Prevention of cardiovascular events with antiplatelet treatment: does time of intake matter for aspirin and ADP receptor blockers?

Dirk Sibbing1,2,*; Lisa Gross1,3; Dániel Aradi3,4
1Department of Cardiology, University Hospital of Ludwig-Maximilians-University, Munich, Germany; 2DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany; 3Department of Cardiology, Heart Center Balatonfüred, Hungary; 4Heart and Vascular Center, Semmelweis University, Budapest, Hungary

Summary
Long-term evidence supports a clustering of cardiovascular events in the early morning. Several studies have shown that platelet hyper-reactivity to various stimuli is also present at this period of the day. However, the idea of treatment strategies reflecting the circadian variation in platelet reactivity has been largely neglected so far, and this is true despite the huge number of patients being treated with these drugs. Some pharmacodynamic data suggest that early-morning platelet hyper-reactivity may be overcome by shifting aspirin intake to the bedtime. However, there is lack of evidence whether shifting the time of intake or splitting the daily dose of P2Y12-inhibitors with a regular QD dosing (clopidogrel or prasugrel) to the evening would be effective to overcome platelet hyper-reactivity or to suppress the excess of cardiovascular events observed during morning hours. Further research is warranted to clarify whether such a simple and costless effort like dose shifting or splitting may be beneficial to prevent cardiovascular events.

Keywords
ADP receptors, antiplatelet agents, clinical trials, antiplatelet drugs, platelet pharmacology

Introduction
It is a well-recognised phenomenon that the occurrence of adverse cardiovascular events follows some circadian variation with a peaking of events during the early morning hours (1). This interesting observation was first discovered some decades ago, and as outlined in ▶Table 1, numerous other clinical studies or post-hoc analyses of randomised clinical trials have confirmed a higher rate of ischaemic events in the (early) morning hours (1–13). Many potential mechanistic causes behind this phenomenon have been hypothesised; one of these is a circadian variation in platelet aggregability, which was first described by Tofler et al. in 1987 (14) and has been the subject of several subsequent studies (for an overview of mechanistic studies see ▶Table 2) (14–21).

According to the practice in numerous landmark trials and according to current guidelines (22), a dual antiplatelet therapy consisting of aspirin and an adenosine diphosphate (ADP) P2Y12 receptor inhibitor represents the standard of care in patients with an acute coronary syndrome (ACS) and in patients undergoing percutaneous coronary intervention (PCI). For these antiplatelets, a delayed onset of action, the phenomenon of inter-individual drug response variability and the fact that some patients do not show an adequate response to these drugs have been the subject of numerous experimental and clinical studies in recent years (23). In contrast, however, the idea of treatment strategies reflecting the circadian variation in platelet reactivity has been largely neglected so far, despite the huge number of patients being treated with these drugs. Nevertheless, the time of drug intake could matter for both aspirin and P2Y12-inhibitors.

Aspirin
The cyclooxygenase 1 (COX-1) inhibitor acetylsalicylic acid, commonly referred to as aspirin, is still considered as the cornerstone of antiplatelet treatment to prevent adverse cardiovascular events across a broad spectrum of cardiovascular morbidities including coronary artery disease (CAD). Current ESC guidelines (22) recommend a maintenance dose of 75–100 mg daily, usually taken as one tablet per day in the morning and thereby reflecting the irreversible nature of COX-1 inhibition by aspirin. However, solid evidence with respect to the optimal timing or a splitting of the dose for a twice-daily (BD) intake is lacking so far. While large-scale clinical trials are missing, numerous smaller studies have provided interesting results with respect to the antiplatelet action of aspirin over time. In 150 patients with CAD, Henry et al. have shown that...
the drug itself, with a once daily intake, does not provide a stable 24-hour (h) platelet inhibition but shows a steady increase of platelet aggregation and thromboxane A₂ levels over time and after the last aspirin intake (24). Several other studies reported insufficient platelet inhibition by low dose aspirin at the end of the dosing interval as well (25–29). A recent study by Christensen et al. in 47 patients with CAD and type 2 diabetes suggested that diurnal platelet reactivity may be particularly important in patients with

Table 1: Clinical studies and the morning peak of ischaemic events.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Event</th>
<th>Key results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller et al. (2)</td>
<td>1987</td>
<td>2203</td>
<td>Cardiac death</td>
<td>Increased incidence between 7 and 11 AM</td>
</tr>
<tr>
<td>Willich et al. (3)</td>
<td>1987</td>
<td>429</td>
<td>Sudden cardiac death</td>
<td>Peak incidence from 7 to 9 AM</td>
</tr>
<tr>
<td>Pelte et al. (4)</td>
<td>1998</td>
<td>99</td>
<td>Myocardial ischaemia</td>
<td>Increased incidence between 6 AM and noon</td>
</tr>
<tr>
<td>ISIS-2 Collaborative Group (1)</td>
<td>1992</td>
<td>12,163</td>
<td>Myocardial infarction</td>
<td>Increased incidence between 8 and 11 AM</td>
</tr>
<tr>
<td>Mahmoud et al. (7)</td>
<td>2011</td>
<td>124</td>
<td>Definite stent thrombosis</td>
<td>Peak of early stent thrombosis at 7 AM</td>
</tr>
<tr>
<td>Mogabgab et al. (8)</td>
<td>2012</td>
<td>35,492</td>
<td>ACS</td>
<td>No morning peak in patients with chronic kidney disease</td>
</tr>
<tr>
<td>Mogabgab et al. (9)</td>
<td>2013</td>
<td>13,608</td>
<td>Transient ischaemia</td>
<td>Increased incidence between 10 PM and 8 AM</td>
</tr>
<tr>
<td>Mogabgab et al. (10)</td>
<td>2013</td>
<td>45,218 (National Cardiovascular Data Registry)</td>
<td>ACS</td>
<td>No morning peak.</td>
</tr>
<tr>
<td>Kanth et al. (11)</td>
<td>2013</td>
<td>519</td>
<td>ACS</td>
<td>Morning peak at 11:30 AM</td>
</tr>
<tr>
<td>Patton et al. (12)</td>
<td>2014</td>
<td>811</td>
<td>Definite stent thrombosis</td>
<td>No morning peak. Nadir from 12 AM to 6 AM</td>
</tr>
<tr>
<td>Ruwald et al. (13)</td>
<td>2015</td>
<td>1,790</td>
<td>ACS</td>
<td>No morning peak.</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome, STEMI = ST-segment elevation myocardial infarction.

Table 2: Mechanistic studies on circadian variations in platelet aggregation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of subjects</th>
<th>Parameter</th>
<th>Key results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofler et al. (14)</td>
<td>1987</td>
<td>15</td>
<td>Platelet aggregability (ADP, epinephrine)</td>
<td>Increasing platelet aggregability between 6 and 9 AM</td>
</tr>
<tr>
<td>Jafri et al. (15)</td>
<td>1992</td>
<td>9</td>
<td>Platelet function (beta-thromboglobulin, platelet factor 4)</td>
<td>Peak at 3 PM, lowest between 7 and 8 AM</td>
</tr>
<tr>
<td>Dalby et al. (16)</td>
<td>2000</td>
<td>15</td>
<td>Platelet aggregation (ADP, epinephrine)</td>
<td>Peak at 5 PM</td>
</tr>
<tr>
<td>Sawada et al. (17)</td>
<td>2002</td>
<td>24</td>
<td>Platelet sensitivity to NO</td>
<td>Increase in non-smokers between 9 AM and noon</td>
</tr>
<tr>
<td>Scheer et al. (18)</td>
<td>2010</td>
<td>12</td>
<td>Platelet aggregation</td>
<td>Peaks at noon and 11 PM</td>
</tr>
<tr>
<td>Henry et al. (24)</td>
<td>2011</td>
<td>150</td>
<td>Platelet aggregation (LTA)</td>
<td>Once daily aspirin does not provide stable 24-h antiplatelet protection</td>
</tr>
<tr>
<td>Scheer et al. (19)</td>
<td>2011</td>
<td>12</td>
<td>Platelet activation (platelet surface activated glycoprotein Iib-IIia, GPIb and P-selectin, platelet count, ATP release, aggregability, plasma epinephrine)</td>
<td>Peak for platelet surface activated glycoprotein Iib-IIia, GPIb and P-selectin, platelet count, ATP release, aggregability, plasma epinephrine between 3 and 8 PM</td>
</tr>
<tr>
<td>Kozinski et al. (20)</td>
<td>2011</td>
<td>59</td>
<td>Platelet inhibition by clopidogrel</td>
<td>Lowest at 10 AM</td>
</tr>
<tr>
<td>Bonten et al. (21)</td>
<td>2014</td>
<td>14</td>
<td>COX-1 dependent platelet activity</td>
<td>Morning increase reduced by intake of aspirin at bedtime compared with on awakening</td>
</tr>
<tr>
<td>Christensen et al. (29)</td>
<td>2015</td>
<td>47</td>
<td>Platelet aggregation (Multiplate)</td>
<td>Patients with coronary artery disease and type 2 diabetes had increased platelet aggregation at the end of the 24-hour aspirin dosing interval</td>
</tr>
</tbody>
</table>

ADP = adenosine diphosphate, COX-1 = cyclooxygenase 1, LTA = light transmission aggregometry, NO = nitric oxide.
diabetes mellitus (29). Partly, production of new platelets may account for the insufficient platelet inhibition by low-dose aspirin at the end of the dosing interval. Since the provided platelet inhibition by aspirin is not stable over time and there is a peak in early-morning platelet reactivity, prior studies suggested that aspirin should be administered during the evening rather than in the morning (30). Just recently, in a randomised controlled cross-over study, Bonten et al. (21) reported on the impact of timing of aspirin intake (bedtime vs on awakening) on markers of platelet reactivity in healthy subjects (n=14). Key results of the study were that COX-1 dependent platelet reactivity markers were lower during the early morning hours, considered as the most vulnerable phase for the occurrence of cardiovascular events, when aspirin was taken at bedtime instead of awakening (21). Based on their results, the authors suggested taking low-dose aspirin at bedtime. Interestingly, a study by Perneby et al. in 15 healthy volunteers suggests that the impact of timing of aspirin intake cannot be overcome by using higher QD doses of aspirin, as once daily dosing in the morning was associated with considerable recovery of arachidonic acid induced platelet aggregation after 24 h, even after 960 mg aspirin (25). In addition, a large randomised clinical trial (CURRENT OASIS 7) (31) showed no clinical benefit regarding ischaemic events when high-dose aspirin was used in patients with an ACS. Instead, there was a higher risk for gastrointestinal bleeding. Although the morning peak phenomenon is considered a matter of fact based on prior reports, we need to highlight that not all studies found an increase in COX-1-dependent platelet reactivity; this may be in part due to methodical heterogeneities in platelet function assessment (20). Finally, it is also unknown whether a morning peak in platelet reactivity is only a “bystander” or is in "cause-effect relation" with higher incidence of cardiovascular events. Since a prior study (14) showed lack of morning peak in subjects remaining supine and inactive, it is plausible that sympathetic activation may be an important, common pathway towards higher occurrence in cardiovascular events and increased platelet activity via α₁-adrenergic stimulation (32).

However, a number of prior mechanistic studies question the frequently practiced QD (once per day) administration of aspirin in the morning hours. Better alternatives could be a splitting of the dose to a BD (twice per day) regimen, or taking the drug in the late evening hours to cover the most vulnerable phase of platelet reactivity in the early morning hours with a maximum of platelet inhibition. Future clinical trials should verify the potential benefits (reduced morning peak in cardiovascular events) and explore possible harms (gastrointestinal side effects) of bedtime-aspirin or splitted-dose concepts in patients with CAD and/or a history of recent PCI.

### P2Y<sub>12</sub> receptor blockers

Early-morning platelet hyper-reactivity may not only influence aspirin dosing regimens but may also have important consequences on P2Y<sub>12</sub>-inhibitor treatment. However, due to differences in receptor binding between various P2Y<sub>12</sub>-inhibitors, the potential impact in clinical use may differ. Due to reversible binding to the P2Y<sub>12</sub>-receptor, ticagrelor maintenance dose (90 mg) is administered in a BD fashion, which does not leave any room for dose splitting or for switching from a usual morning to an evening intake. Despite this theoretical advantage over other P2Y<sub>12</sub>-inhibitors taken QD, data is lacking for ticagrelor so far on suppressing the circadian variation of ischaemic events (esp. stent thrombosis) in the published pivotal landmark trials of this drug (PLATO and PEGASUS-TIMI 54 [33–35]).

For clopidogrel, a diurnal variation of stent thrombosis with a clustering of events between 6 AM and 2 PM was reported in a post-hoc analysis of the TRITON-TIMI 38 trial (9). During this time period, the greatest reduction in stent thrombosis events was found for prasugrel vs clopidogrel, suggesting that increased platelet reactivity at that period was more successfully overcome by the potent P2Y<sub>12</sub> inhibitor prasugrel than by clopidogrel. In line with this, Kozinski et al. reported that on-treatment platelet reactivity during clopidogrel treatment is indeed increased by 55% at 10 AM compared to 6 AM (20). Thus, the diurnal efficacy of QD dosing regimens is not only dependent on diurnal variability in platelet reactivity and platelet turnover, but also on the absolute level of platelet inhibition achieved by the drug. However, there is lack of evidence whether shifting morning clopidogrel to the evening would be effective to overcome the morning platelet hyper-reactivity and no data exist on the potential benefits of splitting the daily dose (75 mg) in a BD manner.

Finally, in many clinical circumstances, aspirin and a P2Y<sub>12</sub> inhibitor are given together to protect the patient from stent thrombosis and from recurrent myocardial infarction. Also in such a scenario, most patients are taking both drugs together in the morning hours. It is unknown whether the data regarding the diurnal variation of on-treatment platelet reactivity are also relevant in the context of dual antiplatelet therapies (DAPT) because there is a well-known interplay between P2Y<sub>12</sub> receptor signalling and COX-1 inhibition pathways questioning the relevance of results from monotherapy patients (21). Results from the small study of Kozinski et al. (20) among patients on aspirin plus clopidogrel suggest that the diurnal variation of ADP-dependent platelet reactivity is also present in patients on DAPT treatment. Referring to this, it might be worth investigating whether splitting DAPT intake with e.g. aspirin treatment in the morning and ADP blocker treatment in the evening is beneficial in terms of platelet reactivity levels or clinical outcome.

### Conclusions

Long-term evidence supports a clustering of cardiovascular events in the early morning hours (Table 1). Several studies have shown that platelet hyper-reactivity to various stimuli is also present at this period of the day (Table 2). However, whether platelet activation is a bystander marker of another mechanism or is the main driver of the excess events is still unknown. Although sufficiently powered clinical trials are lacking, some pharmacodynamic data suggest that platelet hyper-reactivity may be overcome by...
shifting aspirin intake to the bedtime. Of note, data is lacking on the optimal time and mode of intake for P2Y12-inhibitors. Further research is warranted to clarify whether such a simple and costless effort of dose shifting or splitting may be of any use to prevent cardiovascular events. While diurnal variation of platelet reactivity is a well-described phenomenon, it is unclear whether the extent of the diurnal fluctuation is larger in patients with conditions associated with elevated platelet reactivity, such as those with ACS or diabetes mellitus. Future studies may assess and compare the amount of diurnal variation in stable vs ACS and diabetic vs non-diabetic patients. Further on, while data is available on a diurnal variation of ischaemic events (myocardial infarction, stent thrombosis) no such data is available on diurnal differences in bleeding events and further studies are needed here as well.

Realistically thinking, clinical studies comparing the impact of morning vs bedtime antiplatelet intake on hard endpoints such as early morning cardiovascular events are difficult to organise due to the large sample size required and the presumed lack of interest from sponsors. Therefore, adequately performed mechanistic studies are still important and may guide our decision-making in the future. For now, we are left with trusting the concept of a routine morning intake of antiplatelets drugs, but we must be aware that this concept was never questioned so far by dedicated clinical studies.

Conflicts of interest
None declared.

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References