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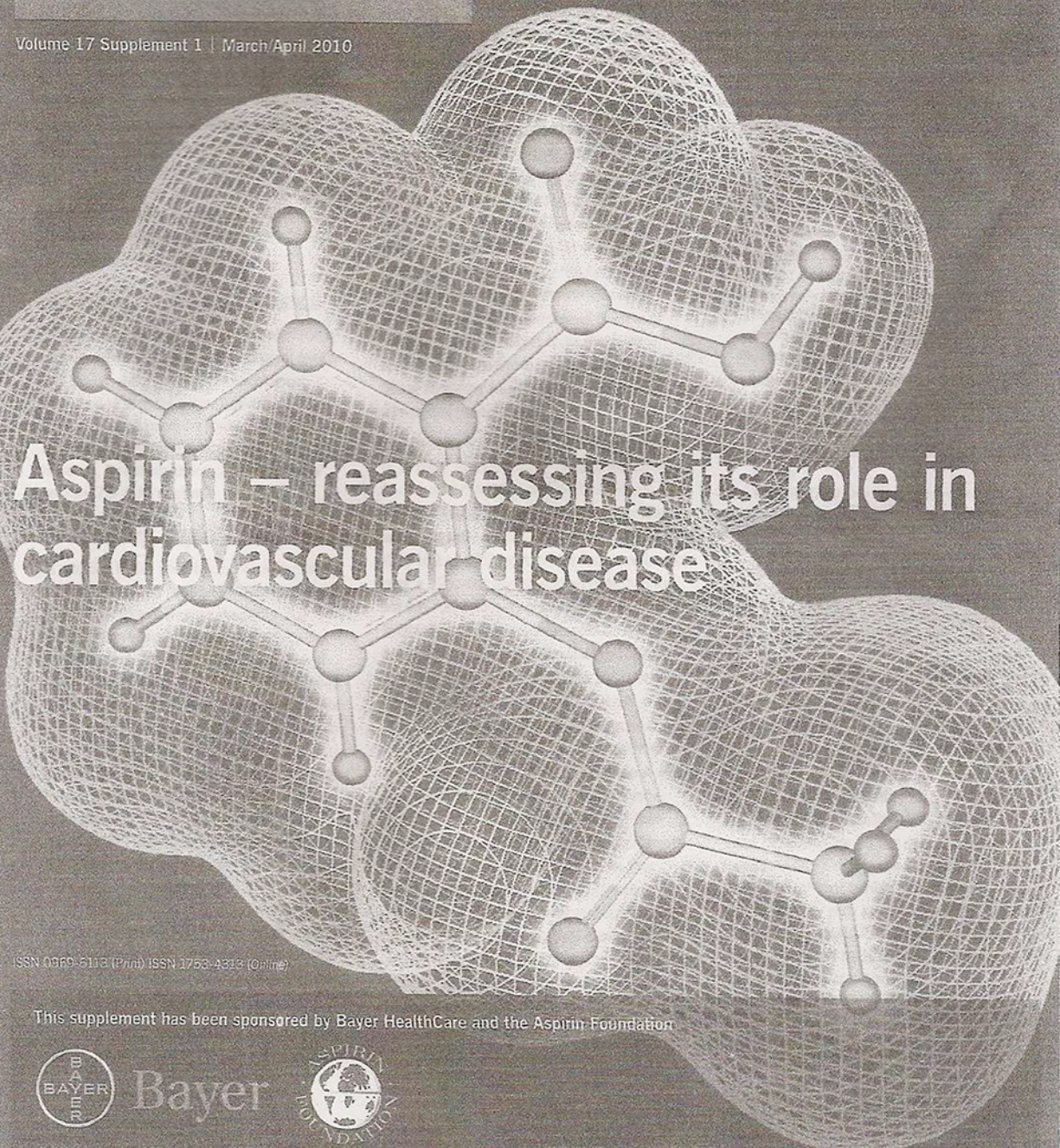

Aspirin – reassessing its role in cardiovascular disease

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What is aspirin resistance?

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Variable and sometimes ineffective drug treatment is not uncommon in the treatment of cardiovascular disease.[1] In most cases lack of patient compliance is the explanation but other reasons may also exist. In the case of aspirin, "low responsiveness" or "resistance" to aspirin in pharmacological terms would mean that the compound fails to reach its therapeutic goal, i.e. inhibition of platelet COX-1-dependent thromboxane formation. However, *in vivo* there might be also changes in platelet sensitivity or "residual" platelet activity independent of aspirin treatment, probably unrelated to the drug's pharmacodynamic actions.[2]

Defining aspirin resistance

There is no universally accepted definition of aspirin resistance. In pharmacological terms, this means insufficient pharmacological inhibition of platelet cyclooxygenase-1 (COX-1)-derived thromboxane formation, with subsequent insufficient inhibition of platelet function, by standard antiplatelet doses of aspirin (75–300 mg/day).

Measuring aspirin resistance

In addition to the uncertainty regarding setting normal values and confidence intervals to define aspirin resistance, another major problem is the selection of appropriate methods for its determination. Measurement of inhibition of serum thromboxane quantitatively determines the pharmacological potency of aspirin to block the platelet COX-1 as seen from reducing the capacity of formation of an end product, i.e. thromboxane B_2. However, serum thromboxane has no direct equivalent in terms of platelet aggregation or total body thromboxane generation.[3] Further, serum thromboxane has no physiological or clinical correlate *in vivo* because the locally generated amounts of thromboxane at a site of thrombus formation *in vivo* are several orders of magnitude lower. In fact, in about 99% of cases aspirin does effectively block platelet COX-1, and thus pharmacological resistance does not account for clinical resistance.

In vitro platelet assays bypass the issue of COX-1-dependent thromboxane formation and have further significant limitations. Platelets are removed from the circulation, preventing the prothrombotic effects of shear stress and contact with blood cells and the vessel wall. Preactivation may occur and may be more marked in hyperreactive platelets. The assay usually involves stimulation by a single agonist whereas *in vivo* multiple agonists exert synergistic effects. Anticoagulants may modify platelet aggregation differently.[4] Furthermore, there are no generally accepted normal ranges or assay standards and the reproducibility of assays is uncertain. Finally, there are important autocrine and paracrine functions of platelet-derived thromboxane, such as stimulation of platelet secretion or the thromboxane-dependent release of inflammatory mediators from platelets, such as sphingosine-1 phosphate.[5] None of these secretory functions will be detected by measuring platelet aggregation.

The assessment of aspirin resistance in terms of platelet function is highly assay-dependent. In one well-designed double-blind study, the ASPECT trial,[6] 125 outpatients with coronary artery disease received three doses of aspirin (81, 162 or 325 mg/day) for four weeks each over a 12-week period and were tested for aspirin resistance by seven methods. The methods using arachidonic acid as an agonist suggested that the incidence of resistance to aspirin was low (0% to 6%) but others (including collagen-induced aggregation and the platelet function analyser) suggested that it might be as high as 27%. The efficacy of aspirin appeared to be dose-dependent when measured by some, but not all, methods. The ASPECT trial clearly shows also that repeated drug administration gives different results. It is also interesting to note that aspirin "resistance" as defined by urinary excretion of a thromboxane metabolite in this study "identifies" the highest percentage of aspirin "low responders".[6] However, *in vitro* platelet aggregation in platelet-rich plasma is much more sensitive to agonists such as ADP after anticoagulation by citrate than by antithrombins such as hirudin.[4]

Mechanisms of aspirin resistance

Although true pharmacological resistance to aspirin appears to be rare, two different forms of pharmacological variability of aspirin effects in platelets may be defined: drug-related and disease-related mechanisms. **Table 1** gives an overview.

Table 1. An overview of aspirin resistance

Drug-related
Pharmacokinetics
• Insufficient bioavailability (low-dose enteric-coated preparations)
• Prevention of access to binding sites inside the COX-1 channel by NSAIDs (ibuprofen, indomethacin) and pyrazoles (dipyrone)
Pharmacodynamics
• Impaired sensitivity of platelet COX-1 (CABG)
• COX-1 gene polymorphisms (A842G / C50T)
Disease-related
• Platelet hyperreactivity ("residual platelet activity")
• Platelet stimulation by aspirin-insensitive mechanisms (ADP, shear stress, others)
• Platelet stimulation by COX-2-dependent (platelet-mediated) TX formation
• Platelet "sensitising" by isoprostanes

Key: ADP=adenosine diphosphate; CABG=coronary artery bypass graft; COX=cyclooxygenase; NSAIDs=non-steroidal anti-inflammatory drugs; TX=thromboxane

Drug-related mechanisms

Drug-related mechanisms may be pharmacokinetic or pharmacodynamic in nature. The former include low bioavailability or, more importantly, the interaction with non-steroidal anti-inflammatory drugs (NSAIDs). Insufficient bioavailability of aspirin has been described for 75 mg enteric-coated formulations.[7] This agrees with the finding of Gurbel *et al.*[6] that aspirin "resistance" occurs less frequently with increasing aspirin doses and repeated doses.[6] The dosage of aspirin should be raised to 100 mg/day or more. The prevalence of a "true", i.e. pharmacological "resistance" to aspirin is currently estimated to be about 1%.[6,8,9]

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