Why we should not skip aspirin in cardiovascular prevention

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Summary
Since more than 20 years, aspirin is an approved and established first-line antiplatelet medication in cardiovascular prevention. This is partially due to its unique mode of action which is not shared with any other antiplatelet agent as well as the reliability of its pharmacological efficacy: inhibition of platelet COX-1 and subsequent thromboxane formation in almost every patient. Aspirin acts synergistic with ADP-antagonists in dual antiplatelet therapy of acute coronary syndromes (ACS) and percutaneous coronary interventions (PCI) and is also approved for long-term secondary prevention. Patients with atrial fibrillation are an exception and benefit more from anticoagulants. After the introduction of the new oral anticoagulants (NOACs), i.e. direct inhibitors of factor Xa or thrombin formation, there is a renewed discussion about the role of antiplatelet agents, specifically if additional dual antiplatelet treatment is still necessary for an optimum clinical effect or whether one component, such as aspirin might be skipped in favor of other classes of oral antiplatelet agents, such as ADP-antagonists. The available data are insufficient to recommend this because of a low number of studies and a still uncertain benefit/risk (bleeding) ratio. More research on aspirin as a chemopreventive appears also to be necessary and is going on, in particular in individuals at high-risk for vascular thrombotic diseases (diabetics, preeclampsia, venous thrombembolism).

Zusammenfassung

A piece of history
Acetylsalicylic acid (aspirin) was introduced into clinical use for primary and secondary prevention of cardiovascular thrombotic events (myocardial infarctions) in consequence of the Physicians Health and ISIS-2 trials, both studies first published in 1988 (1–3). Since then the positive results with aspirin as a first choice antiplatelet agent in prevention of ischemic events have been repeatedly confirmed by the antiplatelet/antithrombotic trialists' collaboration. The last available edition, this time performed on the basis of individual patient data on a standardized two years observation basis, was restricted to patients with previous myocardial infarction, stroke and/or transient ischemic attacks. This analysis also included 16 studies comparing aspirin to placebo. The results confirmed an about 20% risk reduction of serious vascular events by aspirin: 6.7 vs. 8.2% per year (p < 0.0001) (4). The same paper also contained a metaanalysis of 6 large randomized trials of aspirin on 95 000 patients in primary prevention. There was a modest but significant (p < 0.001) benefit in reduction of (nonfatal) myocardial infarctions, by 0.06% per year, at the expense...
of an increased risk of extracranial and gastrointestinal bleedings, by 0.03%. Thus, the risk (bleeding) in relation to the benefit of preventing ischemic events by aspirin in primary prevention is considerably higher than in secondary prevention. As a result, the actual (2012) guidelines of the European Society of Cardiology – at some variance with those of some US-American Societies (5) – do not recommend aspirin prophylaxis anymore in persons without cardiovascular and cerebrovascular diseases (grade III, level B).

In contrast to the controversially discussed issue of primary prevention (5, 6), apparently all guidelines on secondary prevention do recommend aspirin as a first choice antiplatelet drug in the absence of contraindications. Specifically, aspirin is actual guideline standard medication in acute coronary syndromes (ACS), since CURE (7) in combination with an ADP receptor antagonist as part of a dual antiplatelet therapy (DAPT). There is also established clinical benefit in secondary long-term prevention after ACS and percutaneous coronary interventions (PCI) or stenting. Most recent data even suggest significant benefits of aspirin vs. placebo in secondary prevention of unprovoked venous thromboembolism (8). Thus, the main field is in thrombosis prevention, where aspirin prophylaxis is being successfully used since decades and still continues to be.

Why should this established and proved use, until now in many thousands or even millions of patients worldwide, be skipped?

A general argument would be that more effective alternatives have become available, including new drugs with reduced risk – of (severe) bleeding, higher efficacy or a combination of both. There is clearly need for improved antithrombotic treatment of ACS, considering a 10–12% event rate patients of death or myocardial infarction in patients one year following PCI. Improved efficacy can obviously not be reached by increasing the aspirin dose as this will not result in any stronger clinical benefit or only, if simultaneously high-dose clopidogrel-comedication (150 mg/day) is used (9). Replacing clopidogrel in DAPT by a stronger acting and more reliable ADP antagonist, such as prasugrel and ticagrelor is clinically more effective according to the TRITON-TIMI-38 (10) and PLATO (11) trials, but also resulted in an increased bleeding tendency. Thus, more potent antiplatelet treatment might be of limited additional clinical benefit but does increase bleeding.

New treatment strategies

Regarding the pathophysiology of ACS, thrombin is coming increasingly into focus because of its central position for both platelet activation and coagulation. This has also renewed the interest in selective inhibitors of thrombin formation and action. The use of anticoagulants such as warfarin, in treatment and secondary prevention of acute myocardial infarction is not new, impressive 30–50% reduction rates in reinfarction rates were reported already 60 years ago (12). Its successful use in combination with aspirin in secondary (13) and primary prevention (14) was also reported. However, with the exception of stroke prevention in atrial fibrillation, the use of anticoagulants in prevention of atherothrombotic events was and is limited because of the high risk of severe and fatal bleeding. Additionally, only about 60% of warfarin-treated patients are in the desired therapeutic range of INR. This is less than wanted for effective prevention of a life-threatening disease.

New direct anticoagulants and triple therapy

Heparin plus GP IIb/IIIa antagonists and/or bivalirudin are alternative anticoagulants in patients undergoing PCI. Bivalirudin caused significantly less major bleeding and improved short-term net clinical outcome as compared to heparin plus GP IIb/IIIa blockers in three major clinical trials – always on top of aspirin (15). An entirely new approach was the design and development of new direct oral anticoagulants (NOACs). Rivaroxaban was the first drug which was approved by the EMA in 2013 for antithrombotic treatment of ACS on top of DAPT. Others are likely to follow. Moreover, the WOEST trial in patients with atrial fibrillation who needed PCI has provided first evidence that removal of one antiplatelet drug – this time aspirin – in combination with an anticoagulant (warfarin) might be equipotent to the triple therapy but causes less bleeding (16).

This review is focused on the following topics:

- comparative pharmacology of aspirin vs. other antiplatelet agents,
- time-dependent changes in the mode of platelet activation in ACS with particular focus on the role of thrombin,
- aspirin vs. other antiplatelet agents in long-term secondary prevention and
- unsolved issues with aspirin and future aspects. Evidence is presented that there is no reason to skip aspirin as an antiplatelet antithrombotic.

Comparative pharmacology of aspirin versus other antiplatelet agents

Aspirin acts nonspecific but fast and reliable

In contrast to other antiplatelet agents, such as ADP-antagonists or GP IIb/IIIa-receptor blockers, aspirin is not a platelet specific agent. Transacetylation by aspirin is a nonselective reaction which becomes preferentially detectable in platelets because of their insufficient protein synthesis. Irreversible COX-1 inhibition as the pharmacological mode of action of aspirin then results in prevention of platelet-COX-1-derived thromboxane formation, the only significant COX-product of platelets, having both autocrine and paracrine functions.

The antiplatelet action of aspirin does not require metabolic conversion (bioactivation). Rather the opposite is true. Subjects with established coronary artery disease appear to have a small but significantly elevated aspirin esterase activity in plasma which might be associated with a (slightly) reduced antiplatelet effect of aspirin (17, 18).

Aspirin also acts rapidly in vivo. After oral dosing of 500 mg about 30 min are required for a therapeutically relevant inhibition of thromboxane formation by
Marker | Aspirin | Clopidogrel | Aspirin plus | GP IIb/IIIa inhibitors
---|---|---|---|---
CD40 ligand | x | x | x | x
C-reactive protein | x | x | x | x
Interleukin-6 | x | x | x | x
MAC-1 | x | x | x | x
MCP-1 | x | x | x | x
M-CSF | x | x | x | x
PLA formation | x | x | x | x
P-selectin (CD62) | x | x | x | x
TF-PCA | x | x | x | x
TNF-alpha | x | x | x | x

Tab. 1: Effects of antiplatelet agents and their combination on inflammatory markers (Muhlestein, 2010)

Is aspirin “resistance” an issue of concern?

Aspirin “resistance”, i.e. a reduced antiplatelet effect, is another controversial issue regarding the antiplatelet effects of aspirin. Part of these controversies might be due to different definitions (32). While a pharmacological failure of aspirin to act is very random, about 1% or less as mentioned above (21), a clinical “resistance”, i.e. treatment failure, is more frequent and, in the range of 20–30% according to the method of determination (33). This high number reflects the different clinical conditions of platelet activation – in most cases not aspirin-sensitive – rather than a failure of the drug to act. For example, in the inflammatory conditions of advanced-stage atherosclerosis, non-platelet sources of prostaglandin-endoperoxides, the immediate precursors thromboxane A₂ may increasingly contribute to thromboxane production by the platelet thromboxane synthase, for example, via an up-regulated COX2 in vascular endothelial cells or in monocytes/macrophages. This allows for transcellular precursor exchange and platelet COX-1-independent thromboxane formation which is less sensitive to aspirin. In this context, it is interesting to note that about 30% of total body thromboxane formation as measured from urinary excretion of a thromboxane index metabolite, is insensitive to inhibition by aspirin (34). This strongly suggests stimulation of platelets and procoagulant pathways by aspirin- and/or thromboxane-insensitive pathways and multiple mechanisms are probably involved in the poor clinical outcome of aspirin “resistant”
patients (35, 36). An overview on important mechanisms of aspirin “resistance” is shown (▶ Tab. 2).

The clinical relevance of different clinical conditions for the clinical efficacy of aspirin is still under discussion. Specifically, there are doubts, whether the risk of cardiovascular events in patients with stable angina can be determined by measuring platelet function (37). One large-scale prospective registry study in patients undergoing PCI confirmed that intensified P2Y12 blockade improved antithrombotic efficacy at the expense of bleeding but found no significant association between “high on treatment aspirin sensitivity” and ischemic events, including death and stent thrombosis (38) while another large-scale observational registry trial reported the opposite, i.e. high on treatment aspirin sensitivity was associated with a higher risk of death or stent thrombosis (39). Both studies differ in several methodological aspects, including determination of platelet function which is a key issue of comparability of studying platelet function ex vivo (33). Thus, the clinical relevance of lower than usual inhibition of platelet function by aspirin for the cardiovascular risk is unclear but at all likelihood has little or nothing to do with a failure of aspirin to block platelet-dependent thromboxane formation.

### Time dependent changes in ACS

**Thrombin – the “switch” between platelets and coagulation**

One of the earliest events subsequent to plaque rupture in ACS is availability of tissue factor and subsequent thrombin generation which “explodes” in the propagation phase of coagulation. These events occur at the surface of activated platelets. The vast majority of thrombin – 96% – is formed in this propagation phase (40). Thrombin is the most potent platelet stimulus and amplifies its formation by positive feedback to factor V (FV) at the platelet surface. Notably, the amounts of thrombin formed are in the high nanomolar range (40) and will first stimulate its major platelet receptor, PAR-1. The required concentrations are in the picomolar range and several orders of magnitude lower than the affinity constants for fibrinogen, i.e. fibrin formation (41, 42). Thus, the first response after thrombin formation is stimulation of platelet function and subsequent activation of the platelet GP IIb/IIIa-receptors. Activated platelets then provide the matrix for further bulk thrombin formation and there is a clear feedback also to thromboxane production which acts as both an initiating and amplifying event.

Neither aspirin nor any ADP-antagonist can block high-thrombin-induced platelet functions (secretion) or its multiple actions within the clotting cascade. However, aspirin in contrast to ADP antagonists was found to inhibit (retard) clotting associated thrombin formation ex vivo (43–45) and has also been found to act synergistically in this respect with low-dose rivaroxaban in

#### Tab. 2

<table>
<thead>
<tr>
<th>Pharmacological factors (rather random)</th>
<th>Clinical conditions (rather frequent)</th>
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<tr>
<td>incomplete inhibition of platelet COX-1</td>
<td>aspirin-insensitive platelet activation (thrombin, ADP, collagen)</td>
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<tr>
<td>variations in plasma aspirin esterase activity</td>
<td>non-platelet sources of PG-endoperoxides</td>
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<td>upregulated COX-2 in systemic inflammation and advanced atherosclerosis</td>
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<td></td>
<td>shortened platelet turnover rate (diabetes mellitus)</td>
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an experimental setting (46). Clopidogrel (on top of aspirin) was also found to inhibit thrombin-induced platelet-fibrin clot formation (47). This suggests that aspirin-induced inhibition of thrombin formation might be a consequence of its antiplatelet effect, since this action is lost in case of aspirin “resistance” (48). Nevertheless, aspirin-sensitive thrombin formation has been shown in ACS (49) (▶ Fig. 2) and might contribute to the overall clinical benefit.

The initial procoagulatory event in ACS is thrombin formation

The initial thrombin “burden” in ACS with subsequent thrombin-induced platelet stimulation has also consequences for the efficacy of antiplatelet treatment. For example, prasugrel (60 mg) and ticagrelor (180 mg) loading was effective only in about half of STEMI patients 2 h after PCI while at least 4 h were required for a full effect (50, 51). Similar results were obtained by Trenk et al. (2013) who additionally showed that “high on treatment platelet reactivity” to prasugrel and ticagrelor in both STEMI and NSTEMI patients disappeared the day after PCI. Thus, in the early phases of ACS, there appears to be a time frame, when ADP-antagonists, the partners of aspirin in DAPT, are less active than at later time points. In addition to pharmacokinetics (retarded absorption by morphine cotreatment) there might be a pharmacodynamic reason for this “resistance” against ADP-antagonists: platelet stimulation by thrombin, possibly triggered by release of tissue factor after rupture of an atherosclerotic plaque. From all currently approved antiplatelet agents, only GP IIb/IIIa-antagonists are able to reduce this HTPR (52).

Triple vs. dual antithrombotics – should we skip aspirin?

Triple therapy, i.e. the combination of DAPT with an anticoagulant is used in patients with atrial fibrillation who need an acute coronary intervention. The WOEST study has suggested that use of one antiplatelet agent alone (clopidogrel) in combination with warfarin is sufficient to reduce the rate of thrombotic events in patients with atrial fibrillation undergoing PCI and additionally yields lower rates of bleeding than in the triple group (16). Only GP IIb/IIIa-antagonists are able to reduce this HTPR (52).

Another issue is ACS. A recent meta-analysis has shown that single antiplatelet treatment with aspirin plus NOAC vs. aspirin alone reduced the rate of major adverse cardiac events (MACE) by 30% (HR: 0.70; 95% CI: 0.59–0.84) while the rate of clinically significant bleeding increased with 79% (HR: 1.79; 95% CI: 1.54–2.09). Addition of an oral anticoagulant to DAPT with aspirin and clopidogrel decreased the incidence of MACE modestly (HR: 0.87; 95% CI: 0.80–0.95) but increased bleeding more than twofold (HR: 2.34; 95% CI: 2.06–2.66) (54). The ATLAS-ACS-2-TIMI-51 trial on rivaroxaban in ACS showed a significant survival benefit with the lower rivaroxaban dose of 2.5 mg bid, but not with the higher dose of 5 mg bid. The prize was a threefold higher major bleeding rate including intracranial bleeding. Though the investigators (55) and even an actual expert review (56) stated that this study was a comparison of a NOAC versus “placebo” it was in fact a trial on guideline-directed DAPT in ACS using aspirin plus clopidogrel with and without additional rivaroxaban. Thus, there are still several questions regarding the advantages of NOACs in ACS and more information is definitely needed, before aspirin can be “skipped” in this indication.

Fig. 2

Time-dependent changes in plasma thrombin activity (TAT complexes) and 11-DH-TXB2 levels in patients with and without prolonged resting angina. Effect of high-dose (900 mg) iv. aspirin (Yasu et al. 1993)
Fig. 3 Absolute risk and incidence ratios (IRRs) of 40,000 aspirin treated patients in secondary prevention of cardiovascular and cerebrovascular events as compared with upper GI bleeding (UGIB). Data for 1st year after the acute event; in 30% of patients aspirin was discontinued, mainly (ca. 70%) because of non-adherence (“saw no effect”, “forgotten” etc, < 10% for safety reasons!) (Soriano et al, 2013).

Aspirin vs. other antiplatelet agents in long-term prevention

Aspirin and bleeding risk

Bleeding is the most feared event of antithrombetics and antiplatelet agents – in particular in long-term use. A large meta-analysis of 31 randomized trials with low-dose aspirin (75–325 mg/day), mostly long-term cardiovascular prevention trials, showed an overall increased risk of severe bleedings in aspirin users: OR 1.54 (95% CI: 1.34–1.74), mainly gastrointestinal and cerebral bleedings. There was no increase in the number of fatal bleeds: OR: 1.22 (95% CI 0.78–1.89) (57). A more recent analysis of the incidence of upper GI bleeding of the same group on 40,000 aspirin treated patients compared regular aspirin users with those who discontinued prescribed aspirin (secondary prevention of MI) for different reasons, mainly (70%) (!) because of non-adherence. During the first year after the acute event, non-users suffered five more cardiac and three more cerebrovascular events per 1000 patients and had 0.4 less upper GI bleeding (Fig. 3) (58). Another metaanalysis on data for aspirin long-term (primary) prevention reported that the incidence of bleedings tended to become reduced with longer use and that the number of fatal extracerebral bleedings after use for ≥5 years was even significantly reduced (59). The latest available study on benefit-risk ratio of aspirin in long-term prevention of rethromboses in patients with previous unprovoked unprovoked venous thromboembolism (VTE) is the INSPIRE collaboration, reevaluating the data of the placebo-controlled WARFASA and ASPIRE trials on an individual patient analysis (8). In 1224 patients, the authors reported an annual incidence of severe bleedings of 0.5% for aspirin vs. 0.4% in the placebo group (p: n.s.) as opposed to a 42% reduction in recurrent VTE by aspirin treatment (HR: 0.58; 95% CI: 0.40 – 0.85; p = 0.005).

Aspirin vs. other antiplatelet agents in secondary prevention

Aspirin is established and guideline-conform long-term treatment in secondary prevention. According to the antiplatelet/antithrombotic trialists secondary prevention data, aspirin reduces the overall incidence of new atherothrombotic events by about 25% (60). The benefit-risk ratio in long-term secondary prevention of aspirin is comparable to clopidogrel according to the CAPRIE data (61). There are no data with other single ADP antagonists so far. The efficacy of aspirin is also evident from possible rebounds after withdrawal of aspirin (62) and a small study has even shown that withdrawal of low-dose aspirin (80 mg) (plus PPI) because of gastric ulcer bleeding in high-risk patients, might increase mortality (63). Another large trial, the PEGASUS trial in secondary prevention of >21,000 patients with prior myocardial infarction has just been published. The study confirmed the superiority of combined treatment vs. aspirin alone in reduction of MACE but at the expense of a more than doubled risk of severe bleedings (80).

Unsolved issues with aspirin and future aspects

Aspirin vs. other antiplatelet agents in prevention of patients at vascular risk

The combined use of aspirin with clopidogrel in primary prevention of asymptomatic individuals with risk factors did not reduce the vascular risk but even increased mortality (64). Aspirin alone is also not recommend by the EMEA for primary prevention as noted above. However, for efficacy, the dose interval is also a variable. A recent comparison of 81 mg/day aspirin vs. 100 mg every other day to healthy women...
Fig. 4 Maximum aggregation intensity (MAI) with LTA-AA 0.5 mg/ml  
a) according to once per day (OPD) 150 mg or twice 75 mg per day regimes (BID) (n = 92). Black circles represent patients resistant to aspirin with LTA-AA. Gray circles represent patients responding to aspirin. Patients were considered as significantly resistant to aspirin treatment when MAI was ≥20%.

b) in patients with resistance to OPD treatment regimen after change to two times treatment (bid) (n = 25); mean MAI (percentage) is given as means ± SD (Dillinger et al. 2012).

– mimicking the protocol of the Womens’ Health study, showed that the once daily administration produced stronger and less variable inhibition of platelet function than the 100 mg every second day (65). This suggests that the platelet turnover rate is a variable of aspirin’s antiplatelet effect even in healthy volunteers, in particular at (very) low doses. An enhanced platelet turnover rate in certain diseases, therefore, might shorten the time of sufficient blockade of platelet COX-1 after aspirin administration and, thereby, reduce its antiplatelet effect and clinical efficacy.

An interesting study which is currently underway is the “GLOBAL-LEADERS” trial in cardiocoronary prevention of 16000 “all comé” stented coronary patients with ACS or stable angina (NCT:01813435). Patients will be rando-

The issue of diabetics

Two large available studies on primary prevention in diabetics, the POPADAD and JPAD studies were negative, possibly due to or at least influenced by the study design. For example, the POPADAD trial was probably underpowered because of an only 2.9% event rate instead of the expected 8.0% and an aspirin compliance of only 50% of patients at the end of the 7-years’ study period (66). Enhanced platelet turnover rates are known for patients with diabetes mellitus. This was associated with a lower sensitivity to and shorter duration of the antiplatelet effect of aspirin as well (67–70). This might contribute to or even explain the low efficacy of aspirin as a cardiocoronary preventive in diabetics (71).

Interestingly, twice daily aspirin (at the same total dose) was found to be more effective than once daily in diabetics with coronary artery disease (72, 73) (Fig. 4). Moreover, in a significant proportion of patients with coronary artery disease, there is pharmacological aspirin “resistance”, i.e. enhanced thromboxane formation and a time-dependent disappearance of the antiplatelet effect of aspirin within the 24 h dosing interval. This effect was independent of the aspirin dose but possibly related to inflammatory conditions (74). New large, prospective trials on aspirin in primary prevention of diabetics, such as ASCEND and ACCEPT-D, are underway. It will be interesting to learn more about the time course of platelet-dependent thromboxane formation in these and other populations at enhanced cardiovascular risk and enhanced platelet turnover rates.
Venous thromboembolism

In addition to prevention of myocardial infarction and stroke, aspirin is currently entering further fields of thrombosis prevention. This includes its use for long-term prevention of venous thromboembolism, especially in patients with the idiopathic form of the disease (8) as well as its acute use as VTE-prophylactant in major surgeries after an initial phase of heparin (dalteparin) versus continuuation of dalteparin (EPCAT-trial) – no difference in clinical outcome was seen (75). A recent comprehensive review is available (76).

Preeclampsia

Aspirin appears to be one of the very few medications that are effective in pre-eclampsia, i.e. pregnancy-induced hypertension with edema. There is not much known about its mode of action, but probably, it is also thromboxane related. The particular attractive issue of (early) aspirin besides its efficacy is its good tolerance by both the mother the fetus and the apparent absence of any significant toxicity to the fetus (77). This unique combination combined with decades of clinical experience was probably the reason why aspirin prophylaxis (ca. 100 mg/day) recently became treatment recommendation in the US and several European countries for women at increased risk for preeclampsia.

Colorectal cancer

Probably the most exciting current field of aspirin research is its possible use as a chemopreventive for primary and secondary prevention of colorectal cancer (CRC). Observational studies suggest a 40–50% reduction in the incidence rates by regular aspirin intake (78). Interestingly, recent metaanalyses suggest that the survival benefit in long-term cardiovascular prevention studies might result from nonvascular reasons though its mode of action is not well understood yet (59, 79). Thus, CRC might become an attractive candidate for chemoprevention also in this indication.

Conflict of interest

The author is member of advisory boards of Bayer Healthcare and Daiichi/Sankyo-Lilly and also received speaker’s honoraria from these companies as well as CORREVIO.

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