

Emmanuel sorted out the confusion by undertaking a meta-analysis only including studies involving low dose aspirin started before 16 weeks.[10] He also considered patients in separate groups according to whether they had severe or mild preeclampsia. It's telling that out of 352 studies reviewed for the meta-analysis, only four (involving 392 women) met his strict criteria.

Results showed when compared with controls, aspirin started at <16 weeks was associated with a significant reduction in severe (relative risk: 0.22, 95% CI: 0.08 to 0.57) but not mild (relative risk: 0.81, 95% CI: 0.33 to 1.96) preeclampsia. From this, Emmanuel concluded that severe and mild preeclampsia have different pathophysiologies and that only severe preeclampsia is susceptible to the benefits of aspirin.

Everything changed with the publication of this paper. It really opened our eyes to the possibility of using aspirin in preeclampsia, and led my other hero, Kypros Nicolaides, to undertake the definitive ASPRE study[7] (see earlier) demonstrating that preeclampsia can be avoided by taking aspirin. Above anyone, Kypros can be credited with establishing our modern approach to treating preeclampsia with aspirin.

Why are you such a big aspirin fan?

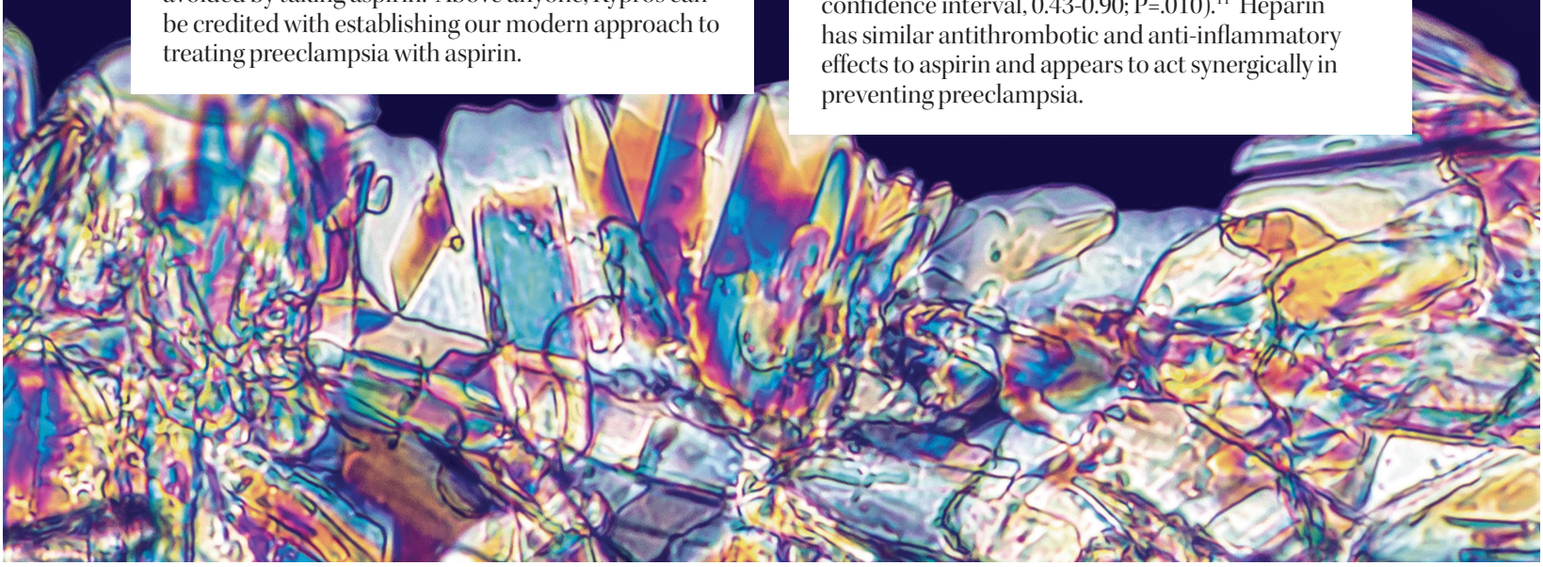
To me, the way aspirin has helped pregnant women avoid the devastation of preeclampsia has been nothing short of a miracle. In recent years aspirin has been responsible for one of the biggest reductions in maternal and foetal mortality ever. In fact, aspirin has proved so successful at preventing preeclampsia that we now struggle to find enough women with the condition to recruit to our clinical trials!

I've always supported the concept of prevention over cure, and to my mind aspirin represents the most important preventive drug in the history of medicine. I love the way aspirin can be used to avoid the development of a range of conditions including CVD, cancer, and preeclampsia. I think the reason for its wide-ranging effects comes down to the way aspirin tackles inflammation, a common root pathway for so many different pathologies.

I also like the fact aspirin is so cost effective and can be used in low-income countries where treatment resources are scarce. While it's unlikely health services in developing countries have the funds for preeclampsia screening, it would be cost effective for them to prescribe aspirin, a drug with few side effects, to all pregnant women as a precautionary measure to avoid preeclampsia. Although of course further studies would be needed in these settings to confirm this hypothesis.

What studies have you undertaken with aspirin?

I've been interested in exploring whether we can improve aspirin benefits in preventing preeclampsia. This year I published a meta-analysis, involving 2795 pregnant women from 15 studies, which found that adding low molecular weight heparin to aspirin was more effective than aspirin alone in preventing preeclampsia development (odds ratio, 0.62; 95% confidence interval, 0.43-0.90; P=.010).[11] Heparin has similar antithrombotic and anti-inflammatory effects to aspirin and appears to act synergically in preventing preeclampsia.



What studies are you now undertaking with aspirin and preeclampsia?

I'm interested in exploring whether giving aspirin prior to invitro fertilization (IVF) could improve the odds of achieving a successful pregnancy. In theory, aspirin given prior to pregnancy might have several benefits including preventing thrombosis, improving the microcirculation and maternal endothelium, and reducing inflammation and oxidative stress.

In our study, which started in early 2021, we are randomising women on our IVF waiting list to six months of aspirin or a placebo prior to implantation. As well as looking at outcomes such as achieving successful pregnancy, we'll also be following up women for preeclampsia as there have been observations women undergoing IVF are more prone to developing the condition. Ultimately, we want to see if aspirin taken prior to pregnancy makes a difference to the course of pregnancy and both maternal and foetal CV health.

I'm also got funding for a cohort study to explore the long-term health consequences of preeclampsia. I hope to enrol four thousand women to gain new insights into how aspirin might mitigate the long-term consequences of preeclampsia.

Are there any other studies you would like to do in aspirin?

The current practice is to discontinue aspirin at 36 weeks due to the possibility of bleeding risks associated with delivery. However, because most preeclampsia occurs after 36 weeks it's likely to be beneficial for women to continue taking aspirin right up to the time of the birth. I'd therefore like to perform a study randomising women at risk of preeclampsia into two groups, one treated with aspirin up to 36 weeks and the other up to delivery. The study would show whether the strategy of continuing aspirin could reduce incidence of late onset preeclampsia and whether there are any adverse effects.

Tell us a surprising fact about aspirin.

Our bodies appear to have circadian rhythms influencing the effectiveness of aspirin. People who take aspirin at bedtime, as opposed to in the morning, get better protection from heart attacks and strokes, and greater reductions in blood pressure, plasma renin activity and cortisol excretion compared to those taking it in the morning. Potential explanations for this effect include the possibilities that aspirin is better absorbed by the gastrointestinal tract at night, and that aspirin taken at bedtime is better placed to attenuate morning peaks of platelet reactivity. Whatever the reason, this appears to be a real effect and we routinely advise pregnant women at risk of preeclampsia to take aspirin at night.

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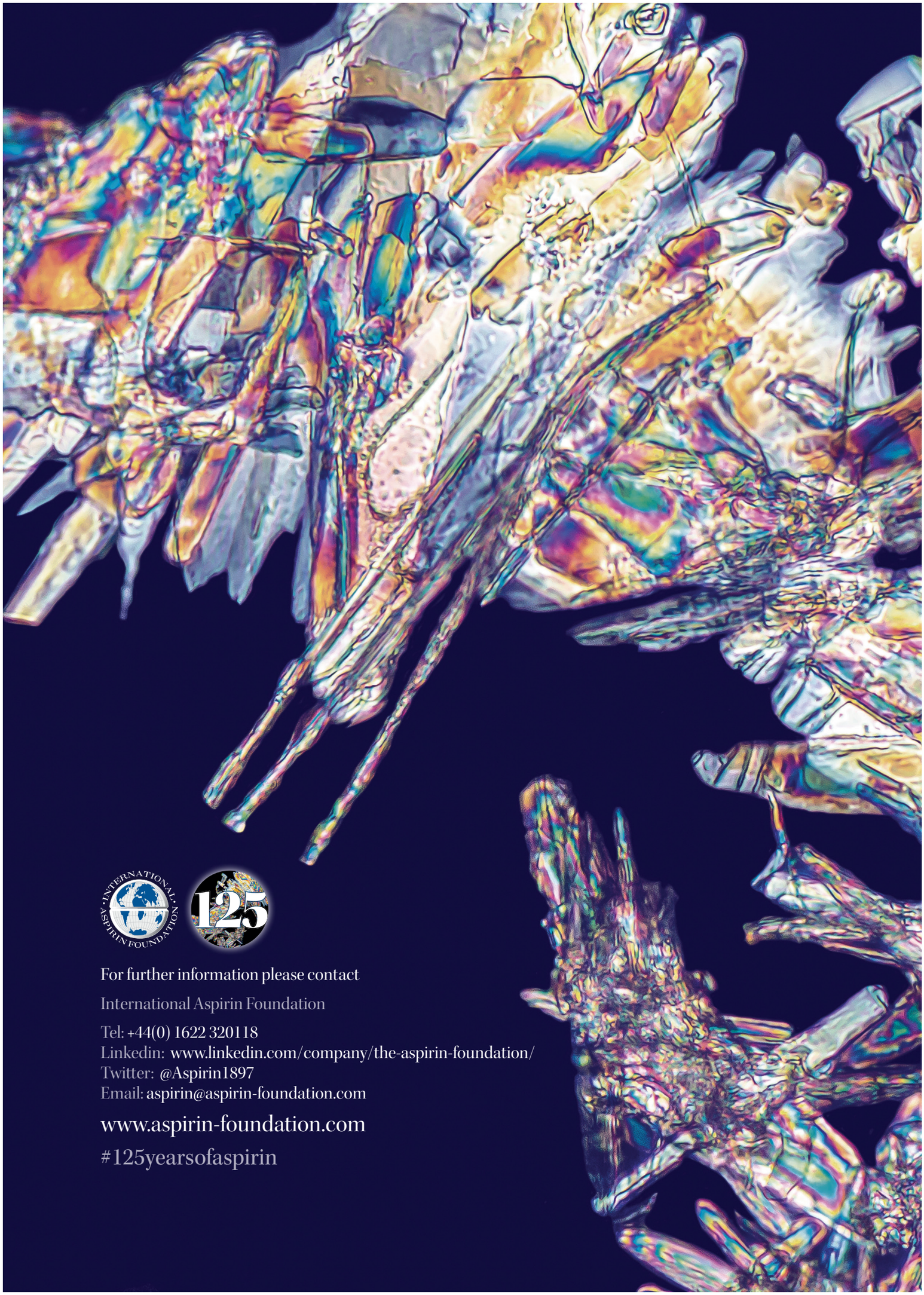

For further information please contact

International Aspirin Foundation

Tel: +44(0) 1622 320118
Linkedin: www.linkedin.com/company/the-aspirin-foundation/
Twitter: @Aspirin1897
Email: aspirin@aspirin-foundation.com

www.aspirin-foundation.com

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