Can we improve the efficacy of low-dose aspirin?

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Platelets provide primary haemostasis, but also play important roles in the development of atherothrombosis, resulting in stroke and acute coronary syndromes. Cardiovascular events remain the number one cause of death worldwide, and antiplatelet therapy is a cornerstone in the prevention and treatment of cardiovascular disease. At the turn of its 115th anniversary, aspirin remains one of the most widely used antiplatelet drugs. Still, treatment with aspirin continues to spark debate on well-known topics such as optimal dosing to optimise the benefit-risk ratio, the suggested presence of aspirin “low-responders” and its role in combination antithrombotic therapy after coronary stenting. An interesting study presented by Bonten et al. (1) in this issue of Thrombosis and Haemostasis highlights another important, but so far unexplored topic: the optimal timing of once-daily aspirin intake.

Aspirin has a short plasma half-life of only 20 minutes, yet once daily intake of aspirin doses as low as 40 mg prevents atherothrombotic events through cumulative inhibition of platelet aggregation (2). Accordingly, daily low-dose aspirin (75–150 mg) is recommended in patients at risk of first-time or recurrent cardiovascular events (3, 4). Aspirin is usually taken on awakening, although evidence regarding the optimal timing of intake is lacking.

Platelet aggregation shows some circadian rhythm with a morning peak that coincides with the well-known morning peak of myocardial infarction (5, 6). Consequently, there is an interest in this biological variation both to explain the phenomenon and to develop new therapeutic strategies. Due to its short half-life, only platelets circulating at the time of aspirin intake are inhibited and, therefore, aspirin-induced platelet inhibition may depend on the timing of aspirin intake. The clinical message from the study by Bonten et al. (1) is that taking aspirin at bedtime instead of in the morning may reduce the risk of cardiovascular events in the morning.

This message is based on the presumptions that 1) platelet aggregation is higher in the morning and that 2) the platelet inhibitory effect of aspirin is not sustained during the usual 24-hour (h) dosing interval. Evidence supporting a circadian platelet rhythm mainly comes from platelet function studies of healthy, untreated individuals (7–9), whereas evidence of increased platelet aggregation at the end of the 24-h dosing interval with aspirin arises from studies in patients with coronary artery disease (10–12). Interestingly, a circadian variation with higher gastric mucosal resistance in the evening has also been reported (13), which may help to avoid unfavourable discontinuation of low-dose aspirin (14).

Several mechanisms likely contribute to platelet hyperreactivity during treatment with antiplatelet drugs (15). With respect to aspirin, insufficient platelet inhibition may in part be explained by its short half-life and the fact that new platelets produced by megakaryocytes are continuously released into the blood from the bone marrow (16). Indeed, as many as 10^11 platelets are produced every single day, and in vitro experiments using mixtures of aspirin-free and aspirin-treated platelets have shown that full aggregation is observed with only a few percent of aspirin-free platelets present (17). The low number of uninhibited platelets needed to induce considerable platelet aggregation likely rely on the ability of new platelets to release thromboxane A2, thus triggering aggregation of the total platelet pool. This hypothesis is in accordance with previous work of FitzGerald et al. who as early as 1983 showed that both thromboxane metabolites and platelet aggregation progressively recovered within 24 h upon administration of a thromboxane synthase inhibitor (18), and similar findings were reported in recent studies after administration of aspirin (10, 19).

Bearing these results in mind, the results presented by Bonten et al. may not be overwhelmingly surprising, but still deserve considerable attention owing to the simple but elegantly designed study (1). In a randomised open-label cross-over trial, the authors investigated the hypothesis that intake of low-dose aspirin at bedtime may attenuate the morning peak of platelet aggregation. Using this dosing strategy, cyclooxygenase (COX)-1-dependent platelet reactivity in the morning was reduced by intake of aspirin at bedtime compared with on awakening.

Irreversible COX-1 inhibition by aspirin normally compensates for the short half-life, but renewal of the drug target shortens the duration of COX-1 inhibition and may even dictate new dosing strategies particularly in patients with accelerated platelet turnover, such as essential thrombocythaemia (20) or diabetes mellitus (11, 21). Several studies have explored the potential benefit of increased aspirin doses or twice-daily dosing, with the former strategy being suboptimal. Thus, it has previously been shown that even 960 mg of aspirin is not able to fully inhibit platelet aggregation through 24 h (22), whereas twice-daily, low-dose aspirin administration results in greater platelet inhibition than a once-daily regimen (18, 19, 23, 24). Importantly, subtle diurnal differences in COX-1 inhibition may be dwarfed by the fact that thromboxane A2 plays a limited role overall.
in platelet reactivity and even complete COX-1 inhibition often may be inadequate to prevent atherothrombotic events, as demonstrated by the importance of effective P2Y_{12} inhibition, in addition to COX-1 inhibition, in preventing cardiovascular events.

The study by Bonten et al. was performed on a relatively small number of healthy volunteers, and one may speculate if similar findings would have been obtained in a clinical setting of aspirin-treated patients with coronary artery disease. This should be investigated, but since platelet turnover is slightly higher in patients with coronary artery disease (25), one would expect that a similar – or even higher – benefit of bedtime aspirin dosing would be observed. More evidence lending support to clinical implications of Bonten’s findings comes from the Physicians’ Health Study, a randomised, double-blind, placebo-controlled trial of alternate-day aspirin (325 mg) intake among 22,071 male physicians. During a five-year follow-up period, aspirin reduced the incidence of non-fat fatal myocardial infarction by 59% during the morning hours, compared with a 34% reduction for the remaining hours of the day (26).

Accordingly, aspirin intake abolished the circadian variation and morning peak of infarctions.

Daily low-dose aspirin is strongly recommended for all patients with cardiovascular disease, but platelet inhibition with once-daily aspirin declines through 24 h, and the optimal dosing strategy remains unknown. The pharmacodynamic study by Bonten et al. provides a rational basis for clinical trials assessing the efficacy and safety of a novel dosing strategy that may improve the efficacy of low-dose aspirin.

Conflicts of interest
Erik L. Grove has received speaker honoraria from AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Pfizer and Sysmex and has participated in advisory board meetings for AstraZeneca, Bayer and BMS. Robert F. Storey has received research grants from AstraZeneca, Eli Lilly/Daiichi Sankyo, and Merck; research support from Accutemetics; honoraria from AstraZeneca, Eli Lilly/Daiichi Sankyo, Merck, NOvartis, Sanofi-Aventis, Accutemetics, and Medscape; consultancy fees from AstraZeneca, Daiichi Sankyo, Merck, Novartis, Accutemetics, Regeneron, Roche, Correvio, and The Medicines Company. Steen D. Kristensen has received speaker honoraria from AstraZeneca, Eli Lilly, Sanofi, and The Medicines Company, and research support from AstraZeneca.

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