Acid acetylsalicylic resistance

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Introduction

Acid acetylsalicylic (aspirin) is widely used as an antiplatelet therapeutic drug in secondary prevention of cardiovascular events in patients with coronary artery disease (CAD)

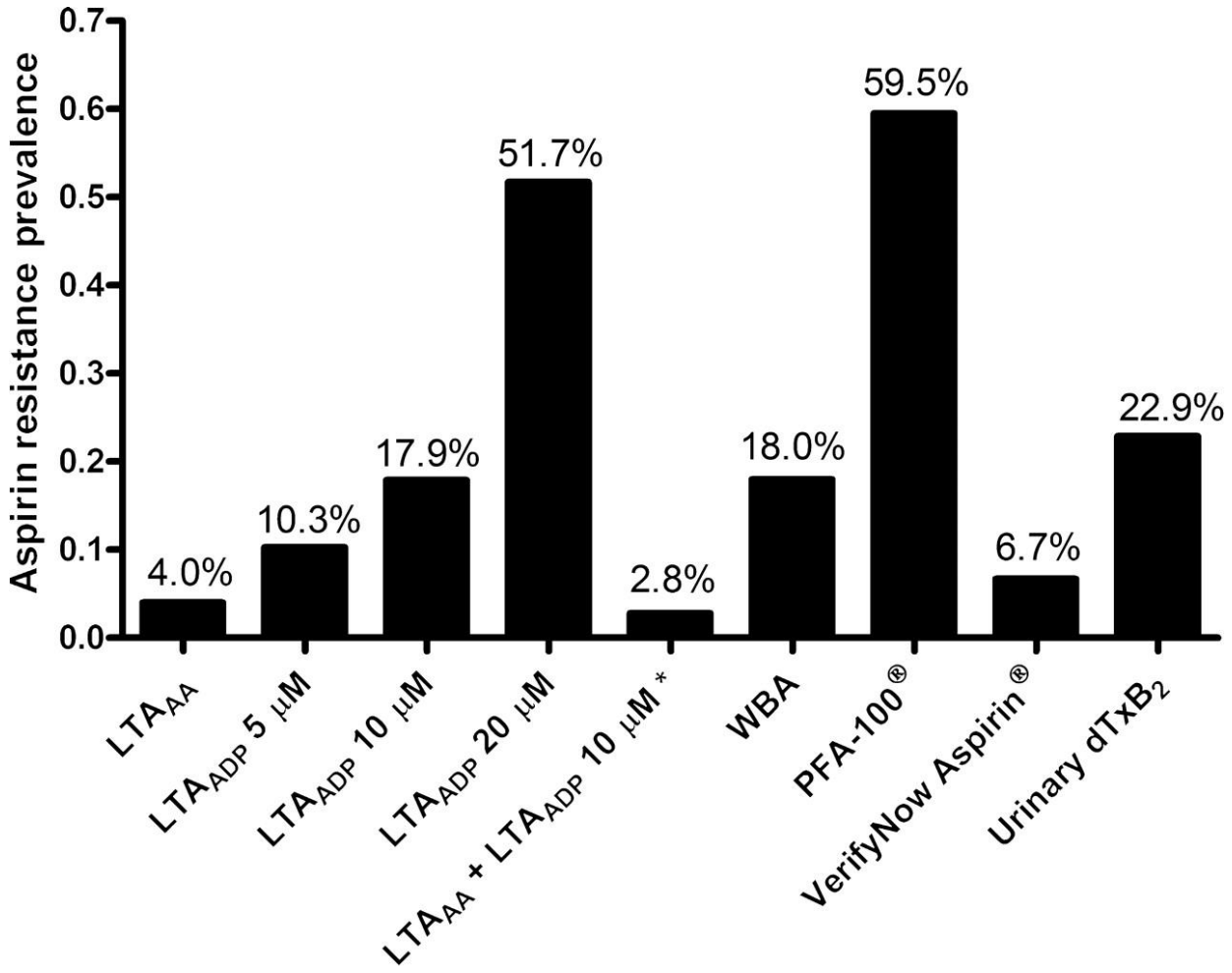
Despite modern methods of treatment, patients with CAD have recurrent cardiovascular events

One of the reasons – aspirin resistance

The question of the clinical significance of markers of resistance to antiplatelet agents and the possibility of personalizing antiplatelet therapy to prevent cardiovascular accidents after revascularization still remains relevant

1. Snoep J.D., Hovens M.M., Eikenboom J.C., van der Bom J.G. Huisman M.V. Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and metaanalysis. Arch Intern Med, 2007, vol. 167, no. 15, pp. 1593–1599
2. Puchin'yan N.F., Furman N.V., Dolotovskaya P.V., Malinova L.I. High residual platelet reactivity during dual antiplatelet therapy, detected by optical aggregometry, and the incidence of atherothrombotic complications after stenting of coronary arteries in patients with coronary heart disease in real clinical practice Ratsional'nya farmakoterapiya v kardiologii, 2016, vol. 12, no. 4, pp. 385–390
3. Pronko T.P., Snezhitskiy V.A., Makarova E.A, Avseenko A.A., Kharitonenko T.V. Features of platelet hemostasisin patients with various sensitivity to antiplatelet therapy in patients with angina pectoris in planned percutaneous coronary intervention. Zhurnal Grodnenskogo gosudarstvennogo meditsinskogo universiteta, 2017, vol. 15, no 5, pp. 503–508

The prevalence of resistance to acetylsalicylic acid



Marie Lordkipanidzé et al. Eur Heart J 2007;28:1702-1708

European Heart Journal

Causes of aspirin resistance

Definition of "Aspirin Resistance"

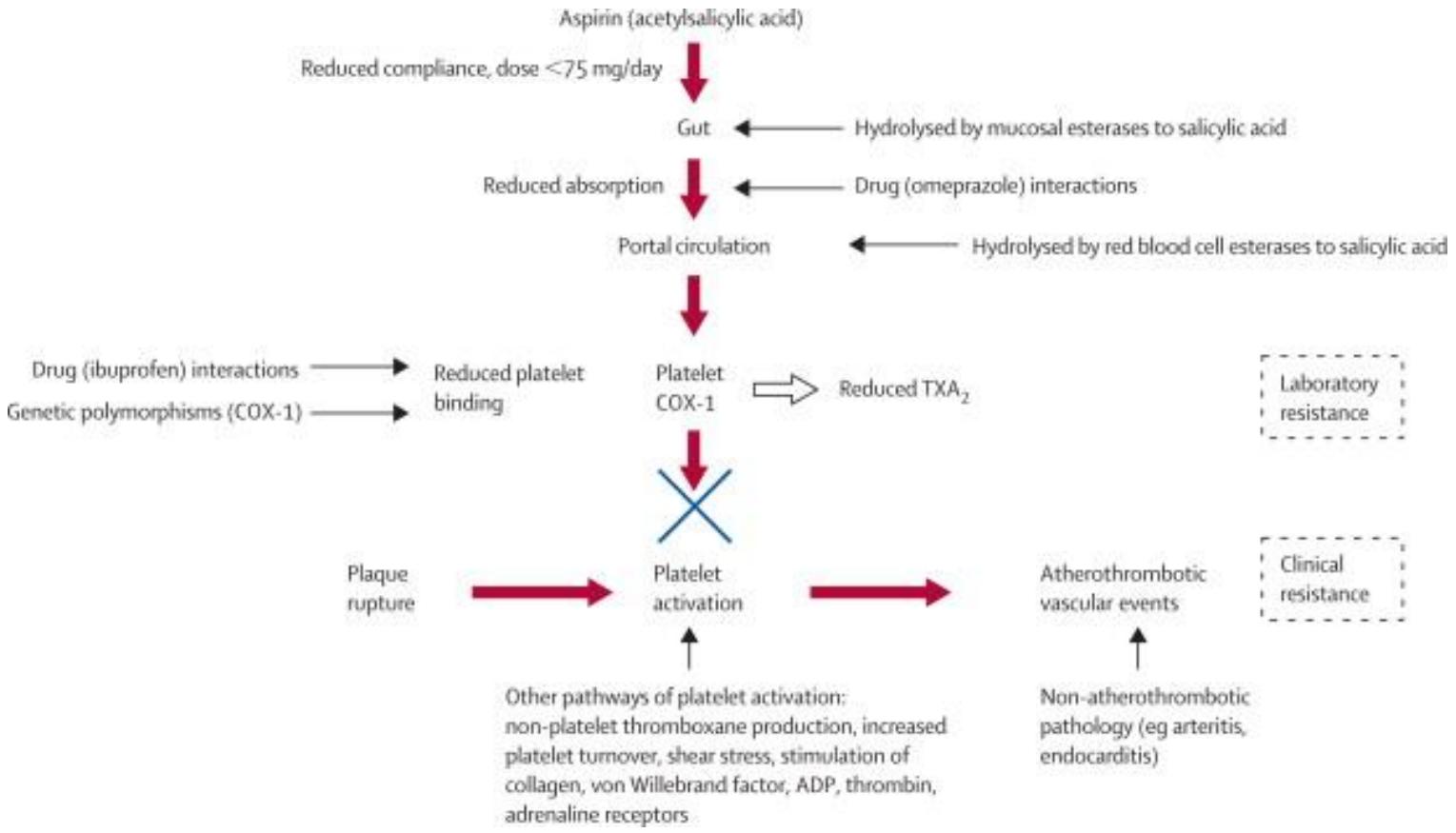
- Clinical failure of prevention
- Biochemical resistance
- Laboratory Phenomenon

Or….

- Patient just doesn't want to take it.

Hankey GJ, Eikelboom JW. Aspirin resistance. Lancet. 2006;367(9510):606-617. DOI: 10.1016/s0140-6736(06)68040-9; Bhatt DL, Topol EJ. Scientific and therapeutic advances in antiplatelet therapy. Nat. Rev. Drug Discov. 2003; 2:15-28. DOI: 10.1038/nrd985; Weber AA, Przytulski B, Schanz A, et al. Towards a definition of aspirin resistance: a typological approach. Platelets. 2002;13(1):37-40. DOI:10.1080/09537100120104890.

Causes of aspirin resistance

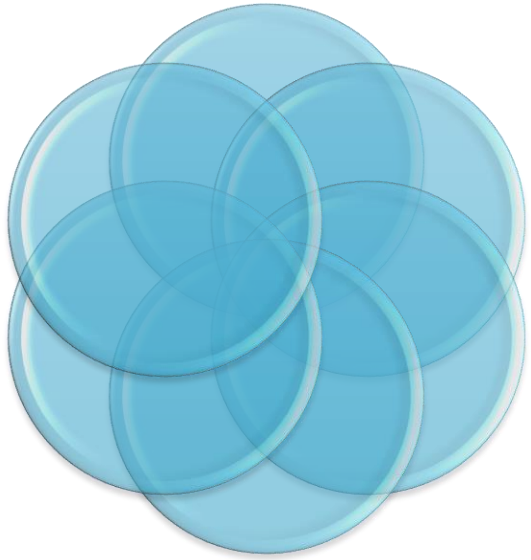


Hankey GJ, Eikelboom JW. Aspirin resistance. Lancet. 2006 Feb 18;367(9510):606-17. doi: 10.1016/S0140-6736(06)68040-9. PMID: 16488805

Other reasons

Due to bioavailability

Other factors



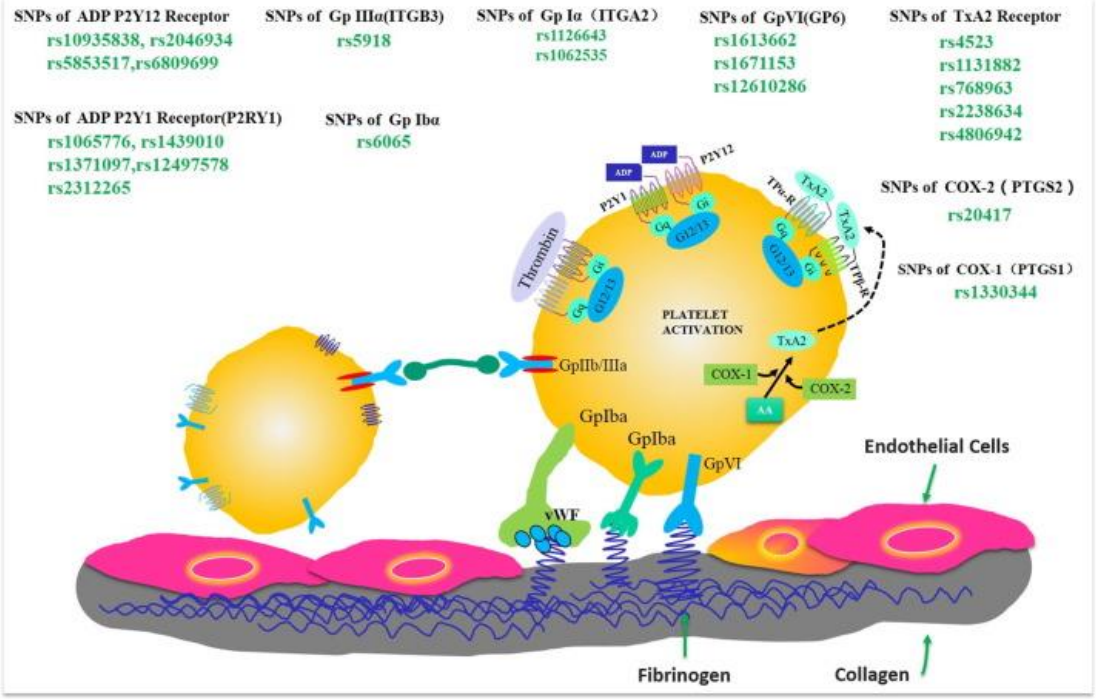
Caused by the functional state of platelets

Markers of inflammation (CRP, interleukins)

Genetic factors (P-selectin gene polymorphism, single nucleotide polymorphisms))

The interaction of platelets with other blood cells

Genetic causes



Du G, Lin Q, Wang J. A brief review on the mechanisms of aspirin resistance. Int J Cardiol. 2016 Oct 1;220:21-6. doi: 10.1016/j.ijcard.2016.06.104. Epub 2016 Jun 23. PMID: 27372038.

Ген	Полиморфизм
ЦОГ-1	C22T
ЦОГ-1	C50T/A842G
ЦОГ-1	G128A
ЦОГ-1	C644A
ЦОГ-1	C714A
ЦОГ-1	C10427A
ЦОГ-1	G1446A
ЦОГ-2	G765C
GPIa	C807T
GPIbα	C5T
GPIIIa	T196C
GPVI	T13254C
ФXIII	G34T
P2Y1	C893T
P2Y1	A1622G
P2Y12	H1/H2

Примечание: Ф — фактор свертывания крови, P2Y1, P2Y12 — тромбоцитарные АДФ рецепторы.

Grinshtein Yu.I., Kosinova A.A., Grinshtein I.Yu. Candidate genes for resistance to acetylsalicylic acid and their association with the risk of developing cardiovascular accidents. Cardiovascular Therapy and Prevention. 2013;12(1):67-72

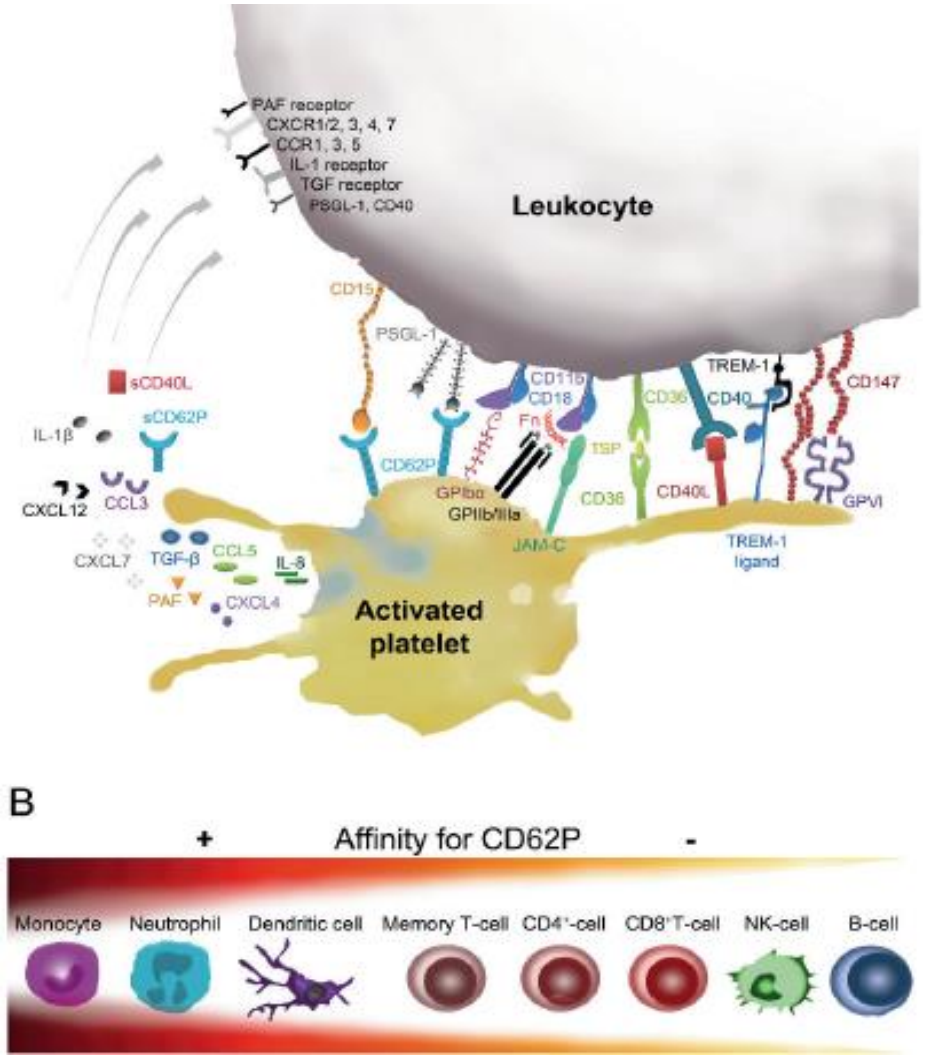
Polymorphisms in the genes of platelet receptor proteins and in the cytochrome P450 gene

Gene (protein)	Localization	Polymorphism	Function
ITGB3 (GpIIb/IIIa) - Fibrinogen receptor	17q21-32	T1565C Leu33Pro rs5819	Platelet aggregation
ITGA2 (GpIa/IIa) - Collagen receptor	5q11.2	C807T Phe224Phe rs1126643	Adhesion, platelet activation
GPIBA - Von Willebrand factor receptor	17p13.2	C482T Thr145Met rs5819	Platelet adhesion to subendothelium
P2RY12 - Platelet ADP receptor	3q24-q25	H1/H2 haplotypes **H1:** **139C** **744T** **no** **52G** / **H2:** **139T** **744C ins801A** **52T**	Platelet aggregation
CYP2C19*2 - Cytochrome P450 gene	10q24.1	G681A rs4244285	Метаболизм лекарств и стероидов

Grinshtein Yu.I., Kosinova A.A., Grinshtein I.Yu., Subbotina T.N., Savchenko A.A. Possible genetic predictors of the development of cardiovascular complications after coronary bypass surgery. Cardiology. 2018;58(7):77-84. https://doi.org/10.18087/cardio.2018.7.10148

The role of platelets

- Platelets are involved in inflammation
- Platelet-leukocyte interaction
- P-selectin - a key role in thrombosis, hemostasis and inflammation



Sviridova S.P., Somonova O.V., Kashiya Sh.R., Obukhova O.A., Sotnikov A.V. The role of platelets in inflammation and immunity. Research and practice in medicine. 2018.5(3). 40-52.

What is P-selectin?

- P-selectin - cell surface protein of α-granules of platelets
- P-selectin is synthesized in endothelial cells and is also found in platelets
- It participates in the formation of platelet-leukocyte complexes
- Increased expression of P-selectin => development of atherosclerosis

Susan C. Fox, Jane A. May, Natalia Dovlatova, Jackie R. Glenn, Andrew Johnson, Ann E. White, Ashwin Radhakrishnan & Stan Heptinstall (2018): How does measurement of platelet P-selectin compare with other methods of measuring platelet function as a means of determining the effectiveness of antiplatelet therapy?, Platelets, DOI: 10.1080/09537104.2018.1434311

Metabolic activity of platelets

Table 1. Chemiluminescent activity of platelet in patients with CHD before and after CABG.

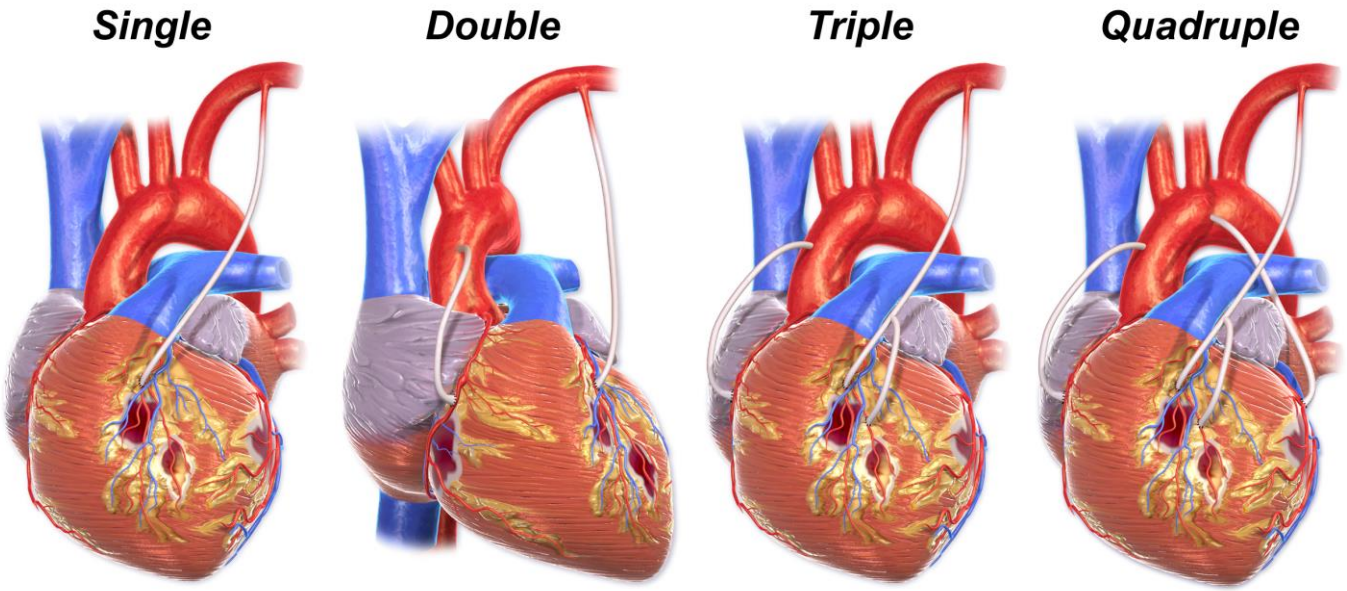
Parameters	Control 1	Before CABG		1 Day After CABG		8–10 days after CABG	
		sASA Patients 2	rASA Patients 3	sASA Patients 4	rASA Patients 5	sASA Patients 6	rASA Patients 7
Spontaneous lucigenin-enhanced chemiluminescence							
Tmax, sec.	213 (80–450)	813 (88–2841) $^{\#}$	185 (35–249) ^{V}	789 (283–2043) $^{\#}$	66 (41–115) ^{V}	938 (565–1908) $^{\#}$	88 (65–420) ^{V}
Imax, r.u.	80 (73–93)	117 (78–566) $^{\#}$	80 (72–92) ^{V}	105 (87–331) $^{\#}$	94 (90–103) $^{\#}$	173 (100–351) $^{\#}$	106 (78–118) $^{\#,V,\otimes}$
S, r.u.× sec. × 10^2	2.38 (1.76–2.75)	3.01 (1.79–7.74) $^{\#}$	2.25 (1.95–3.13)	4.05 (2.44–8.17) $^{\#}$	2.38 (1.97–3.58) ^{V}	4.24 (2.75–6.58) $^{\#}$	2.89 (2.22–3.66)
ADP-induced lucigenin-enhanced chemiluminescence							
Tmax, sec.	96 (49–608)	1036 (346–3743) $^{\#}$	577 (342–1166)	745 (355–1008) $^{\#,\otimes}$	285 (217–341) $^{V,\otimes}$	1266 (621–2198) $^{\#}$	495 (263–1099)
Imax, r.u.	80 (76–127)	127 (84–498) $^{\#}$	81 (73–109) ^{V}	360 (91–595) $^{\#}$	98 (82–106) ^{V}	238 (119–455) $^{\#}$	102 (81–129) ^{V}
S, r.u. × sec. × 10^2	2,75 (1.87–3.65)	4.15 (2.51–10.89) $^{\#}$	2.33 (2.06–3.32) ^{V}	4.86 (2.20–9.50) $^{\#}$	3.05 (2.54–3.48)	4.49 (3.35–7.31) $^{\#}$	2.99 (2.49–3.80) ^{V}
AI	1.01 (0.86–1.87)	1.12 (0.90–1.59)	1.06 (0.92–1.40)	1.11 (0.82–1.40)	1.22 (0.91–1.37)	1.22 (0.99–1.54)	1.09 (1.02–1.17)
Spontaneous luminol-enhanced chemiluminescence							
Tmax, sec.	71 (0–464)	230 (45–1748)	71 (69–81)	336 (71–998)	852 (26–2394) $^{\otimes}$	269 (71–848) $^{\#}$	54 (4–445) ^{V}
Imax, r.u.	80 (77–110)	122 (80–611) $^{\#}$	84 (80–381)	205 (95–490) $^{\#}$	137 (90–167) $^{\#}$	561 (127–1116) $^{\#,\otimes}$	165 (129–388) $^{\#}$
S, r.u. × sec. × 10^2	2.62 (2.22–3.13)	2.96 (2.10–8.99)	3.01 (2.31–3.41)	3.87 (2.71–9.70) $^{\#}$	3.94 (3.20–4.75) $^{\#}$	5.60 (3.96–12.35) $^{\#,\otimes}$	3.63 (3.14–5.08) $^{\#,\otimes}$
ADP-induced luminol-enhanced chemiluminescence							
Tmax, sec.	154 (0–471)	455 (45–2197)	68 (13–743) $^{\#}$	634 (89–1567) $^{\#}$	97 (69–241) ^{V}	631 (264–1483) $^{\#}$	117 (28–530) ^{V}
Imax, r.u.	77 (71–100)	113 (79–519) $^{\#}$	90 (75–342)	294 (96–785) $^{\#}$	145 (88–188) $^{\#}$	690 (156–1346) $^{\#,\otimes}$	156 (120–398) $^{\#,\otimes}$
S, r.u. × sec. × 10^2	2.35 (2.07–3.34)	3.06 (2.24–8.35)	3,27 (2.48–3.58)	5.55 (2.37–11.51) $^{\#}$	3.62 (3.20–5.25) $^{\#}$	6.87 (3.87–20.11) $^{\#,\otimes}$	4.74 (2.60–5.92)
AI	0.99 (0.71–1.26)	1.04 (0.73–1.45)	1.10 (1.04–1.39)	1.09 (0.84–1.32)	1.00 (0.69–1.13)	1.16 (0.85–1.37)	1.06 (0.78–1.28)

The data represent the medians and interquartile ranges (Me (C_{25}—C_{75})). $^{\#}$: $p < 0.05$ vs. control (Mann-Whitney *U* test), ^{V}: $p < 0.05$ between indicators of sASA and rASA patients in each period of the survey (Mann-Whitney *U* test), $^{\otimes}$: $p < 0.05$ vs. with indicators of the patients before CABG (Wilcoxon matched pairs test).

Grinshtein YI, Savchenko AA, Kosinova AA, Goncharov MD. Resistance to Acetylsalicylic Acid in Patients with Coronary Heart Disease Is the Result of Metabolic Activity of Platelets. Pharmaceuticals (Basel). 2020 Aug 1;13(8):178. doi: 10.3390/ph13080178. PMID: 32752170; PMCID: PMC7466119.

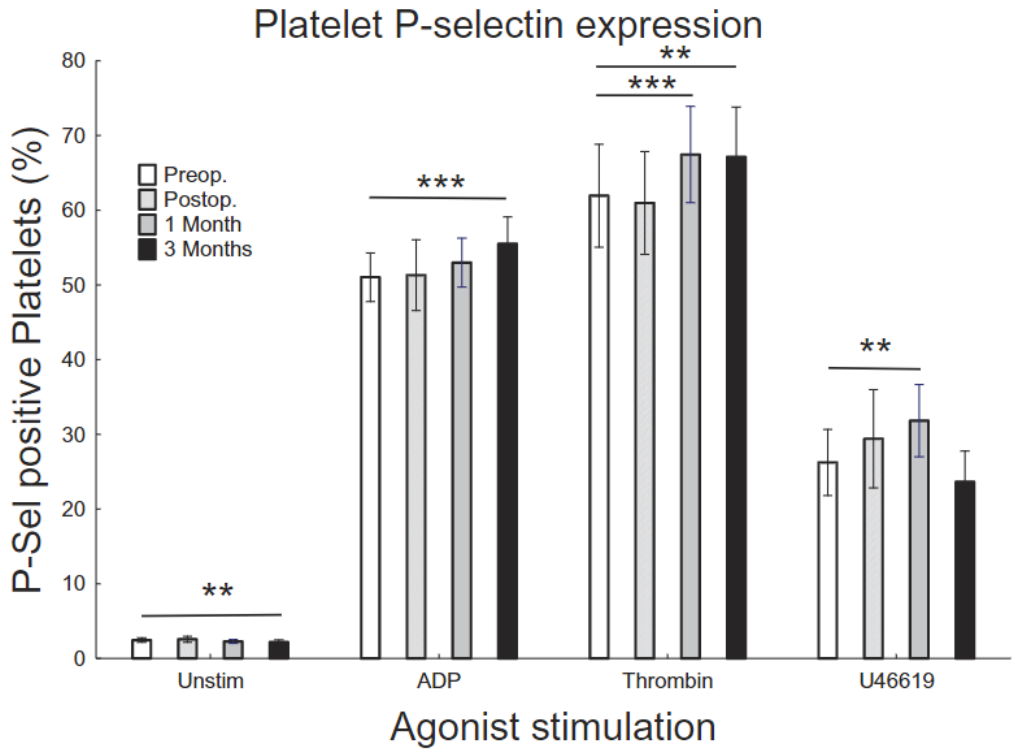
Effect of coronary artery bypass grafting on platelet activity

- There is evidence in the literature that after CABG, the indicators of intercellular interaction and the inflammatory process increase, which leads to the development of resistance to aspirin



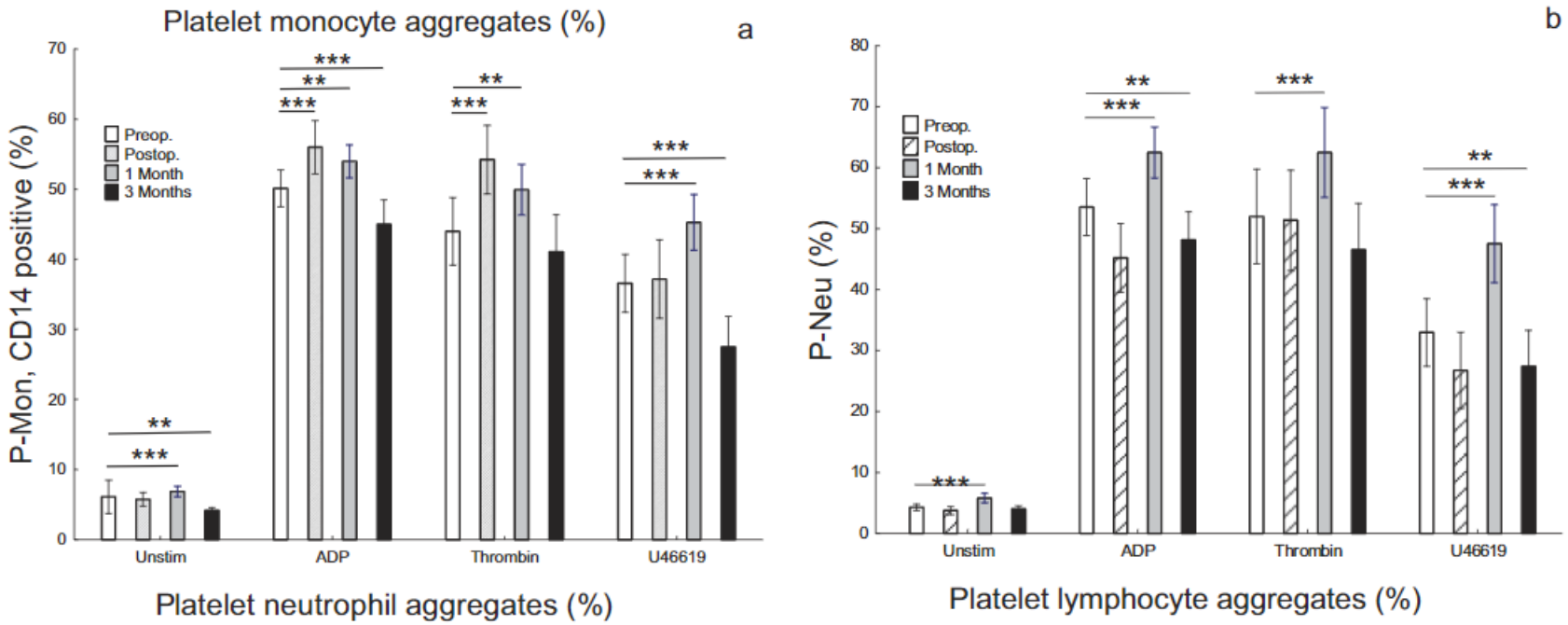
Coronary Artery Bypass Graft (CABG)

The level of expression of P-selectin in patients with coronary artery disease before and after revascularization according to the literature data



Ivert T., Dalén M., Ander C., Stålesen R., Lordkipanidzé M., Hjemdahl P. Increased platelet reactivity and platelet-leukocyte aggregation after elective coronary bypass surgery. Platelets. 2019;30(8):975-981. doi: 10.1080/09537104.2018.1542122. Epub 2018 Nov 13. PMID: 30422037.

The content of platelet-leukocyte aggregates in patients with coronary artery disease before and after revascularization according



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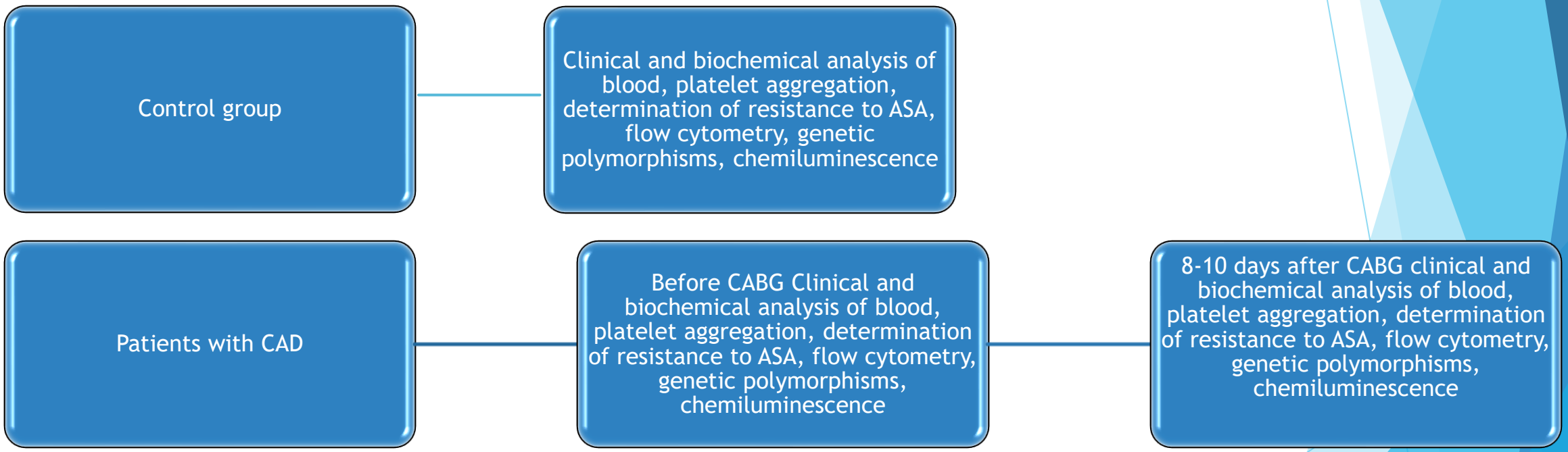
Effect of coronary artery bypass grafting on platelet activity

- Aspirin resistance is reversible due to inadequate suppression of thromboxane A2 in the postoperative period [1]
- Decreased absorption of aspirin in the postoperative period after CABG [2]
- Aspirin resistance develops after CABG and is a reversible process observed within 1 month after surgery [3]
- The use of selective NSAIDs in the postoperative period
- Cardiopulmonary bypass, the release of mediators from damaged cells into the blood, the formation of a large number of young platelets

1. Özkan H, Kiriş İ, Gülmen Ş, Okutan H, Alkaya Solmaz F, Kara KA. Frequency of development of aspirin resistance in the early postoperative period and inadequate inhibition of thromboxane A2 production after coronary artery bypass surgery. Turk Gogus Kalp Dama 2018;26(4):536-543
2. Hattesen A.L., Modrau I.S, Nielsen D.V., Hvas A.M. The absorption of aspirin is reduced after coronary artery bypass grafting. The Journal of Thoracic and Cardiovascular Surgery. 2019 March; 157: 1059-1068
3. Hovens M.M., Snoep J.D., Eikenboom J.C., van der Bom J.G., Mertens B.J., Huisman M.V. Prevalence of persistent platelet reactivity despite use of aspirin: a systematic review. AmHeart J 2007;153:175-81

What do I study?



CAD – coronary artery disease
ASA - acid acetylsalicylic
CABG – coronary artery bypass grafting