Aspirin, which has just celebrated its 111th anniversary, remains one of the most widely used antiplatelet agents worldwide (1). Its high efficacy has made aspirin the cornerstone of treatment in patients suffering from cardiovascular diseases; indeed, daily aspirin therapy reduces the risk of stroke, myocardial infarction and death by approximately 25% (2). Early investigation into aspirin’s pharmacology revealed an asymmetry between its pharmacokinetics and pharmacodynamics (3). Despite aspirin’s short half-life in blood of approximately 30 minutes, once daily aspirin administration in doses as low as 40 mg per day has been shown to induce cumulative, profound and sustained inhibition of platelet function (4). Moreover, there is no clear evidence to suggest that doses higher than 100 mg daily increase aspirin’s anti-thrombotic efficacy, whereas the bleeding risk associated with taking aspirin appears to be dose-dependent (2). For this reason, a fixed regimen of once daily low-dose aspirin has been adopted into all relevant treatment guidelines.

While it is true in most cases that an aspirin a day keeps the doctor away, it would also appear that not all patients benefit from the drug to the same extent as others (5). In this issue of Thrombosis and Haemostasis, Henry et al. have explored whether once daily low-dose aspirin provides sustained inhibition of platelet function throughout the 24-hour dosing interval in 150 stable coronary artery disease (CAD) patients (6). The major finding of the study is that in up to 25% of patients, platelets recover their ability to aggregate within 24 hours of the last aspirin dose, thus potentially leaving patients unprotected against thrombotic events at the end of the dosing interval (6). The study leaves the reader with a number of unanswered questions: (a) what are the underlying mechanisms leading to this uncharacteristically fast recovery of platelet function in some CAD patients taking aspirin daily; and (b) what can be done about it?

To answer the first question, one must first consider whether this phenomenon is substantiated. In this regard, it is interesting to note that this is not the first report of significant recovery of platelet function within 24 hours of aspirin administration. Perney et al. have shown in healthy volunteers that platelets can recover their ability to aggregate within 24 hours of various doses of aspirin ranging from 37.5 mg to 960 mg (7). Recovery of platelet function was also shown in stable CAD patients in a small series of 11 patients on daily aspirin therapy (8). Thus, the study by Henry et al. confirms and extends these findings to a larger CAD population. Taken together, these studies suggest that while aspirin is effective in inhibiting platelet aggregation within one hour of administration (thus eliminating the most common causes of a lack of platelet inhibition by aspirin, such as non-compliance, reduced aspirin bioavailability, and drug interactions), this inhibition is not sustained for the whole dosing interval in certain individuals. This of course begs the question why.

Aspirin inhibits platelet aggregation by irreversibly acetylating a key enzyme in the conversion of arachidonic acid into thromboxane (Tx) A2, namely cyclooxygenase (COX)-1 (9). Because the platelet pool is replenished at a rate of 10–15% per day and 20–30% of uninhibited platelets are required to ensure normal haemostasis (9), administration of a low dose of aspirin once a day is normally sufficient to overcome replenishing of the platelet pool by normal platelet turnover (4). It is therefore an appealing hypothesis that premature recovery of platelet function in CAD patients taking aspirin daily may be due to enhanced platelet turnover.

Although the study by Henry et al. (6) did not explore the underlying mechanisms of accelerated platelet function recovery, there is increasing evidence that enhanced platelet turnover may indeed play a role. Perhaps the most convincing evidence comes from research on patients suffering from essential thrombocythemia (ET), a disease characterised by high platelet generation. In this natural model of enhanced thrombopoiesis, Dragani et al. have shown TxA2 production to be markedly higher 12–18 hours after aspirin dosing in ET patients than in healthy controls treated with the same dose of aspirin (10). Most importantly, in vitro addition of aspirin almost completely abolished platelet TxA2 formation in ET patients, suggesting that aspirin is indeed effective in this population, but once-daily aspirin dosing may be insufficient to counteract the very high platelet turnover (10). Whether a similar mechanism could account for accelerated platelet function recovery in CAD patients can only be hypothesised, but Grove et al. have already demonstrated that CAD patients have significantly higher levels of new, reactive platelets than healthy controls (11). The same group has further explored in 177 CAD patients whether enhanced platelet turnover influenced the efficacy of aspirin to inhibit platelet aggregation (12). Those pa-
patients in whom platelet aggregation was least inhibited by aspirin had the highest immat-ure platelet counts, suggestive of enhanced platelet turnover (12). The same has been shown in patients receiving dual antiplatelet therapy consisting of aspirin and clopidogrel, which suggests that increased platelet turnover may explain less than ideal platelet inhibition by both drugs (13).

Thus, we are left with the question of what can be done in these patients. A reason-
able treatment strategy to mitigate the effect of enhanced platelet turnover would be to increase aspirin dosing frequency, as has been suggested by many of the investiga-
gators cited above (7, 8, 10, 12). Is there any evidence for this to be useful? An inking that it might be comes from studies on pa-
thents suffering from diabetes, another clinical condition characterised by en-
hanced platelet turnover. Rocca et al. have studied 100 diabetic patients taking aspirin daily and divided the population into ter-
tiles of platelet function recovery within the standard 24-hour dosing interval (14). Those patients with substantial recovery of platelet function within 24 hours of aspirin administration were randomised to receive aspirin 100 mg once daily, 100 mg twice daily or 200 mg once daily. While simply increasing the daily dose of aspirin reduced recovery of platelet function to some ex-
tent, increasing the dosing frequency of aspirin to twice daily almost completely abol-
ished platelet function recovery in this group of patients (14). These findings were supported by results from a study by Spectre et al. who have shown in 25 patients suffering from diabetes with vascular comp-
ications that administration of 75 mg aspirin twice a day resulted in a significant decrease in whole blood platelet aggre-
guration compared with 75 mg or 320 mg once daily aspirin therapy (15), thus strengthening the case that this might be a viable treatment option.

Nonetheless, a word of caution is in order. Although the hypothesis suggested in the accompanying article by Henry et al. and others that enhanced platelet turnover overcomes sustained platelet inhibition by aspirin over the standard dosing interval of 24 hours is biologically plausible and intel-
lectually appealing, it is important to note that no prospective and adequately powered
study has so far shown this to be the case. Whether this lack of persistence of platelet inhibition by aspirin during the standard 24-hour dosing regime has any clinical im-
lication also remains to be demonstrated, as is the clinical benefit of increasing the dosing frequency to twice daily. Whether this increase in anti-thrombotic potency will be offset by an increase in bleeding de-
serves further consideration. Thus, a study in a large cohort of CAD patients on daily low-dose aspirin therapy undergoing serial platelet function testing to evaluate whether increased platelet turnover truly correlates with recovery of platelet func-
tion within 24 hours of aspirin administra-
tion, and whether randomisation to twice daily therapy is clinically beneficial, appears justified. Indeed, the value (and variability) of some platelet function assays have been debated (16–18), as have various mechanisms to explain aspirin responsive-
ness, both acutely and chronically (19, 20). Only after large prospective studies, can indi-
vidualisation of aspirin therapy based on the rate of platelet turnover become part of routine clinical practice.

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