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Presentations

Ischemic heart disease: the platelet paradox

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"What we see now is like
a dim image in a mirror;
then we shall see face to face"
(1 Corinthians, 13, 12)

The role of blood platelets in thrombus formation was first identified and clearly described by Giulio Bizzozero at the University of Turin 120 years ago[1-3].

The first centenary of Bizzozero's death has just been celebrated by a symposium on Bizzozero's multifaceted scientific and political activity[4] and several commemorative articles[5-10].

"Every time the vascular wall is damaged – even by a slight pressure by means of a free lancet – or when a foreign body is introduced into the vascular lumen, the earliest phenomenon which can be observed is the accumulation of blood platelets. At first, one observes two to four to six platelets; very rapidly their number grows into hundreds. Among aggregated platelets a few white blood corpuscles are also captured (Fig. 1). One may assume – Bizzozero concludes – that the slightest alteration of vessel walls may lead to widespread thrombosis". Observing thrombus formation by microscope in a small artery of the omentum of a guinea pig, Bizzozero identified a triad of cellular components – endothelium, platelets and leukocytes – that are still presently considered as playing a complex and interrelated role in the pathogenesis of thrombosis and ischemic vascular disease (Fig. 2)[11,12].

Figure 1. *Two small mural thrombi which have formed within a small artery of the omentum of a guinea pig. The larger one contains, among blood platelets, a white blood corpuscle. This figure is reprinted from the original paper of Bizzozero[2].*

Clinical benefits of aspirin against ischemic heart disease

From a therapeutic point of view, the use of aspirin and other antiplatelet drugs has made the history of clinical trials in the last 30 years (Table I)[13] and has contributed to the progressive decline of secondary cardiovascular mortality observed in the same period in many countries[14].

Quite recently, the US Preventive Services Task Force (USPSTF)[15] found good evidence that aspirin decreases the incidence of both fatal and nonfatal coronary artery disease in adults who are at increased risk for heart disease (odds ratio-OR 0.72, 95% confidence intervals-CI 0.60-0.87). Five primary prevention trials were included in the USPSTF's meta-analysis, one performed in Italy in a general practice setting[16,17]. The net benefit of aspirin – even taking into account a non significant increased risk for hemorrhagic strokes but a significant increase

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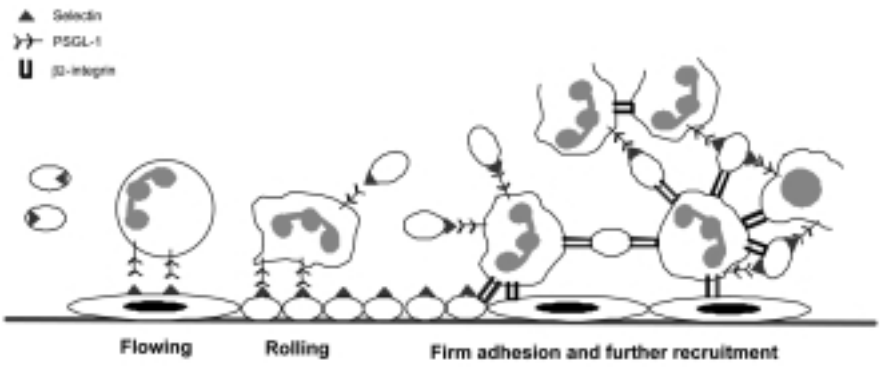

Figure 2. *Hypothetical sequence of the interactions between polymorphonuclear (PMN) leukocytes and activated platelets or injured endothelial cells. Binding of P-selectin (or E-selectin) to P-selectin glycoprotein ligand-1 (PSGL-1) promotes tethering and rolling of PMN leukocytes on vascular surface. PSGL-1-induced activation of PMN β_2-integrin(s) allows stable multicellular interactions. Cathepsin G released by activated PMN leukocytes may facilitate further platelet and PMN recruitment at the vascular injury site. From Cerletti et al.[11], with permission.*

Table I. Proportional effect of antiplatelet therapy on vascular events (myocardial infarction, stroke, or vascular death) in five main high risk categories.

Category of trial	No. trials with data	% Odds reduction (SE)
Previous myocardial infarction	12	25 (4)
Acute myocardial infarction	15	30 (4)
Previous stroke/ transient ischemic attack	21	22 (4)
Acute stroke	7	11 (3)
Other high risk	140	26 (3)
Subtotal: all except acute stroke	188	25 (2)
All trials	195	22 (2)

From Antithrombotic Trialists' Collaboration[13], modified.

(OR 1.7, 95% CI 1.4-2.1) of major gastrointestinal bleeding – is higher with increasing cardiovascular risk, the benefit/harm balance being most favorable in subjects with a 5-year risk ≥ 3% (Table II)[18].

Despite the long-lasting discovery of the role of platelets in experimental thrombosis and the remarkable antithrombotic effect of antiplatelet drugs in several ischemic conditions, there is still little direct evidence that platelets play an important role in the pathogenesis of vascular disease.

The platelet paradox

This "platelet paradox", as defined above, is based on the lack of clinical data showing a direct relationship between platelet number (and/or the values of any platelet function parameters) and the number (and/or severity) of occlusive vascular events. Data showing a reduced vascular risk in thrombocytopenic patients and a proportional increase following transfusion of intact platelets or of some specific platelet constituents such as β_2-thromboglobulin or platelet-factor-4 are also unavailable.

Platelet adhesive molecules as thrombosis markers

In the absence of these improbable experiments, one would consider a convincing argument the results of prospective studies establishing a positive link between soluble adhesion molecules of platelet origin

Table II. Estimates of benefits and harms of aspirin given for 5 years to 1000 patients with various levels of baseline risk for coronary heart disease*.

Benefits and harms	Baseline risk for coronary heart disease over 5 years**		
	1 %	3 %	5 %
Total mortality	No effects	No effects	No effects
Coronary heart disease events (n=)	1-4 avoided	4-12 avoided	6-20 avoided
Hemorrhagic strokes§ (n=)	0-2 caused	0-2 caused	0-2 caused
Major gastrointestinal bleeding events§§ (n=)	2-4 caused	2-4 caused	2-4 caused

* = estimates are based on a relative risk reduction of 28% for coronary heart disease events in aspirin-treated patients and assume that risk reductions do not vary significantly by age; ** = nonfatal acute myocardial infarction and fatal coronary heart disease. Five-year risks of 1, 3 and 5% are equivalent to 10-year risks of 2, 6 and 10%, respectively; § = data from secondary prevention trials suggest that increases in hemorrhagic stroke may be off-set by reduction in other types of stroke in patients at very high risk for cardiovascular disease (≥ 10% 5-year risk); §§ = rates may be 2 to 3 times higher in patients > 70 years. From Sox[18], modified.

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(even if not exclusively) and risk of occlusive arterial disease. This was not the case, however, for soluble P-selectin in a recent meta-analysis[19]. Moreover, the prognostic value of the same protein as a cardiovascular biomarker in healthy women was only significant at a marginal level, lower than that observed for LDL-cholesterol or C-reactive protein[20]. On the other hand, no platelet marker was selected either by the ECAT[21] or the PLAT[22] group to be used to predict the risk of future cardiovascular events in different clinical conditions.

Platelet microparticles

Platelets, after activation or in high shear stress conditions, shed microparticles into the circulation. These particles, by carrying surface receptors for coagulation factors, may provide procoagulant activity at a distance from the site of platelet activation and for a larger period than activated platelets[23]. Elevated levels of microparticles have been reported for patients with unstable angina[24] and diabetes mellitus[25], and in pericardial blood during coronary bypass surgery[26]. However, the functional importance of platelet microparticles in cardiovascular or other diseases remains to be established. In particular, it remains unresolved whether persistent platelet activation with concomitant formation of microparticles is a consequence of the disease or reflects the influence of previously formed microparticles in the circulation[23].

Platelet glycoprotein polymorphisms

In the last years, the hypothesis has been proposed and tested that a polymorphism of the platelet glycoprotein IIIa (that is an integral part of the platelet receptor for fibrinogen)[27] predisposes to a higher susceptibility to coronary thrombosis and to thrombotic complications of coronary stents (Table III)[28]. The contributory role of this polymorphism remains, however, controversial and is not supported by the reported failure of oral glycoprotein IIb-IIIa inhibitors to prevent vascular events[29].

The genetic approach to a better understanding of the role of platelets in clinical thrombosis, despite the limited success, has indicated a new avenue for future research in this field.

Table III. Platelet glycoprotein IIIa polymorphism $Pl^{A1}Pl^{A2}$ and coronary risk: a meta-analysis.

	Pl^{A2} vs Pl^{A1}	
	OR	CI
General population	1.10	1.03-1.18
Younger age		
< 60 years	1.21	1.05-1.38
< 50 years	1.20	0.96-1.50
Males	0.96	0.83-1.12
Both genders	1.18	1.06-1.32
Restenosis	1.31	1.10-1.56
After stent	1.37	1.11-1.70

CI = confidence intervals; OR = odds ratio. From Di Castelnuovo et al.[28], modified.

Promise and reality of individualized treatment

It is conceivable, indeed, that platelets would not necessarily play a comparable role (if any) either in all ischemic clinical conditions or in all individuals. The results of the CAPRIE trial[30] are enlightening in this context as the same antiplatelet drug (clopidogrel) resulted in different relative risk reduction – with respect to aspirin – in three different subgroups (stroke, myocardial infarction and peripheral artery disease). Would it mean that platelets (or the platelet function affected by clopidogrel) play different roles in thrombotic complications occurring in different arterial districts? Alternatively, would aspirin- or clopidogrel-induced platelet inhibition have similar consequences on some arteries but different on others? The results of the Primary Prevention Project trial[16] do not allow to evaluate whether aspirin-induced platelet thromboxane suppression would be comparable in subjects with different cardiovascular risk factors such as diabetes, hypercholesterolemia or hypertension or whether the overall favorable efficacy profile of aspirin treatment would be equally or differently distributed among the various subgroups included in the trial[17].

On the other hand, combining a number of risk factors such as age, sex, systolic blood pressure, diabetes and smoking, the probability of major cardiovascular events in subgroups of the Primary Prevention Project population ranged from 1.0 to 7.8%[31]. It is conceivable that the pathogenetic role of platelets and/or the efficacy of aspirin (or other antiplatelet drugs) might be substantially different with increasing cardiovascular risk[15]. If not, one should assume that different risk factors (such as diabetes or hypertension) would activate in a comparable way one or more intermediate mechanisms (e.g. platelet thromboxane generation) and give rise to a number of equivalent clinical endpoints[17].

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