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'.

INTERNATIONAL ASPIRIN FOUNDATION

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Celebrating the 125th anniversary of the synthesis of acetylsalicylic acid

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.

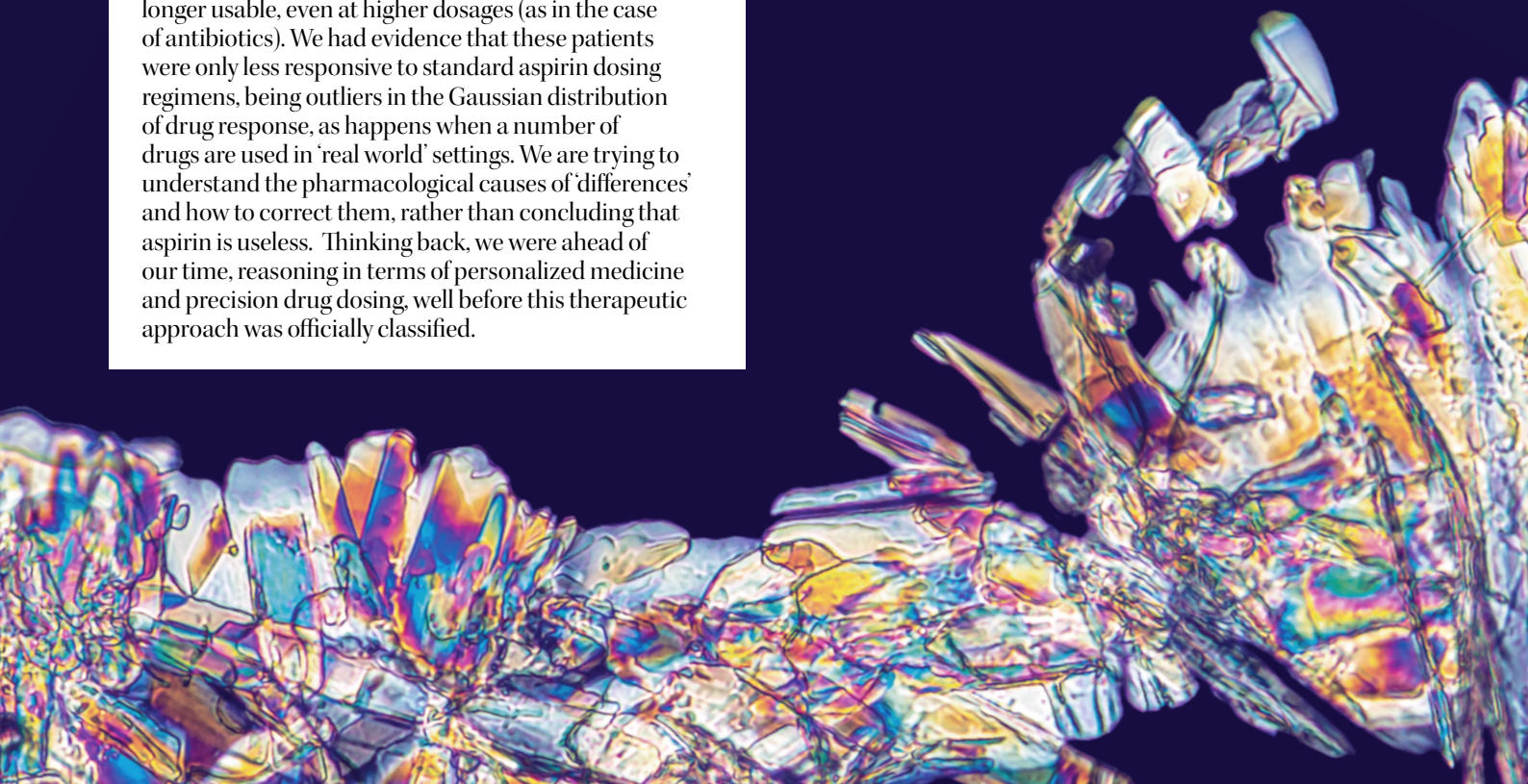
I've been interested in Essential Thrombocythemia (ET), a myeloproliferative neoplasm, as a paradigm to study how platelet turnover impacts aspirin responsiveness. Estimates suggested that up to 50% of ET patients experience a thrombotic events (including MI, ischemic stroke, transient ischemic attack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

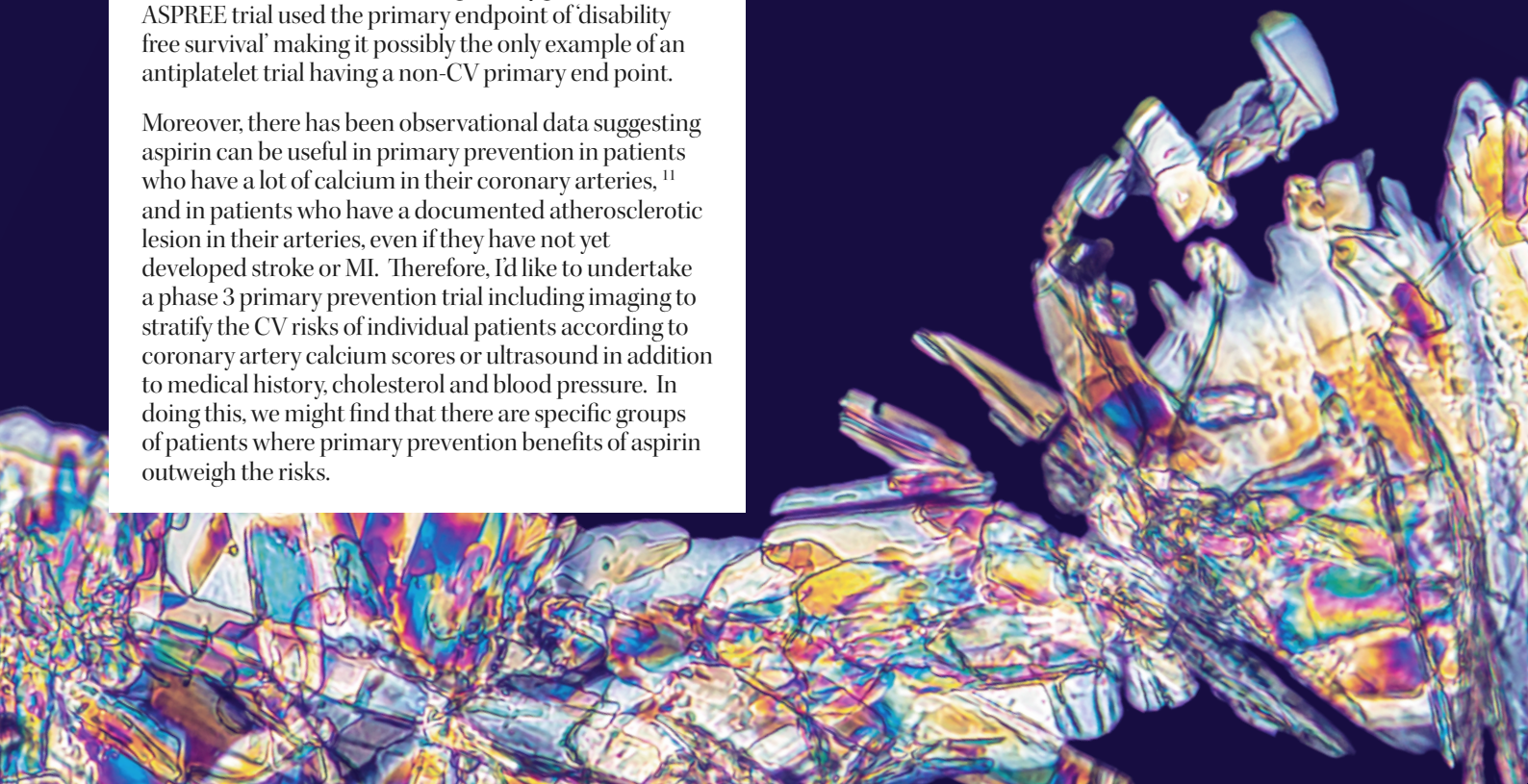
Moreover, there has been observational data suggesting aspirin can be useful in primary prevention in patients who have a lot of calcium in their coronary arteries, [11] and in patients who have a documented atherosclerotic lesion in their arteries, even if they have not yet developed stroke or MI. Therefore, 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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