

Online Supplemental Table S1.

On-treatment platelet reactivity in carriers of recessive alleles of *CYP3A4**22, *PPAR-α* G209A, and *PPAR-α* A208G for the HPR \geq 236 PRU cut off in the main analysis cohort

Genetic variant	HPR+ (n = 324)	HPR- (n = 800)	Crude OR (95% CI)	Adjusted OR (95% CI)
All patients (n = 1,124)				
<i>CYP3A4</i> *22				
*1/*1 or *1/*22 (n = 1119)	322 (28.8)	797 (71.2)	Ref	Ref
*22/*22 (n = 5)	2 (40.0)	3 (60.0)	1.65 (0.27, 9.92)	3.34 (0.46, 24.27)*
<i>PPAR-α</i> G209A				
GG or GA (n = 1047)	308 (29.4)	739 (70.6)	Ref	Ref
AA (n = 77)	16 (20.8)	61 (79.2)	0.63 (0.36, 1.11)	0.89 (0.48, 1.67)*
<i>PPAR-α</i> A208G				
AA or AG (n = 1045)	307 (29.4)	738 (70.6)	Ref	Ref
GG (n = 79)	17 (21.5)	62 (78.5)	0.66 (0.38, 1.15)	0.91 (0.49, 1.68)*
In statin/fibrate users (n = 996)				
<i>PPAR-α</i> G209A				
GG or GA (n = 928)	275 (29.0)	672 (71.0)	Ref	Ref
AA (n = 68)	14 (20.0)	56 (80.0)	0.63 (0.34, 1.15)	0.86 (0.45, 1.66) [§]
<i>PPAR-α</i> A208G				
AA or AG (n = 926)	274 (29.0)	671 (71.0)	Ref	Ref
GG (n = 70)	15 (20.8)	57 (79.2)	0.66 (0.37, 1.19)	0.88 (0.46, 1.67) [§]
In statin/fibrate non-users (n = 124)				
<i>PPAR-α</i> G209A				
GG or GA (n = 115)	32 (33.3)	64 (66.7)	Ref	Ref
AA (n = 9)	2 (28.6)	5 (71.4)	0.63 (0.12, 3.17)	1.18 (0.08, 16.47) [§]
<i>PPAR-α</i> A208G				
GG or GA (n = 115)	32 (33.3)	64 (66.7)	Ref	Ref
AA (n = 9)	2 (28.6)	5 (71.4)	0.63 (0.12, 3.17)	1.18 (0.08, 16.47) [§]

Note:

*CYP3A4**22 = rs35599367, G209A = rs4253728, A208G = rs4823613

Abbreviations: CI = confidence interval, HPR = high on-treatment platelet reactivity, OR = odds ratio, Ref = reference. All p-values for crude and adjusted odds ratios are > 0.05 .

* Adjusted for age, sex, body mass index, smoking, diabetes, previous myocardial infarction, co-medication (calcium channel blockers, statins/fibrates, proton pump inhibitors), impaired renal function, clopidogrel loading, and CYP2C19 metabolizer status.

§ Adjusted for all variables mentioned above, excluding statin/fibrate use

Online Supplemental Table S2. Baseline characteristics for the main analysis cohort and both validation cohorts

	Main analysis (n = 1,124)	Validation cohorts	
		POPular (n = 716)	ICPC (n = 885)
Characteristics	n (%)	n (%)	n (%)
Age, years (mean, SD)	63.9 ± 10.8	63.9 ± 10.0	64.0 ± 10.5
Sex (male)	848 (75.4)	538 (75.1)	656 (74.1)
BMI, kg/m ² (mean, SD)	27.5 ± 4.2	27.3 ± 4.2	28.2 ± 4.5
Smoking habit			
No	632 (56.1)	342 (47.8)	347 (39.2)
Current smoker or stopped < 6 months	247 (22.0)	162 (22.6)	143 (16.2)
Past smoker	238 (21.2)	212 (29.6)	174 (19.7)
Unknown	7 (0.6)		221 (25.0)
Disease history			
Hypertension	936 (83.3)	564 (78.8)	725 (81.9)
Unknown			4 (0.5)
Diabetes	235 (20.9)	145 (20.3)	262 (29.6)
Unknown			1 (0.1)
Myocardial infarction	349 (31.0)	306 (42.7)	196 (22.1)
Unknown			197 (22.3)
Co-medication at baseline			
Beta-blocker	900 (80.1)	559 (78.1)	636 (71.9)
Unknown			43 (4.9)
ACE inhibitor	422 (37.5)	267 (37.3)	337 (38.1)
Unknown		1 (0.1)	270 (30.5)
Calcium channel blocker	314 (27.9)	260 (36.3)	190 (21.5)
Unknown			44 (5.0)
ARB	204 (18.1)	102 (14.2)	106 (12.0)
Unknown			369 (30.4)
Diuretic	313 (27.8)	125 (17.5)	NA
Statin or fibrate	1017 (90.5)	580 (81.0)	630 (71.2)
Unknown			29 (3.3)
Proton pump inhibitor	454 (40.4)	195 (27.2)	286 (32.3)
Unknown			22 (2.5)
Impaired renal function	9 (0.8)	4 (0.6)	19 (2.1)
Unknown		122 (17.0)	112 (12.7)
Clopidogrel loading	395 (35.1)	370 (51.7)	NA
Unknown		12 (1.7)	
CYP2C19 metabolizer			
Normal	821 (73.0)	505 (70.5)	620 (70.1)
Intermediate	274 (24.4)	183 (25.6)	241 (27.2)
Poor	29 (2.6)	20 (2.8)	18 (2.0)
Unknown	-	8 (1.1)	6 (0.7)
CYP3A4*22			
MAF	6.3%		
*1/*1	987 (87.8)	NA	NA
*1/*22	132 (11.7)		

*22/*22	5 (0.4)		
<i>PPAR-α</i> G209A			
MAF	25.4%	25.0%	27.2%
GG	630 (56.0)	402 (56.1)	462 (52.2)
GA	417 (37.1)	270 (37.7)	364 (41.1)
AA	77 (6.9)	44 (6.1)	59 (6.7)
<i>PPAR-α</i> A208G			
MAF	27.0%	26.3%	28.8%
AA	597 (53.1)	387 (54.1)	442 (49.9)
AG	448 (39.9)	282 (39.4)	377 (42.6)
GG	79 (7.0)	47 (6.6)	66 (7.5)

Note:

*CYP3A4**22 = rs35599367, G209A = rs4253728, A208G = rs4823613

Abbreviations: ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, BMI = body mass index, MAF = minor allele frequency, NA = not available, PCI = percutaneous coronary intervention, SD = standard deviation.

Online Supplemental Table S3.

Estimates for the on-treatment platelet reactivity outcome in carriers of recessive alleles of *PPAR-α* G209A, and *PPAR-α* A208G in the POPular validation cohort

Genetic variant	Mean ± SD	Coefficient (95% CI)	
		Crude	Adjusted
All patients (n = 716)			
<i>PPAR-α</i> G209A			
GG or GA (n = 672)	213.0 ± 76.5	Ref	Ref
AA (n = 44)	202.5 ± 71.3	-10.54 (-33.81, 12.73)	-11.31 (-34.52, 11.89)†
<i>PPAR-α</i> A208G			
AA or AG (n = 669)	212.8 ± 76.6	Ref	Ref
GG (n = 47)	205.9 ± 69.2	-7.0 (-29.52, 15.62)	-7.40 (-29.77, 14.98)†
In statin/fibrate users (n = 567)			
<i>PPAR-α</i> G209A			
GG or GA (n = 533)	211.5 ± 77.2	Ref	Ref
AA (n = 34)	192.7 ± 64.3	-18.06 (-44.62, 8.49)	-15.28 (-42.15, 11.60)§
<i>PPAR-α</i> A208G			
AA or AG (n = 529)	211.8 ± 77.3	Ref	Ref
GG (n = 38)	197.2 ± 63.1	-14.54 (-39.76, 10.68)	-13.06 (-38.28, 12.15)§
In statin/fibrate non-users (n = 146)			
<i>PPAR-α</i> G209A			
GG or GA (n = 136)	218.3 ± 72.0	Ref	Ref
AA (n = 10)	231.9 ± 86.9	13.59 (-33.70, 60.89)	11.83 (-37.30, 60.95)§
<i>PPAR-α</i> A208G			
AA or AG (n = 137)	217.7 ± 72.1	Ref	Ref
GG (n = 9)	242.3 ± 85.3	24.61 (-24.95, 74.17)	27.93 (-22.83, 78.69)§

Note: All values are in PRU.

*CYP3A4**22 = rs35599367, G209A = rs4253728, A208G = rs4823613

Abbreviations: CI = confidence interval, SD = standard deviation, Ref = reference. All p-values for crude and adjusted odds ratios are > 0.05.

Symbols:

† Adjusted for age, sex, body mass index, smoking, diabetes, previous myocardial infarction, co-medication (calcium channel blockers, statins/fibrates, proton pump inhibitors), impaired renal function, clopidogrel loading, and CYP2C19 metabolizer status.

§ Adjusted for all variables mentioned above, excluding statin/fibrate use

Online Supplemental Table S4. Odds ratio for high platelet reactivity outcome in carriers of recessive alleles of *PPAR-α* G209A, and *PPAR-α* A208G in the POPular validation cohort

PRU >= 236 PRU cut off

Genetic variant	HPR+ (n = 290)	HPR- (n = 439)	Crude OR (95% CI)	Adjusted OR (95% CI)
All patients (n = 729)				
<i>PPAR-α</i> G209A GG or GA (n = 685) AA (n = 44)	277 (40.4) 13 (29.5)	408 (59.6) 31 (70.5)	Ref 0.62 (0.62, 1.20)	Ref 0.58 (0.27, 1.23)*
<i>PPAR-α</i> A208G AA or AG (n = 681) GG (n = 48)	275 (40.4) 15 (31.3)	406 (59.6) 33 (68.8)	Ref 0.67 (0.36, 1.26)	Ref 0.64 (0.31, 1.30)*
In statin/fibrate users (n = 579)				
<i>PPAR-α</i> G209A GG or GA (n = 545) AA (n = 34)	220 (40.4) 9 (26.5)	325 (59.6) 25 (73.5)	Ref 0.53 (0.24, 1.16)	Ref 0.54 (0.22, 1.33) [§]
<i>PPAR-α</i> A208G AA or AG (n = 540) GG (n = 39)	218 (40.4) 11 (28.2)	322 (59.6) 28 (71.8)	Ref 0.58 (0.28, 1.19)	Ref 0.58 (0.26, 1.31) [§]
In statin/fibrate non-users (n = 147)				
<i>PPAR-α</i> G209A GG or GA (n = 137) AA (n = 10)	56 (40.9) 4 (40.0)	81 (59.1) 6 (60.0)	Ref 0.96 (0.26, 3.58)	Ref 0.81 (0.16, 4.13) [§]
<i>PPAR-α</i> A208G GG or GA (n = 138) AA (n = 9)	56 (40.6) 4 (44.4)	82 (59.4) 5 (55.6)	Ref 1.17 (0.30, 4.56)	Ref 1.27 (0.24, 6.72) [§]

PRU > 208 PRU cut off

Genetic variant	HPR+ (n = 436)	HPR- (n = 688)	Crude OR (95% CI)	Adjusted OR (95% CI)
All patients (n = 729)				
<i>PPAR-α</i> G209A GG or GA (n = 685) AA (n = 44)	365 (53.3) 19 (43.2)	320 (46.7) 25 (56.8)	Ref 0.67 (0.36, 1.23)	Ref 0.76 (0.38, 1.53)*
<i>PPAR-α</i> A208G AA or AG (n = 681) GG (n = 48)	362 (53.2) 22 (45.8)	319 (46.8) 26 (54.2)	Ref 0.75 (0.41, 1.34)	Ref 0.84 (0.43, 1.64)*
In statin/fibrate users (n = 579)				
<i>PPAR-α</i> G209A GG or GA (n = 545) AA (n = 34)	286 (52.5) 13 (38.2)	259 (47.5) 21 (61.8)	Ref 0.56 (0.28, 1.14)	Ref 0.69 (0.30, 1.56) [§]
<i>PPAR-α</i> A208G AA or AG (n = 540) GG (n = 39)	283 (52.4) 16 (41.0)	257 (47.6) 23 (59.0)	Ref 0.63 (0.33, 1.22)	Ref 0.73 (0.35, 1.56) [§]
In statin/fibrate non-users (n = 147)				
<i>PPAR-α</i> G209A GG or GA (n = 137) AA (n = 10)	78 (56.9) 6 (60.0)	59 (43.1) 4 (40.0)	Ref 1.14 (0.31, 4.20)	Ref 1.32 (0.28, 6.34) [§]
<i>PPAR-α</i> A208G GG or GA (n = 138) AA (n = 9)	78 (56.5) 6 (66.7)	60 (43.5) 3 (33.3)	Ref 1.54 (0.37, 6.40)	Ref 2.27 (0.43, 11.93) [§]

Note:

*CYP3A4**22 = rs35599367, G209A = rs4253728, A208G = rs4823613

Abbreviations: CI = confidence interval, HPR = high on-treatment platelet reactivity, OR = odds ratio, Ref = reference. All p-values for crude and adjusted odds ratios are > 0.05.

* Adjusted for age, sex, body mass index, smoking, diabetes, previous myocardial infarction, co-medication (calcium channel blockers, statins/fibrates, proton pump inhibitors), impaired renal function, clopidogrel loading, and CYP2C19 metabolizer status.

§ Adjusted for all variables mentioned above, excluding statin/fibrate use

Online Supplemental Table S5. Estimates for the on-treatment platelet reactivity outcome in carriers of recessive alleles of *PPAR-α* G209A, and *PPAR-α* A208G in the ICPC validation cohort

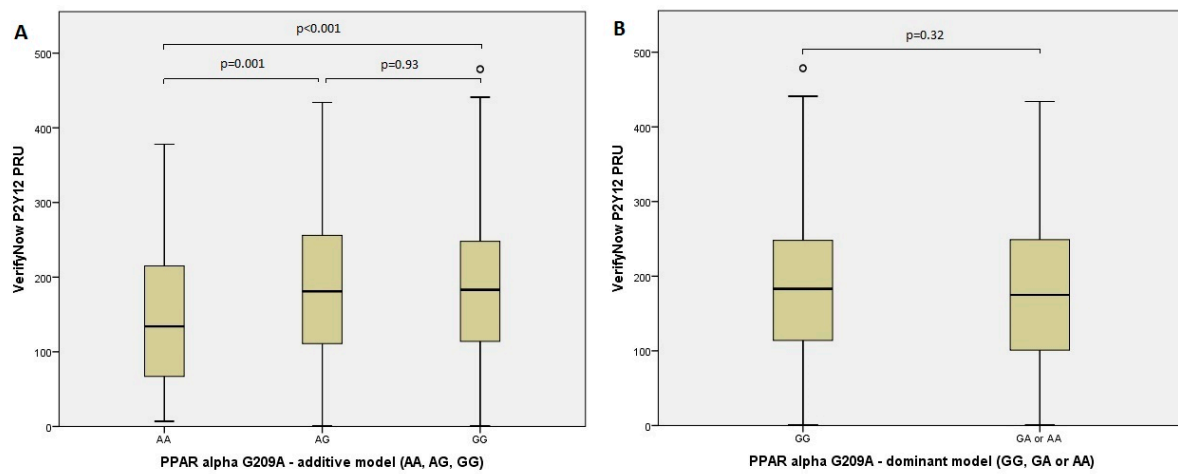
Genetic variant	Beta (95% CI)	Coefficient
		Crude p-value
All patients (n = 882)		
<i>PPAR-α</i> G209A GG or GA (n = 823) AA (n = 59)	-0.028 (-0.024, 0.010)	Ref p = 0.40
<i>PPAR-α</i> A208G AA or AG (n = 816) GG (n = 66)	-0.030 (-0.025, 0.010)	Ref p = 0.46
In statin/fibrate users (n = 628)		
<i>PPAR-α</i> G209A GG or GA (n = 592) AA (n = 36)	-0.021 (-0.024, 0.013)	Ref p = 0.59
<i>PPAR-α</i> A208G AA or AG (n = 587) GG (n = 41)	-0.029 (-0.027, 0.012)	Ref p = 0.46
In statin/fibrate non-users (n = 225)		
<i>PPAR-α</i> G209A GG or GA (n = 204) AA (n = 21)	-0.050 (-0.052, 0.023)	Ref p = 0.45
<i>PPAR-α</i> A208G AA or AG (n = 202) GG (n = 23)	-0.038 (-0.050, 0.028)	Ref p = 0.57

Note:

*CYP3A4**22 = rs35599367, G209A = rs4253728, A208G = rs4823613

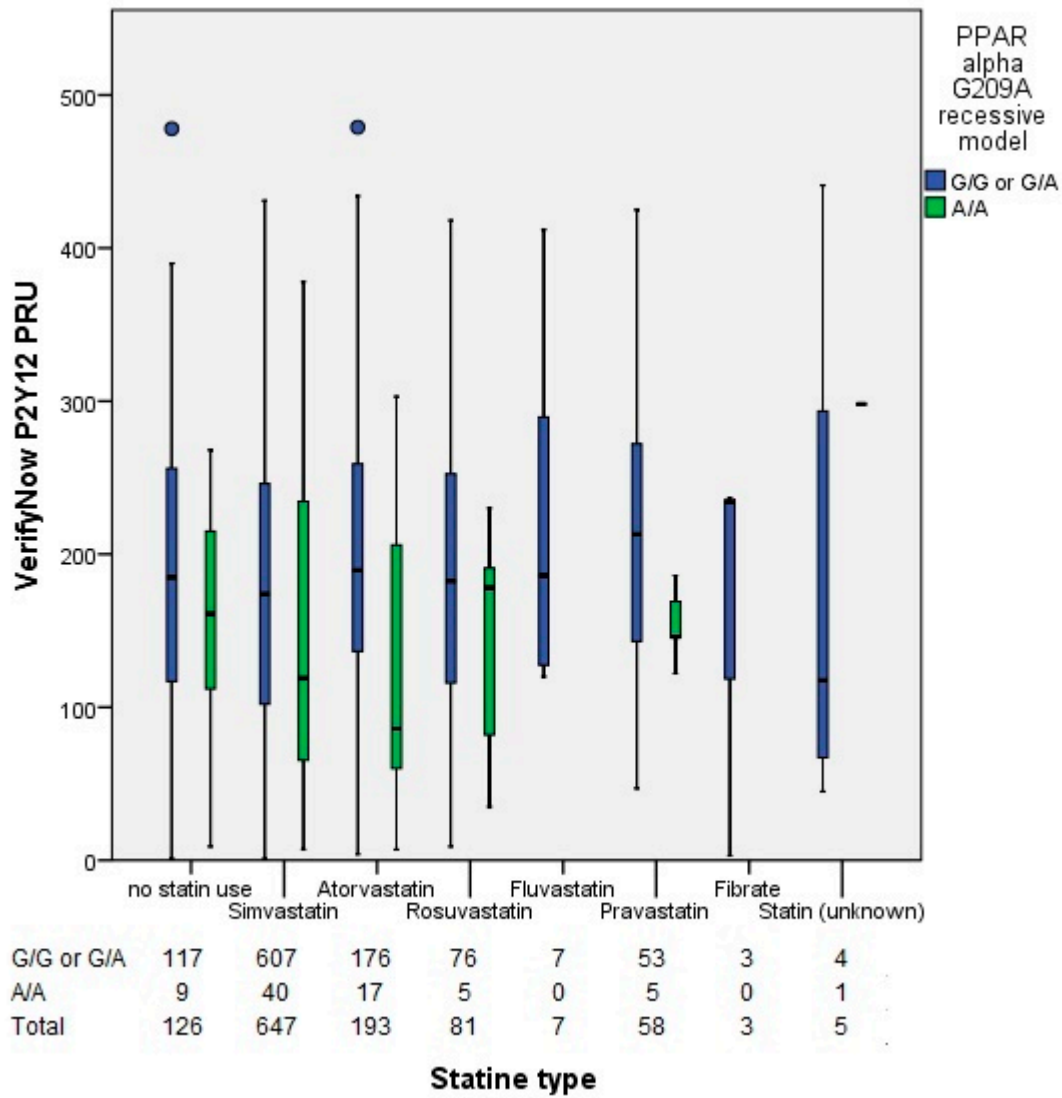
Abbreviations: CI = confidence interval, SD = standard deviation, Ref = reference.

Online Supplemental Figure S1:



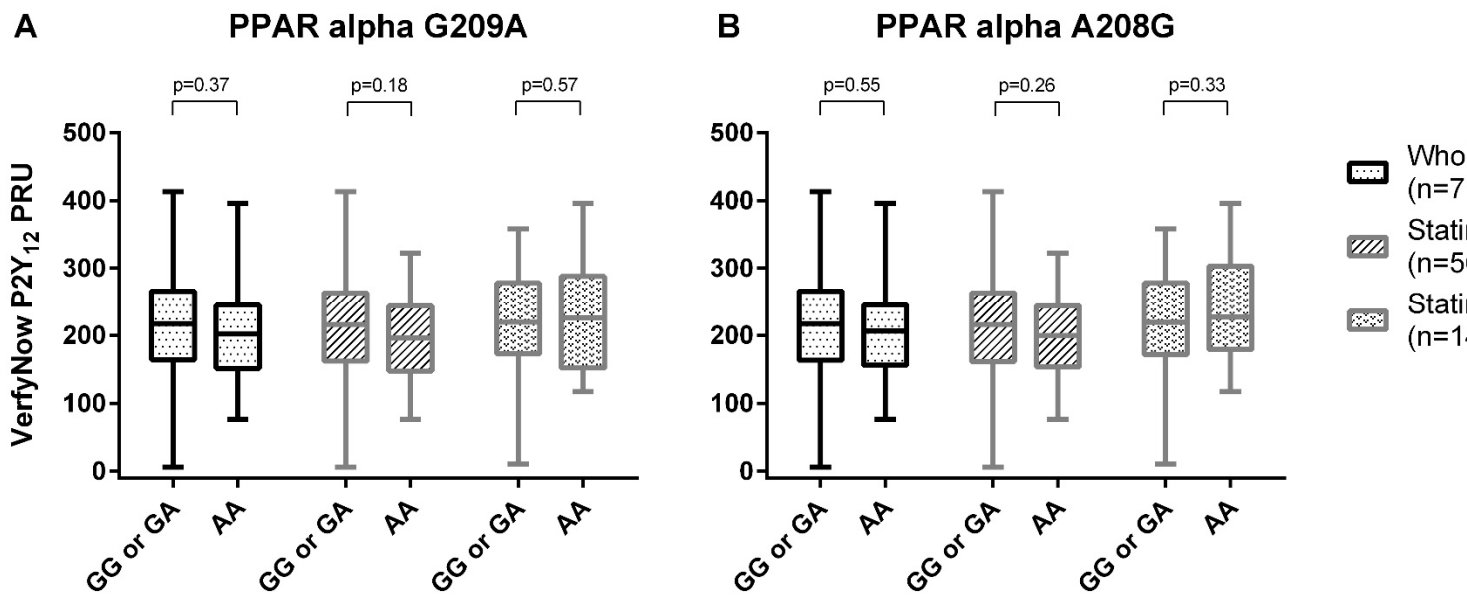
Online Supplemental Figure S1. The on-treatment platelet reactivity in the main analysis cohort, as measured with the VerifyNow[®] assay for PPAR alpha G209A (rs4253728), analyzed in a (a) additive model, (b) dominant model.

Online Supplemental Figure S2:



Online Supplemental Figure S2. The on-treatment platelet reactivity in the main analysis cohort, as measured with the VerifyNow[®] assay for PPAR alpha G209A (rs4253728), stratified according to different statin and fibrate use

Online Supplemental Figure S3:



Online Supplemental Figure S3. The on-treatment platelet reactivity, as measured with the VerifyNow[®] assay: (a) *PPAR-α* G209A (rs4253728), (b) *PPAR-α* A208G (rs4823613) in the POPular validation cohort.

Online Supplementary Data:

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