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.

INTERNATIONAL ASPIRIN FOUNDATION

125

Celebrating the 125th anniversary
of the synthesis of acetylsalicylic acid

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]

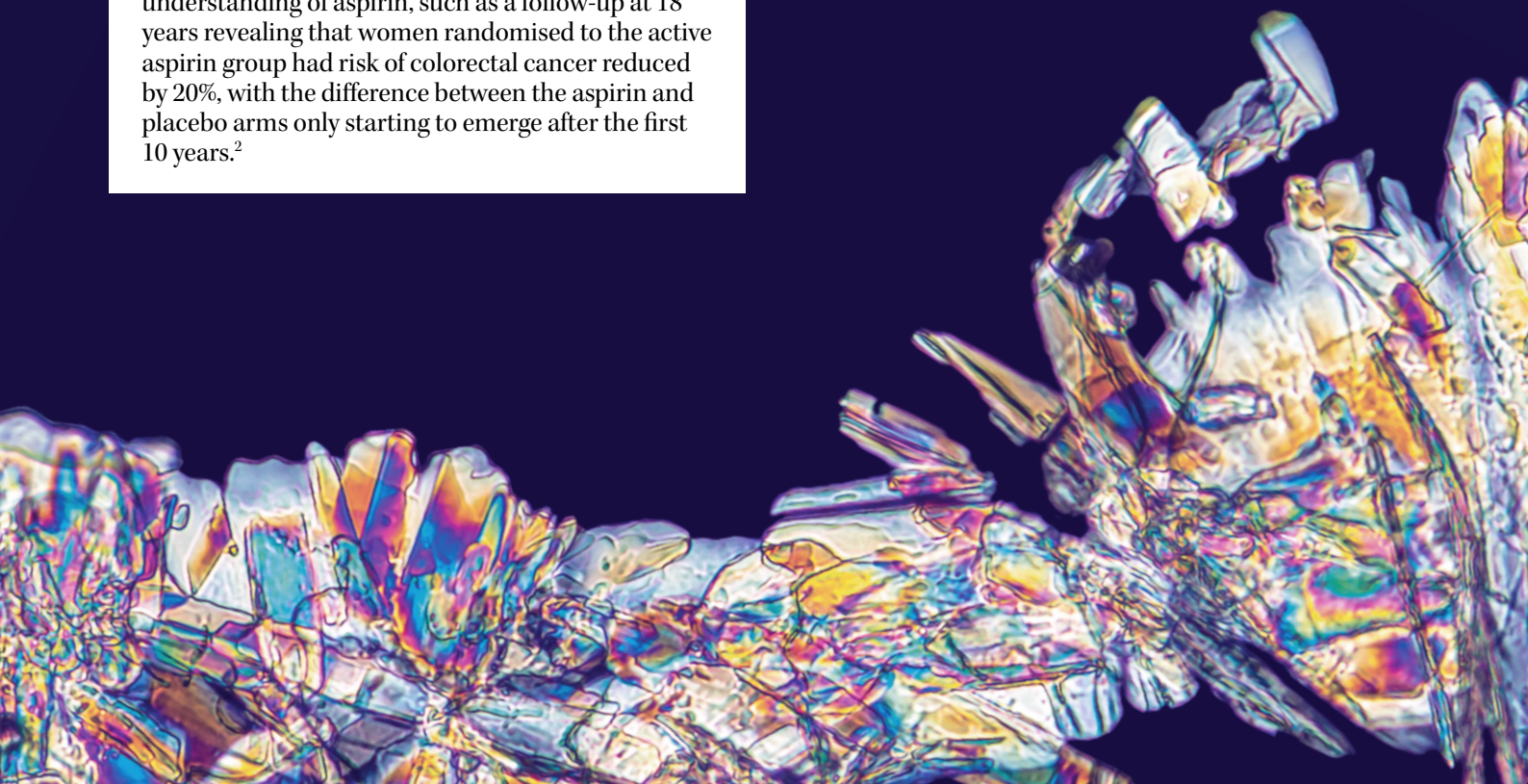
What role does aspirin have to play in the primary prevention of CVD?

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.

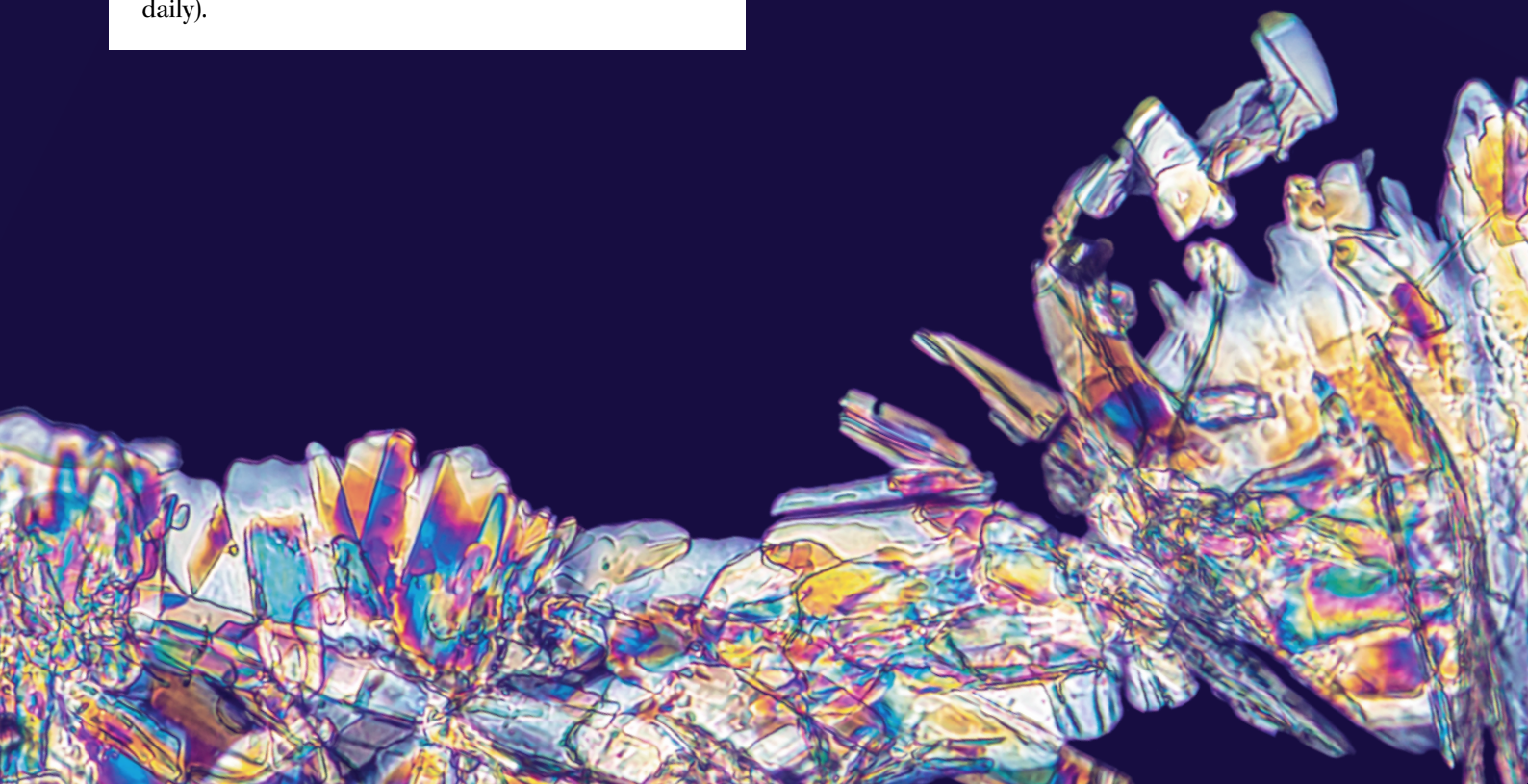
In patients with DM, besides the deleterious effects associated with insulin resistance, an array of mechanisms exist to enhance platelet reactivity including increased synthesis of Thromboxane A2 (TXA2), a potent platelet activator. With this in mind, low-dose aspirin can be used to inhibit platelet 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?

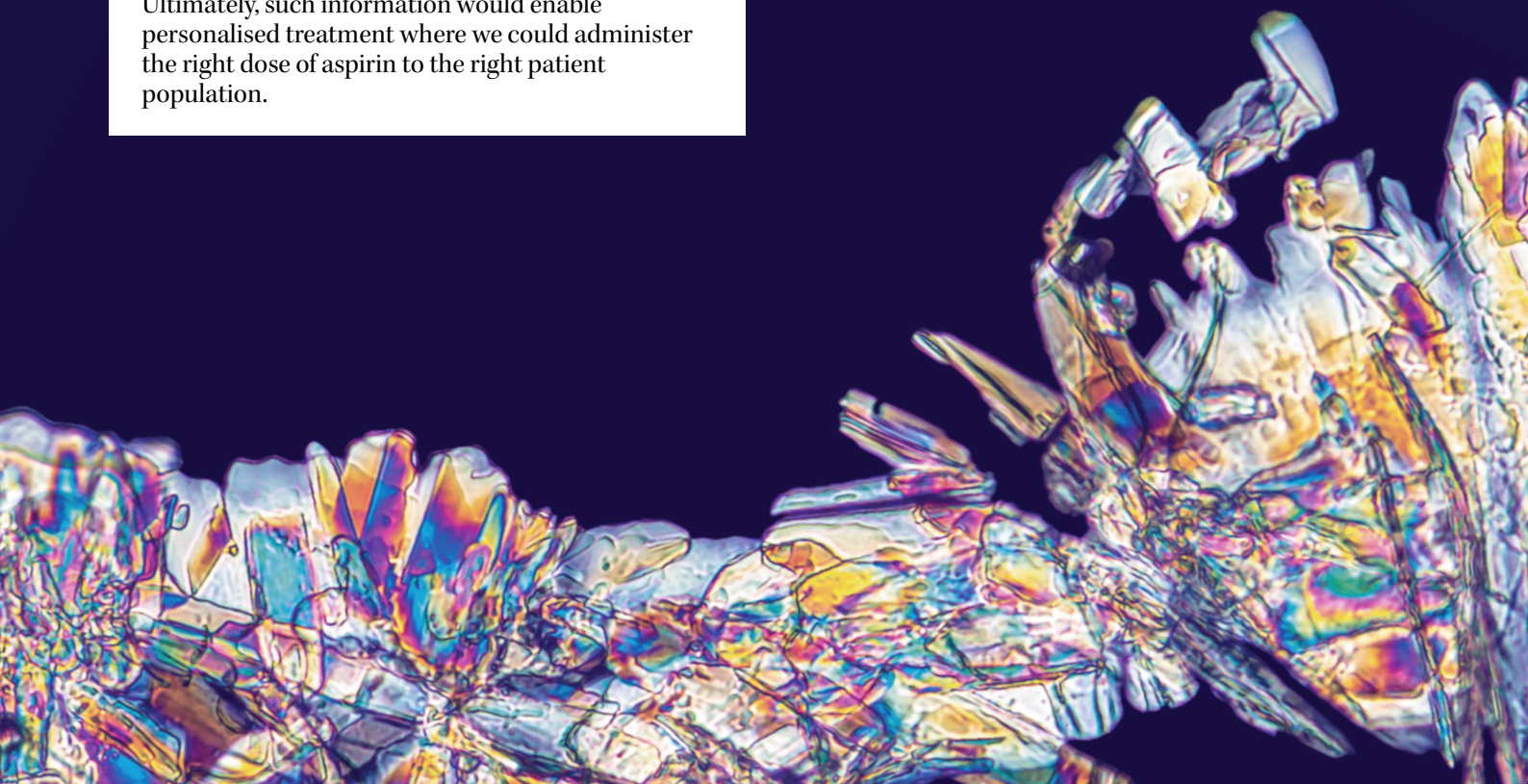
I'm a basic science/translational researcher and would like to increase understanding of links between aspirin and arachidonic acid. We know that aspirin blocks the enzyme cyclooxygenase, involved in converting arachidonic acid to prostaglandins. So, the question arises - what are the multiple down-stream 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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