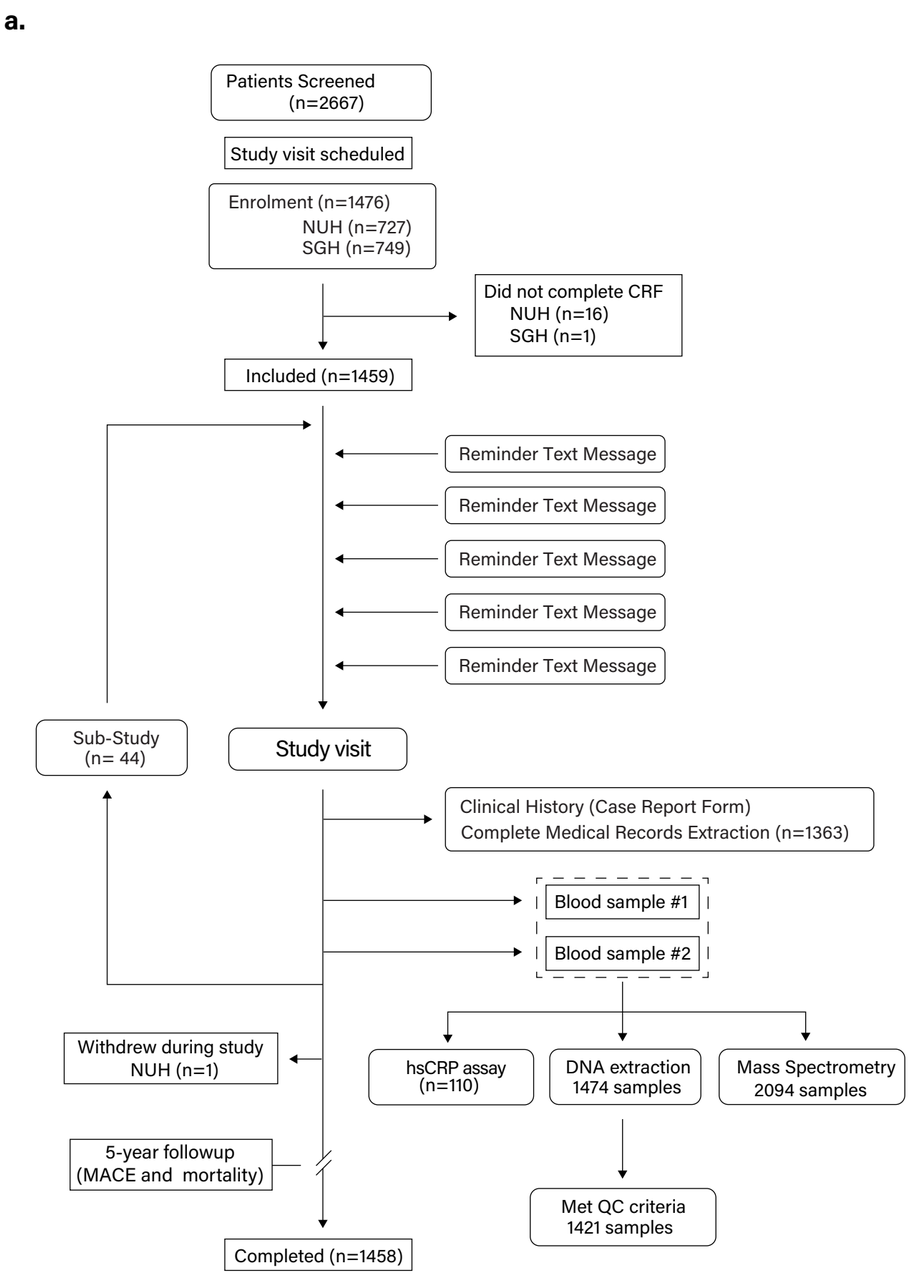
Fig. S1 - Study Design Flowchart



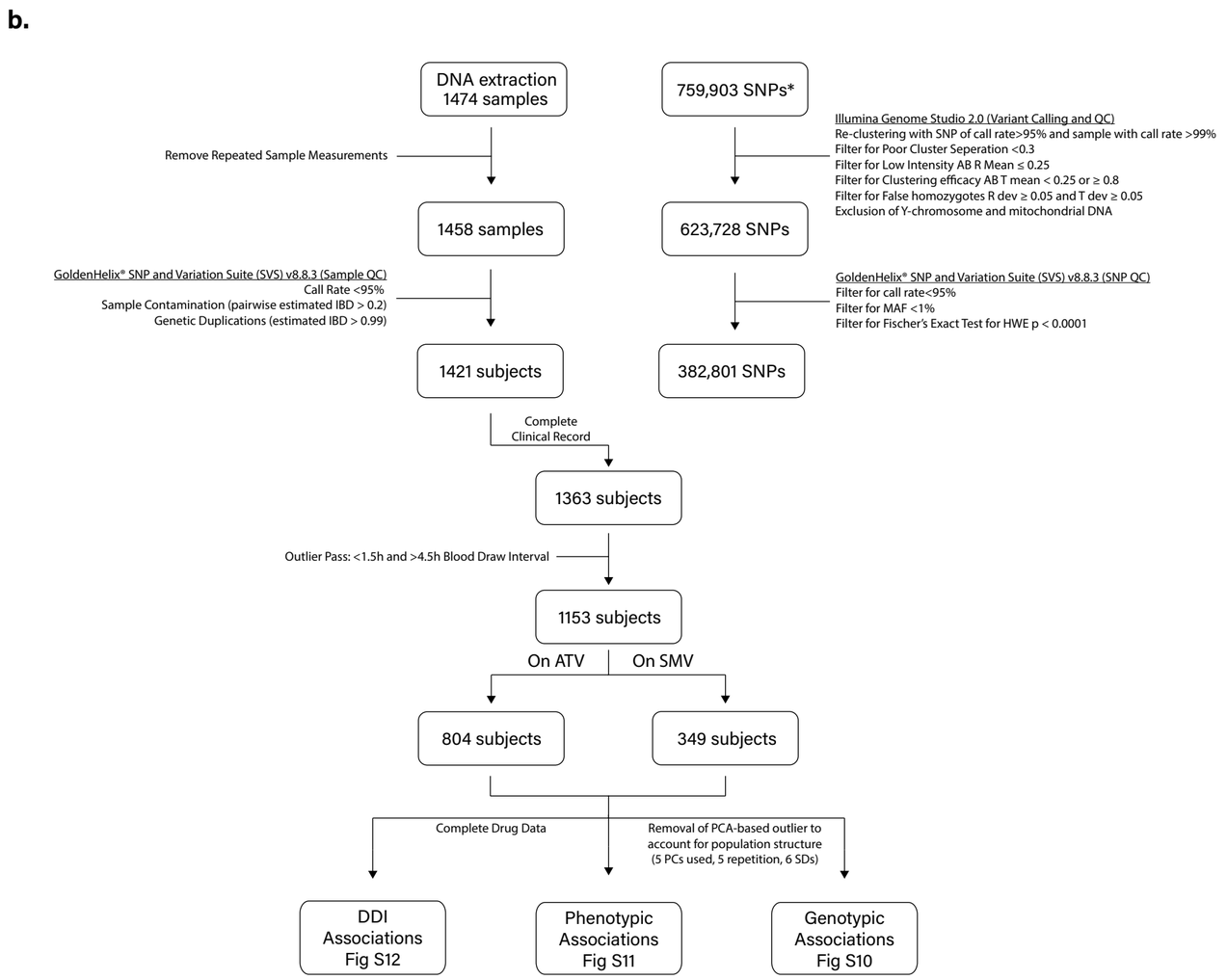


Figure S1 (related to Figure 1). CONSORT Diagram and Genetic QC methodology a) Study Design Flowchart. b) Genetic Sample and SNP QC Flowchart. Digitally transformed ATV phenotypes were used for GWAS Screening and SNP QC(*). Further sample processing are placed in Fig. S10, S11 and S12.

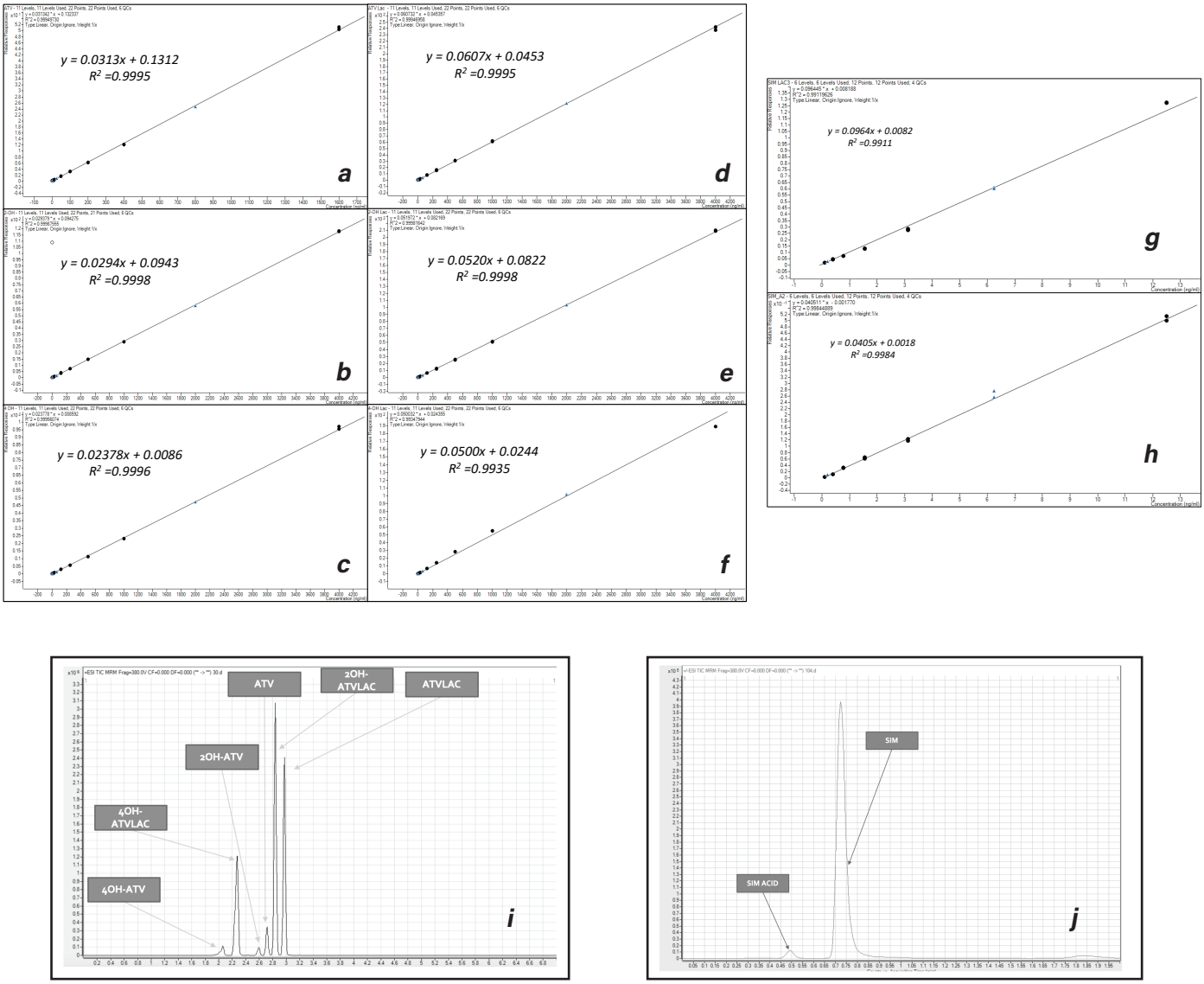


Figure S2 (related to Figure 2, 4) Linearization, Calibration and Chromatographic Separation of Statin Compounds. a) Standard calibration curve based on peak area ratio of analyte spiked in human pooled quality control plasma samples over its stable-isotope internal standard. Detailed calibration parameters of a) ATV, b) 2OHATV, c) 4OHATV, d) ATVLAC e) 2OHATVLAC and f) 4OHATVLAC are in supplemental methods. For ATV in panel (a) the lower limit of quantification (LLOQ) was 0.2 ng/mL, the upper limit of quantification (ULOQ) was 1600ng/mL. For metabolites in panels (b)-(f) the LLOQs were 0.5-1.0ng/mL, the ULOQs were 4000ng/mL. Weightage of 1/x was applied to all linearized curves. g) SMV and h) SMVLAC calibration curves are displayed, LLOQs were 0.1ng/mL, ULOQs were 12.5ng/mL. i) representative MRM chromatogram of statins obtained from plasma samples. Retention times are ATV (2.718min), ATVLAC (2.984min), 2OHATV (2.590min), 2OHATVLAC (2.939min), 4OHATV (2.058min) and 4OHATVLAC (2,272min) and for j) SMC (0.482min) and SMVLAC (0.739min).

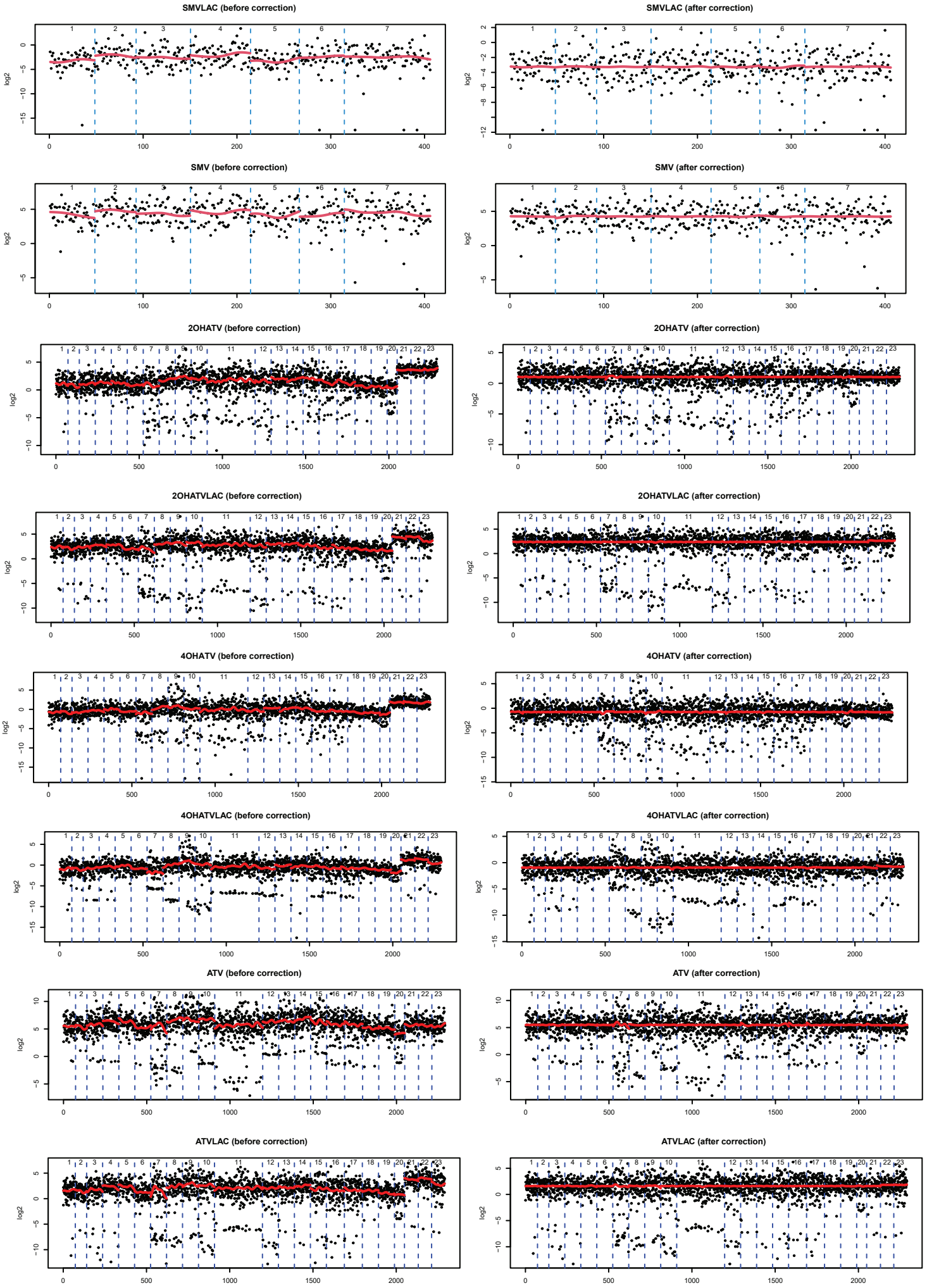


Figure S3 (related to Figure 2, 3, 4, 5) Batch Correction using Kernel Regression. Kernel Regression for Multi-Batch correction of sensitivity drift and bias. y-axis corresponds to log2 transformed values, while x-axis corresponds to run order. Batch numbers are segregated by blue dashed lines, while approximate curve is in red.

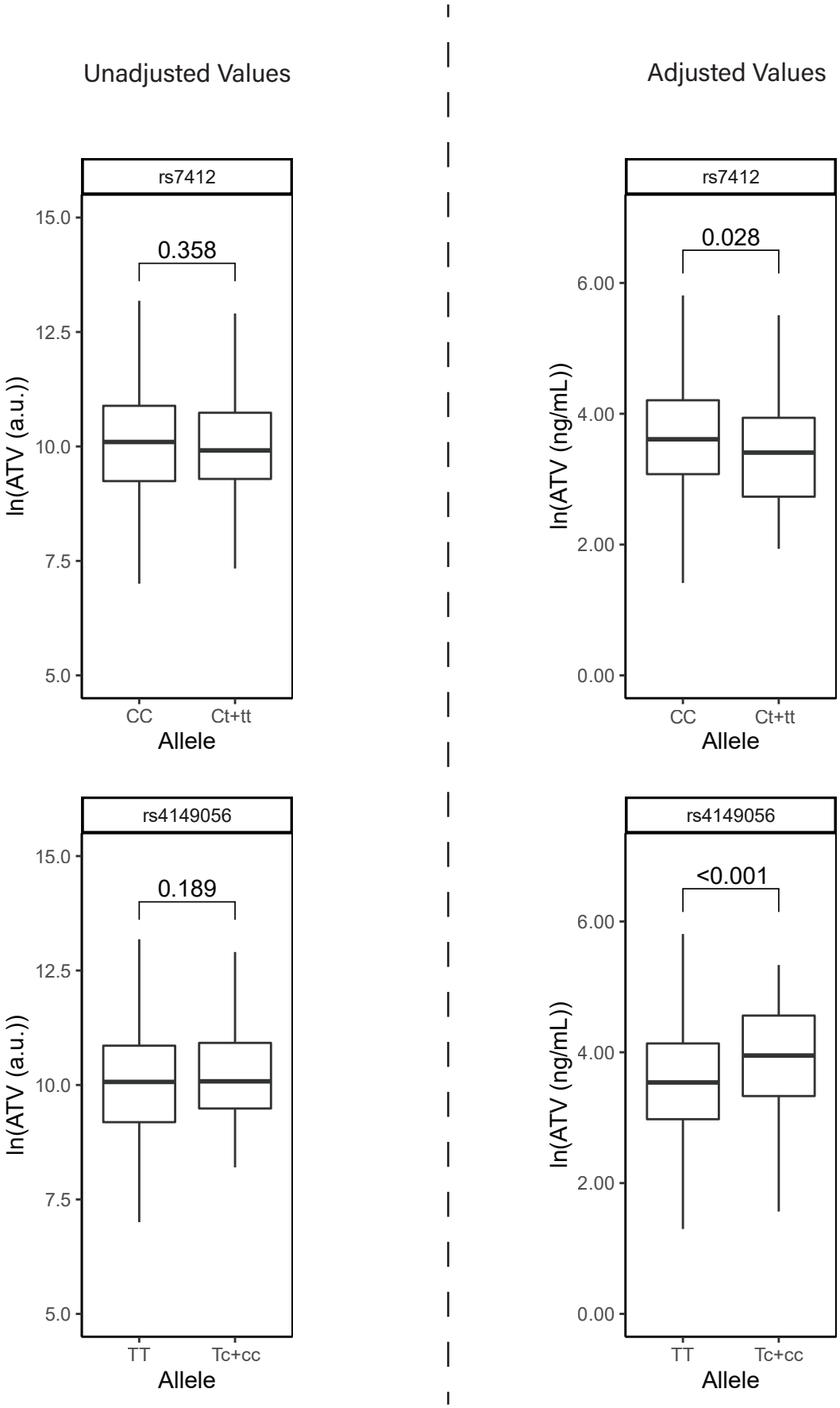


Figure S4 (related to Figure 2, S3) Unadjusted vs Adjusted ATV levels using known genetic associations as validation. Comparison of Unadjusted and Adjusted ATV levels using digital phenotyping. Known associations of genetic factors with ATV are recovered with digital phenotyping protocol. Major Alleles are in capital, while minor alleles are represented in lowercase. Mann-Whitney U-Test P-value is reported in each boxplot.

a.

b.

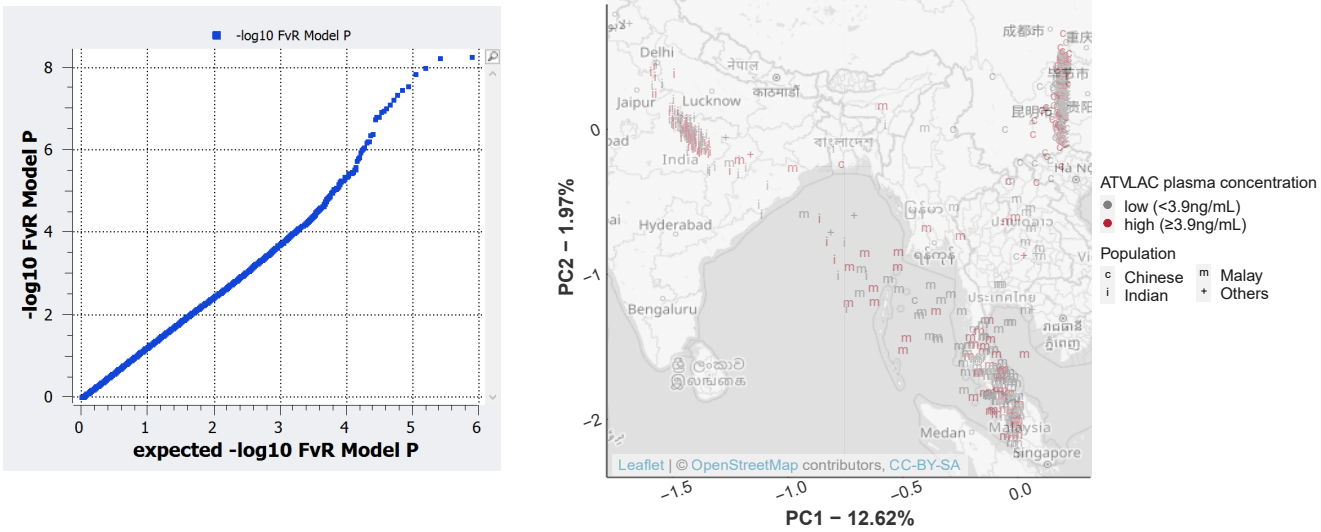


Figure S5 (related to Figure 3) UGT1A Association identified via GWAS. a) QQ-plot of Forward Regression Model b) PCA Plot of all samples with the top 2 genotypic components stratifying into 3 clusters. Self-reported ancestry is represented with alphabetical overlay, and geographical location of China, India and Malaysia were in congruence with genotypic PC strata. Subject with low and high ATVLAC levels are colored gray and red respectively and are evenly distribut-ed across the 3 major population clusters.

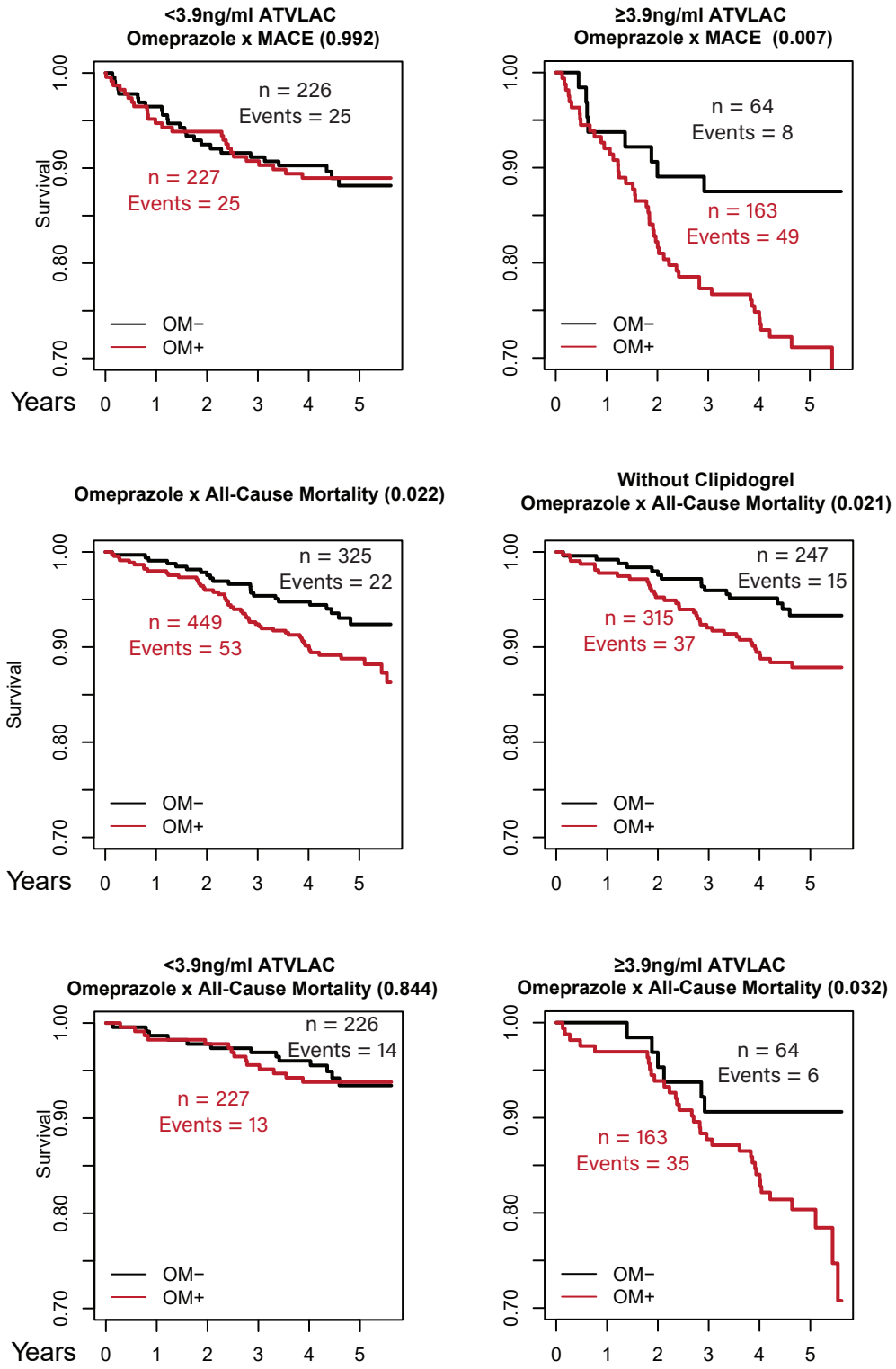


Figure S6 (related to Figure 4) KM plots for Omeprazole vs MACE and All-Cause Mortality under different conditions. (Top) Omeprazole is associated with MACE in high-risk, ATVLAC≥3.9ng/ml patients, but not in low-risk, ATVLAC < 3.9ng/ml patients. (Middle) Omeprazole is associated with all-cause mortality in patients taking ATV. (Bottom) Omeprazole is associated with all-cause mortality in high-risk, ATVLAC≥ 3.9ng/ml patients, but not in low-risk, ATVLAC < 3.9ng/ml patients.

Fig. S7 - Chord Diagram

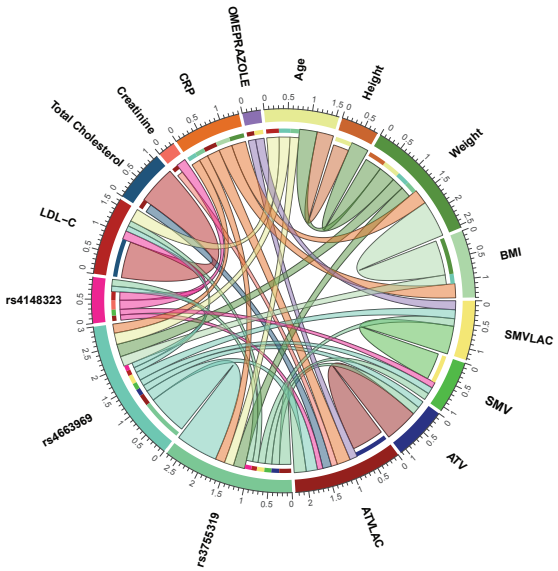
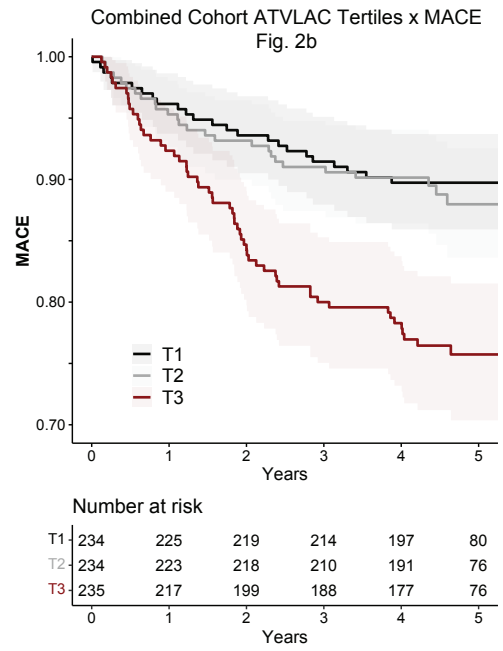
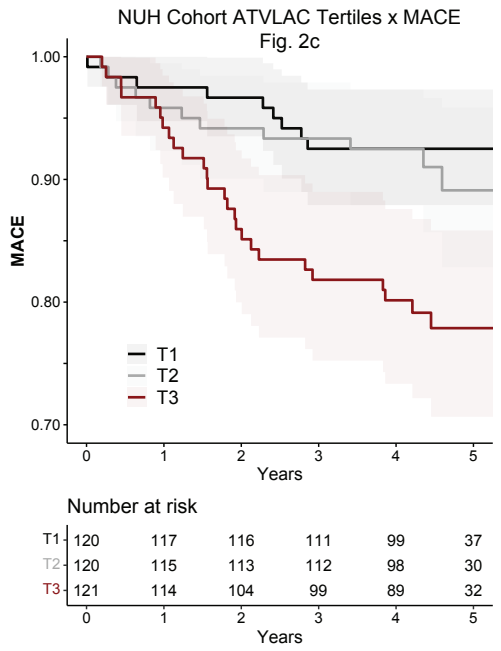
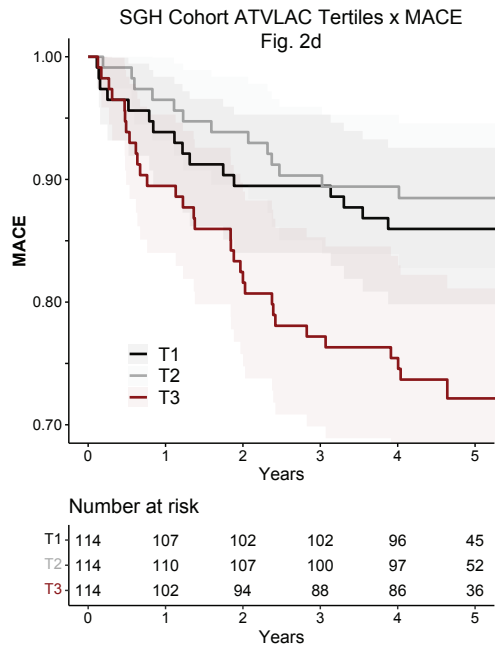
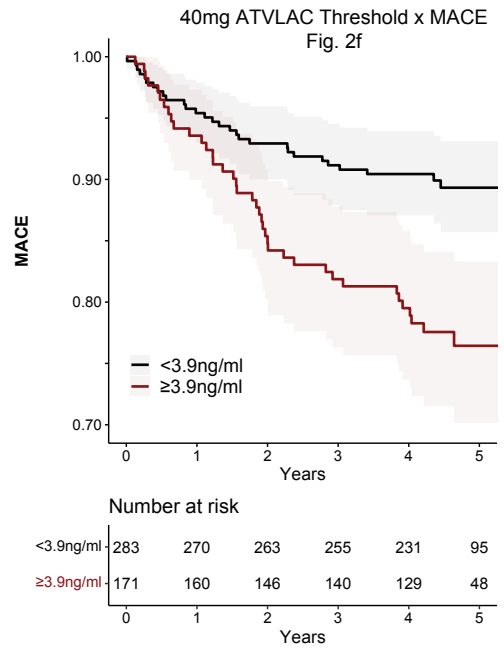


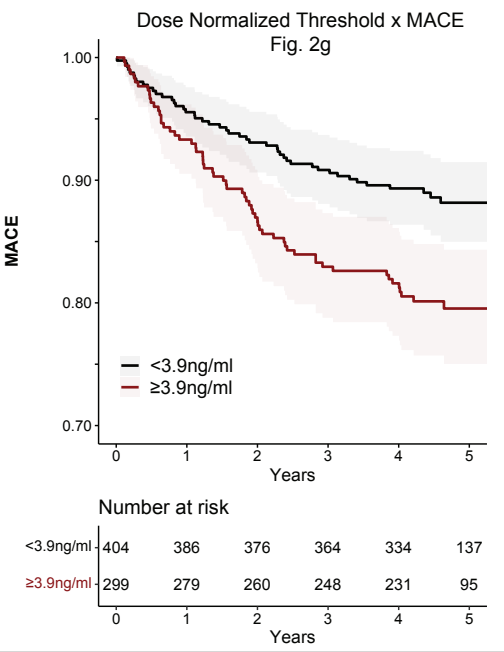
Figure S7 (related to Figure 6) Chord Diagram. Spearman's correlation between the major players described in this paper has been summarized in the chord diagram, with the magnitudes represented in the angular axis

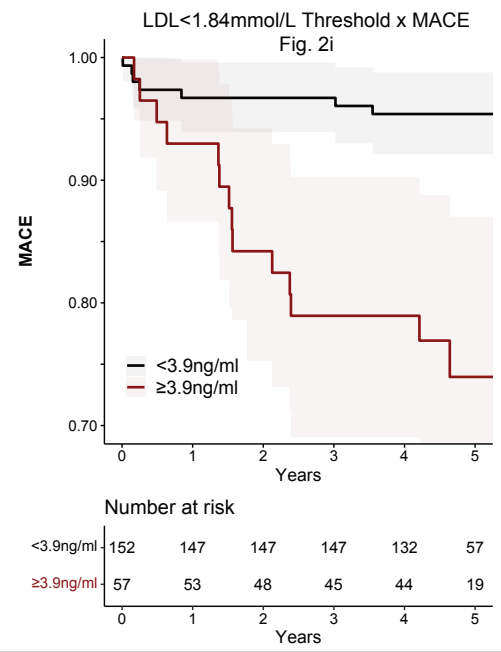


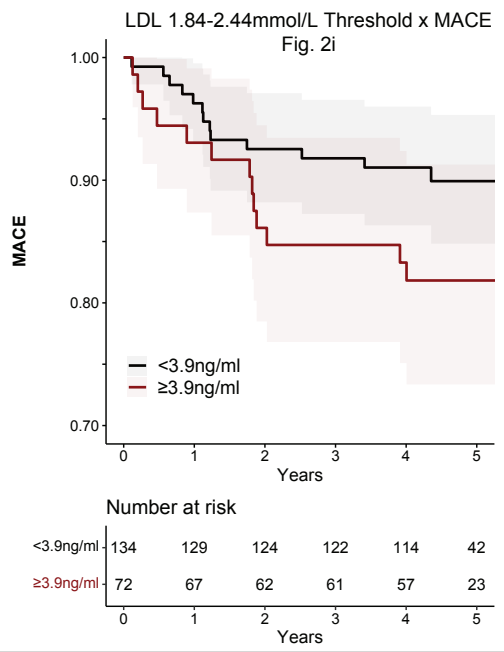


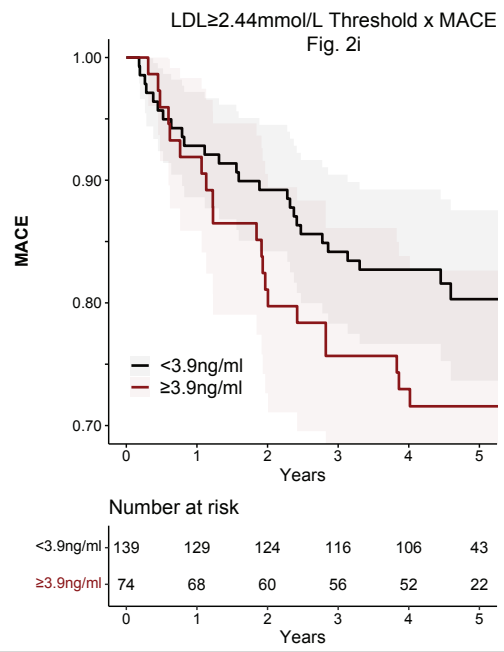


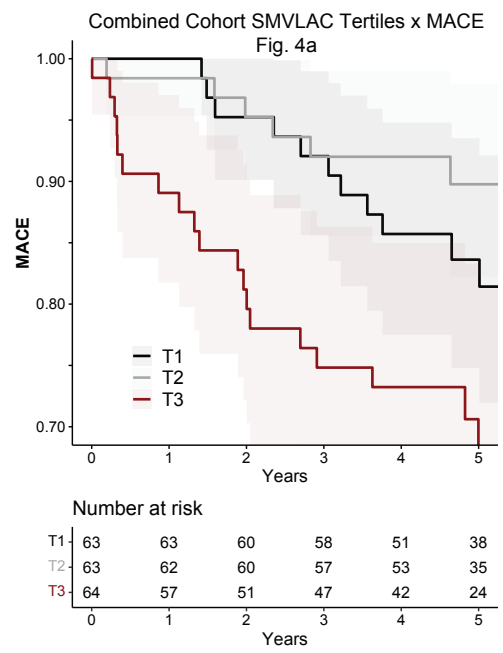


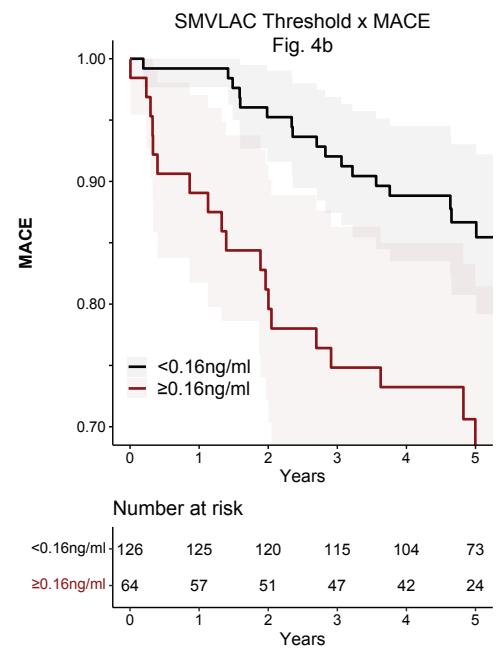


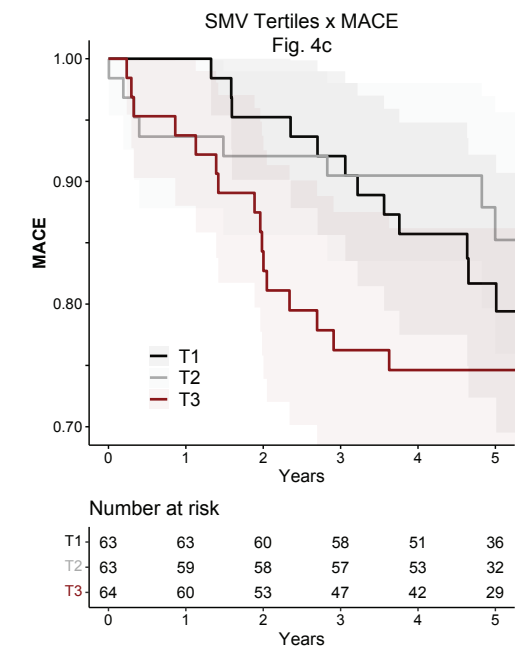


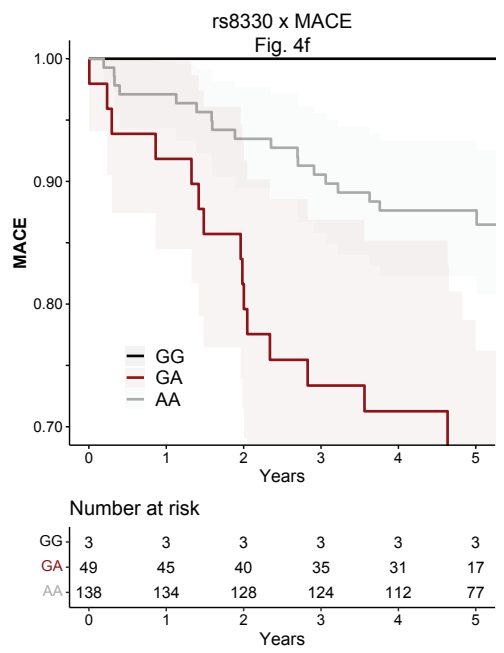


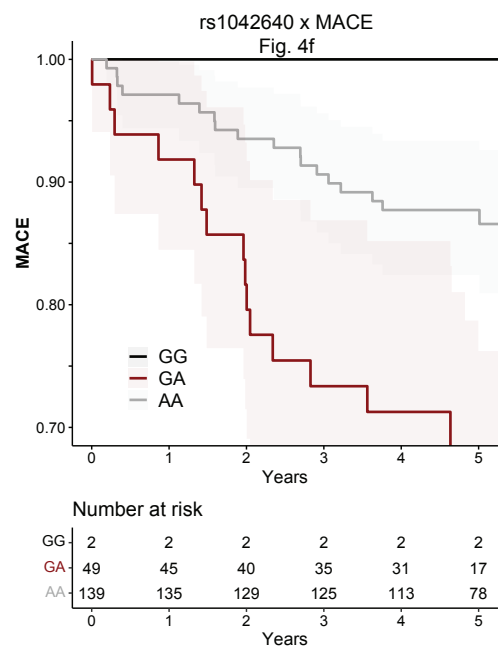












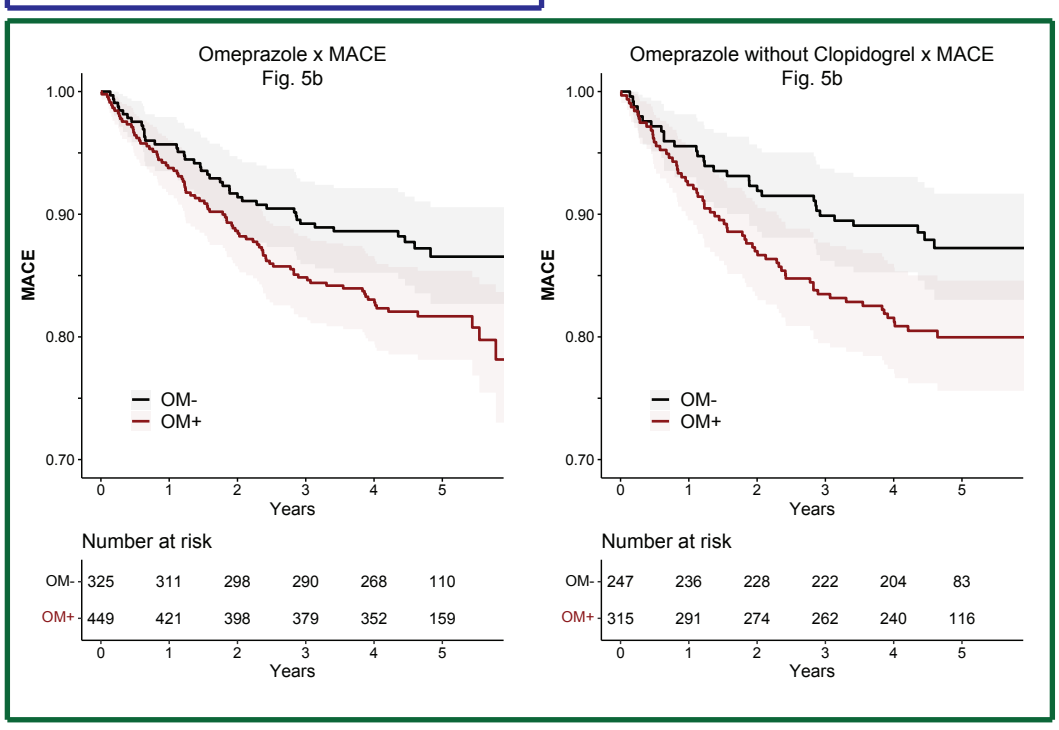


Figure S8 (related to Figure 2, 4, 5) Detailed Main Figure Kaplan Meier Survival Curves. 95% Confidence Interval and Risk Table with year interval are displayed. The KM Curves are grouped by Figure 2 (ATVLAC KMs, black border), Figure 4 (SMVLAC KMs, blue border) and Figure 5 (Omeprazole KMs, green border).

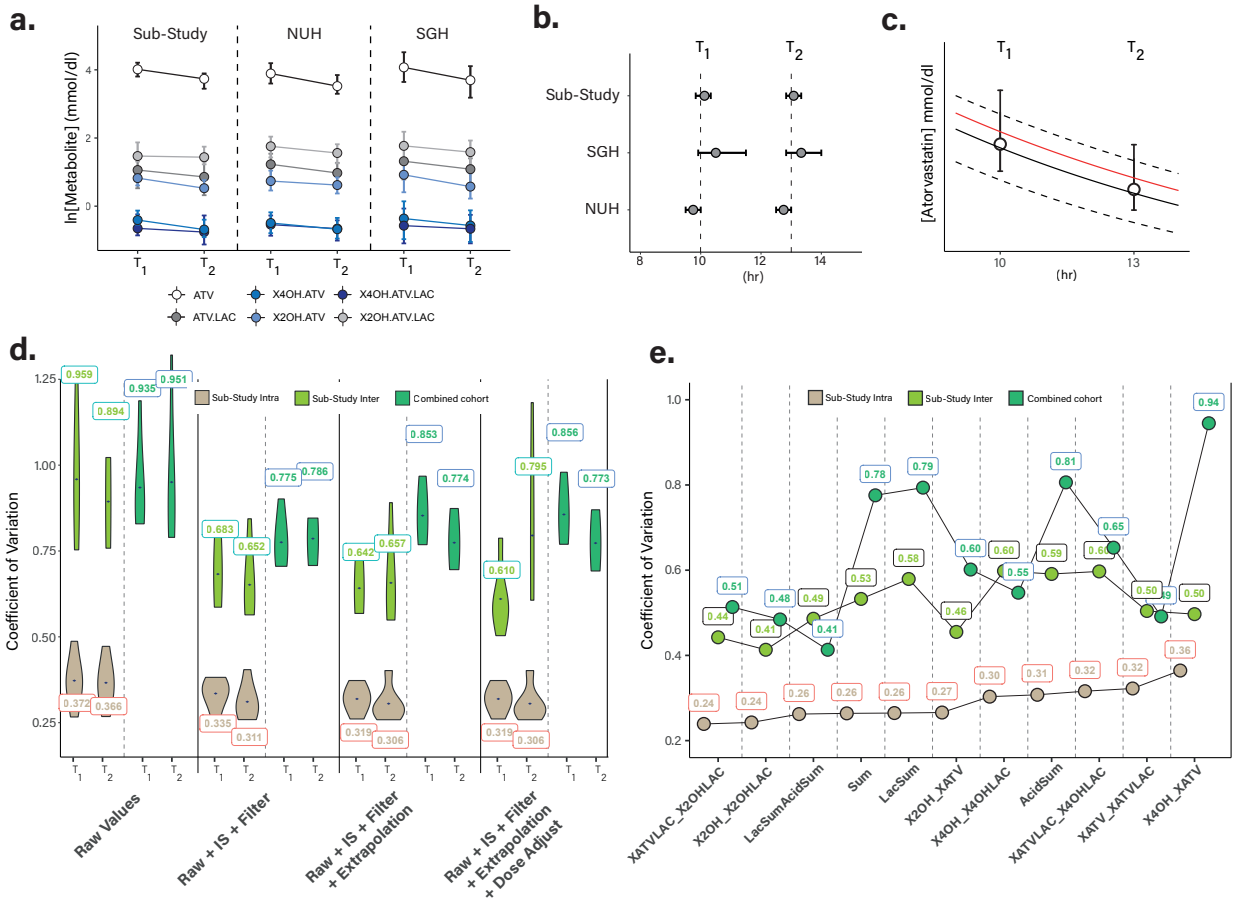


Figure S9 (related to Figure 1, Table S2) Variability and Digital Phenotyping. Optimizing DPT by variability reduction **a)** Comparison of atorvastatin compound concentrations at time-points T1 and T2 in three cohorts, **b)** Variabilities in average time of collection relative to self-reported drug ingestion in three cohorts, **c)** Observed versus previously reported elimination half-life of ATV, **d)** Effects of digital phenotyping on intraindividual and interindividual variance for all analytes, **e)** Variance of synthetic phenotypes ranked from lowest to highest intraindividual variability.

Fig. S10 - Genotypic Associations with Phenotype and MACE

Fig. S10 Population stratification for both genotypic associations with phenotypes and adverse outcomes. Subjects who having missing outcomes data, are population struction outliers via PCA-based outlier tagging (5 Principal Components, 5 Repetitions and 6 Standard Deviations), have incomplete LC/MS Assays or are tagged as outliers for *ATVLAC or †SMVLAC are removed for Genotypic associations with both statin phenotypes and outcomes **(Fig. 3a, e, 4e).**

Fig. S11 - Phenotypic Associations with Outcomes

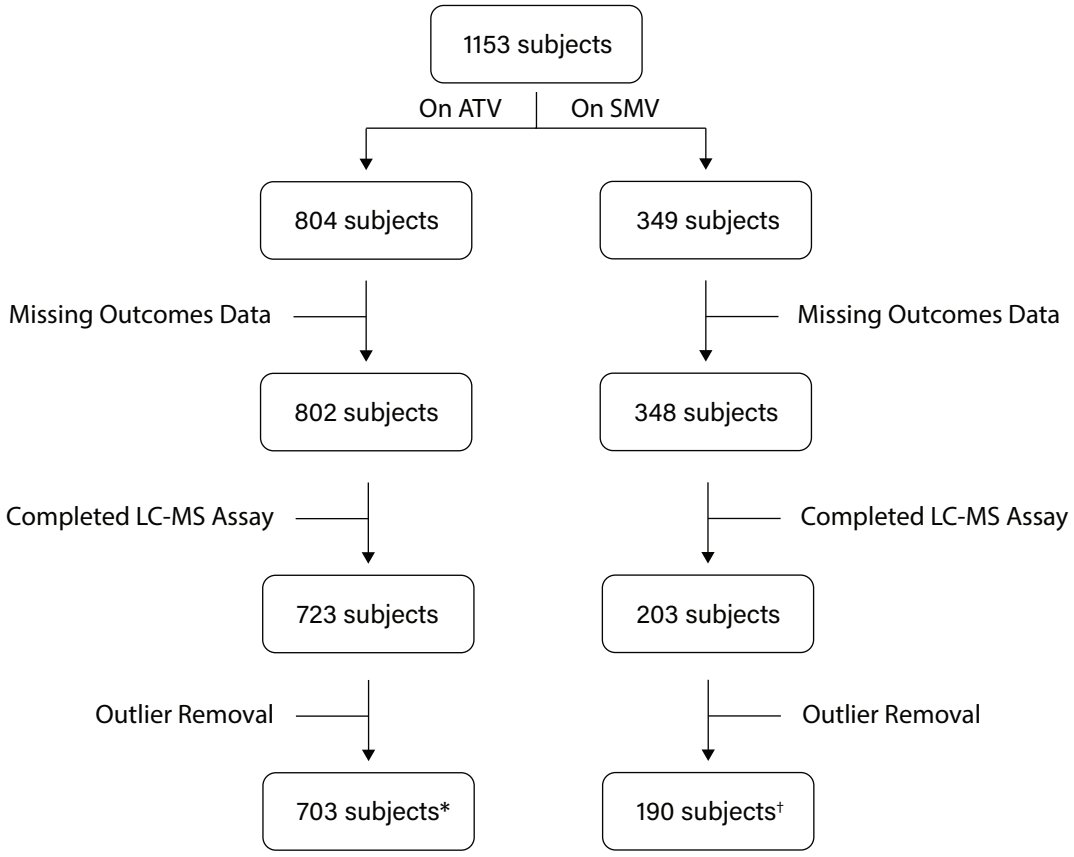


Fig. S11 Population stratification for phenotypic associations with adverse outcomes. Subjects who having missing outcomes data, have incomplete LC/MS Assays or are tagged as outliers for *ATVLAC or †SM-VLAC are removed for outcomes associations with both statin phenotypes **(Fig. 2, Fig. 4a).**

Fig. S12 - Drug-Drug Interactions with phenotypes and outcomes

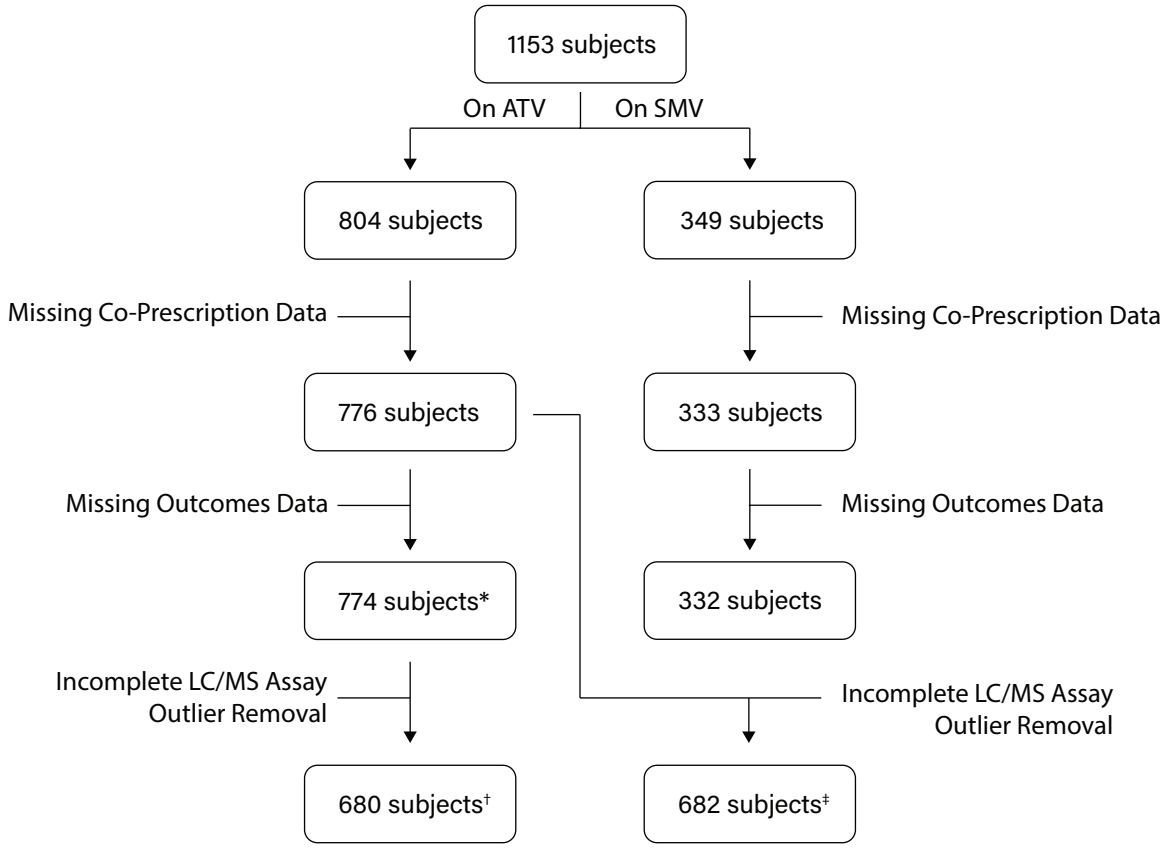


Figure S12 (related to Figure 5) CONSORT Diagram for DDI associations with phenotypes and outcomes. *Subjects with missing co-prescription and outcomes data are removed for DDI associations with outcomes **(Fig. 5a, b, d)**. †Subjects with missing co-prescription and outcomes data, incomplete LC/MS assay and identified as outliers for ATVLAC are removed for DDI associations with ATVLAC and outcomes **(Fig. S6)**. ‡Subjects with missing co-prescription and outcomes data, incomplete LC/MS assay and identified as outliers for ATVLAC are removed for DDI associations with ATVLAC **(Fig. 5e)**

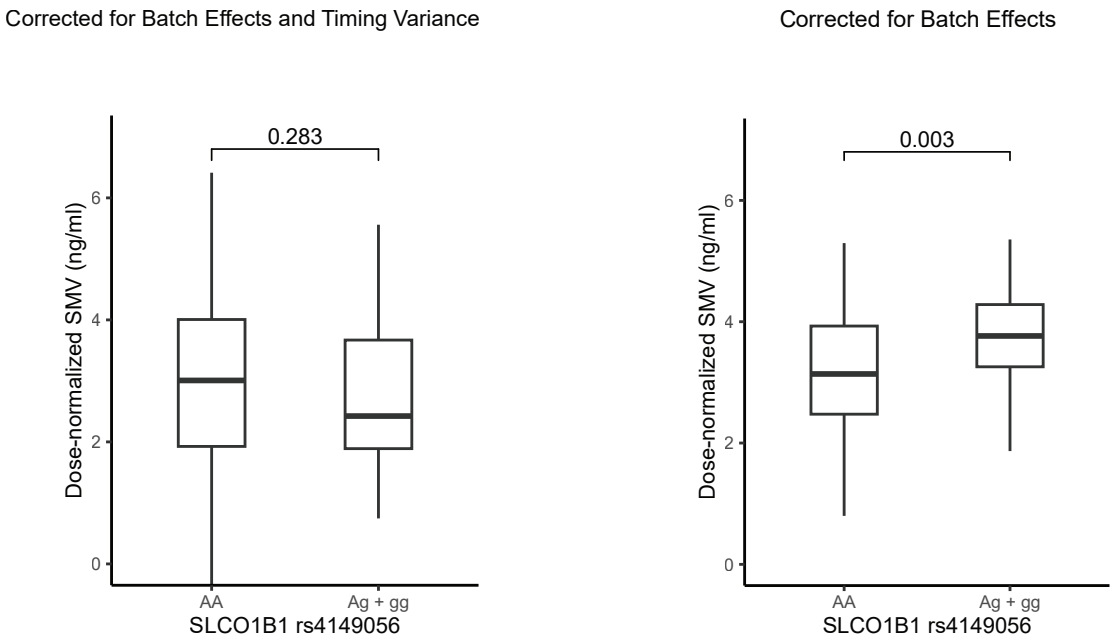


Figure S13 (related to Figure 4) SLCO1B1 association in different correction protocols. Group differences of Dose Normalized (40mg) SMV between homozygous wildtypes of SLCO1B1 rs4149056 against mutants. Mann-Whitney U-Test P-value displayed.

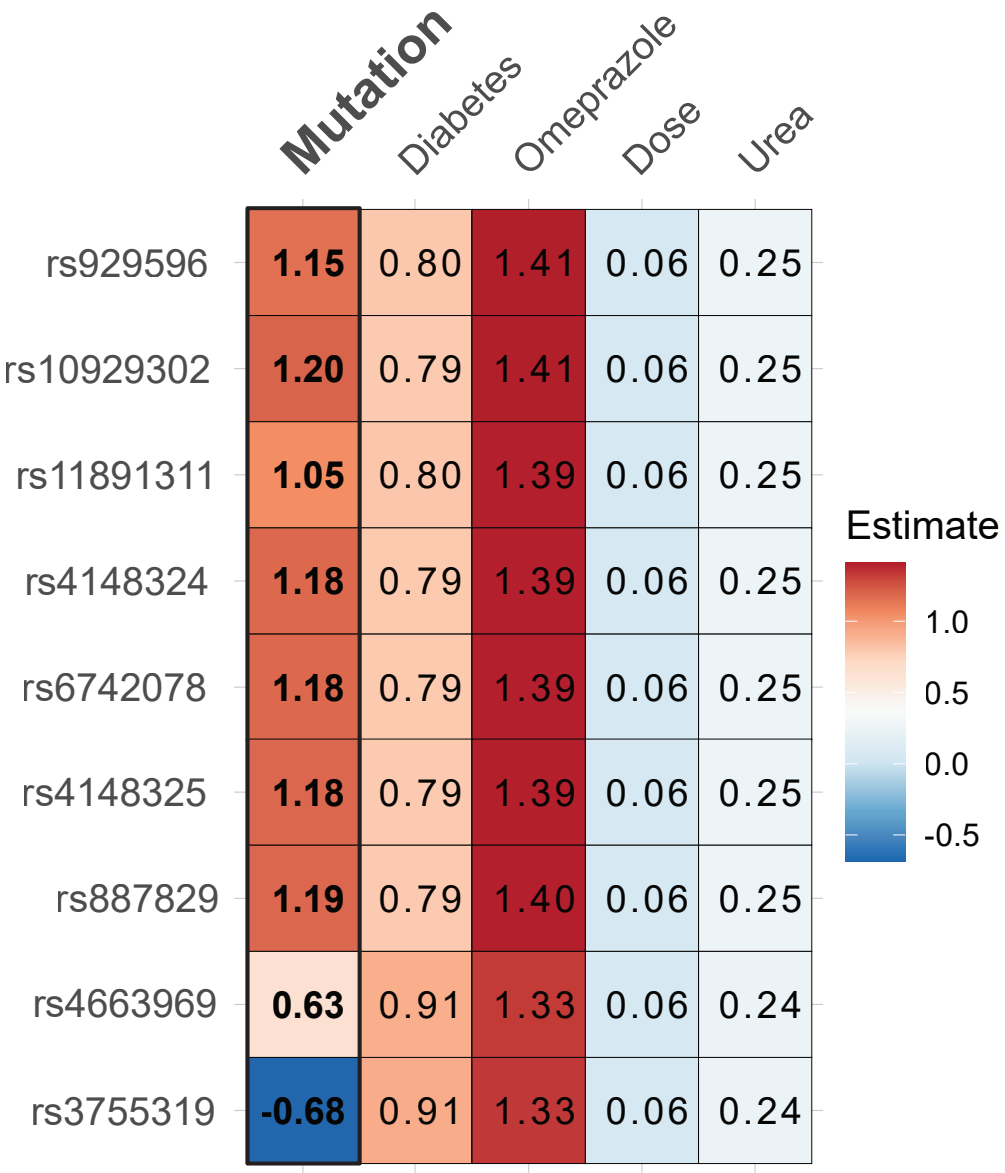


Figure S14 - Multivariable Linear Model Coefficients of additive genetic SNPs and their covariables - Diabetes status, omeprazole co-prescription, dose in mg and urea in mmol/L.

Table S1 (related to Figure 2) – Mass Spectrometry Transitions and Assay Parameters

Drug/Metabolite	Average Molecular Mass	MRM Transition (m/z)	Retention Time (min)	Collision Energy (eV)
ATV	558.6	559.1 > 440.0	2.718	20
d5-ATV	563.6	564.1 > 445.2	2.708	20
2OHATV	574.6	575.2 > 440.2	2.590	25
d5-2OHATV	579.6	580.2 > 445.2	2.584	25
4OHATV	574.6	575.2 > 440.2	2.058	25
d5-4OHATV	579.6	580.2 > 445.2	2.051	25
ATVLAC	540.6	541.1 > 448.0	2.984	20
d5-ATVLAC	545.6	546.1 > 453.2	2.988	20
2OHATVLAC	556.6	557.2 > 448.2	2.939	20
d5-2OHATVLAC	561.6	562.2 > 453.2	2.813	20
4OH-ATVLAC	556.6	557.2 > 448.2	2.272	20
d5-4OHATVLAC	561.6	562.2 > 453.2	2.265	20
SMVLAC	418.6	441.0 > 325.0	0.740	28
d6-SMVLAC	424.6	447.0 > 325.0	0.740	28
SMV	436.6	435.3 > 319.0	0.490	13
d6-SMV	441.6	441.0 > 319.0	0.490	13

Table S1: Drug/metabolite average molecular mass, and other parameters such as the Multiple Reaction Monitoring (MRM) transition (m/z), retention time (min), collision energy (eV) utilised for the LC-MS assays. ATV – Atorvastatin; 2OHATV – 2-hydroxy-atorvastatin; 4OHATV – 4-hydroxy-atorvastatin; ATVLAC – Atorvastatin lactone; 2OHATVLAC – 2-hydroxy-atorvastatin lactone; 4OHATVLAC – 4-hydroxy-atorvastatin lactone; d5/d6 – Deuterated standards.

Table S2 (related to Table 1) – Baseline Characteristics of the sub-study compared to the main cohort

Variable	Sub-study (n=44)	Main Cohort (n=1362)	P-value
Baseline Characteristics (mean±SD)			
Age	57±9.2	59±9.4	0.682
BMI	27.6±4.5	27.0±4.9	0.306
Gender (n%)			
Male	33 (75.0)	1140 (83.6)	0.171
Female	11 (25.0)	223 (16.4)	0.171
Race (n%)			
Indian	11 (25.0)	336 (24.7)	1.000
Chinese	12 (27.3)	687 (50.4)	0.003
Malay	19 (43.2)	322 (23.6)	0.003
Others	2 (4.5)	18 (1.3)	0.217
Statin Type (n%)			
Atorvastatin	25 (56.8)	976 (71.6)	0.041
Simvastatin	19 (43.2)	386 (28.3)	0.040
Atorvastatin Dose (mg)			
5	0 (0.0)	10 (1.0)	1.000
10	1 (4.0)	57 (5.8)	1.000
15	0 (0.0)	1 (0.1)	1.000
20	8 (32.0)	168 (17.2)	0.086
30	0 (0.0)	4 (0.4)	1.000
40	13 (52.0)	626 (64.1)	0.284
50	0 (0.0)	1 (0.1)	1.000
60	0 (0.0)	19 (1.9)	1.000
80	3 (12.0)	90 (9.2)	0.892
Simvastatin Dose (mg)			
5	0 (0.0)	6 (1.6)	1.000
10	2 (10.5)	72 (18.7)	0.528
20	10 (52.6)	167 (43.3)	0.543
30	0 (0.0)	5 (1.3)	1.000
40	7 (36.8)	134 (34.7)	1.000
60	0 (0.0)	2 (0.5)	1.000
Medical History			
Myocardial Infarction	37 (84.1)	1222 (89.7)	0.327
Hypertension	24 (54.5)	829 (60.8)	0.478
Diabetes Mellitus	17 (38.6)	588 (43.1)	0.647
Liver Problems	1 (2.3)	60 (4.4)	0.744
Hypercholesterolemia	27 (61.4)	957 (70.2)	0.255
Biochemical Measurements			
Urea (mmol/L)	5.4 [4.4-7.2]	5.4 [4.8-7.6]	0.574
Chol/HDL Ratio	3.7 [3.1-4.4]	3.8 [3.3-4.3]	0.688
eGFR (ml/min/1.73m^2)	81.4 [65.0-97.3]	81.7 [61.2-91.5]	0.500
Sodium (mmol/L)	138.0 [136.0-140.0]	138.0 [137.0-140.0]	0.609
Potassium (mmol/L)	4.4 [4.0-4.6]	4.3 [4.0-4.6]	0.315
Creatinine (umol/L)	87.5 [79.3-103.5]	87.0 [73.0-105.0]	0.692
LDL (mmol/L)	2.4 [1.76-2.65]	2.15 [1.7-2.7]	0.352
HDL (mmol/L)	1.1 [1.0-1.3]	1.1 [0.90-1.3]	0.304
Total Cholesterol (mmol/L)	4.2 [3.7-4.7]	4.0 [3.4-4.6]	0.072
AST (U/L)	17.5 [14.0-19.0]	25.0 [20.0-31.0]	<0.001
ALT (U/L)	16.0 [13.0-22.0]	23.0 [17.0-32.0]	<0.001
ALP (U/L)	80.0 [63.8-110.8]	80.5 [65.0-101.0]	0.79
Clinical Outcomes (n%)			
Death	7 (15.9)	152 (11.2)	0.440
Stroke	3 (6.8)	43 (3.2)	0.331
AMI	4 (9.1)	93 (6.8)	0.764
MACE	11 (25.0)	233 (17.1)	0.227

Table S2 – Summary Statistics of Baseline Characteristics of Sub-Study and Full Cohort. Chi-Square p-values are reported for count data, while Mann-Whitney U-Test p-value is reported for continuous variables. Age and BMI are reported as mean±SD, while other continuous variables that fail normaility via Shapiro-Wilk Test P<0.05 are reported as Median [IQR]

Table S3 (Related to Figure 2) – Spearman's Correlation of ATV Metabolites, restricted to patients with doses of 40mg.

Class	Variable	ATV Metabolites											
		2OHATV		2OHATVLAC		4OHATV		4OHATVLAC		ATV		ATVLAC	
		ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value
ATV Metabolites	2OHATV	**1.00**	**<0.001**	**0.77**	**<0.001**	**0.72**	**<0.001**	**0.59**	**<0.001**	**0.75**	**<0.001**	**0.53**	**<0.001**
	2OHATVLAC	**0.77**	**<0.001**	**1.00**	**<0.001**	**0.62**	**<0.001**	**0.78**	**<0.001**	**0.73**	**<0.001**	**0.79**	**<0.001**
	4OHATV	**0.72**	**<0.001**	**0.62**	**<0.001**	**1.00**	**<0.001**	**0.77**	**<0.001**	**0.65**	**<0.001**	**0.46**	**<0.001**
	4OHATVLAC	**0.59**	**<0.001**	**0.78**	**<0.001**	**0.77**	**<0.001**	**1.00**	**<0.001**	**0.63**	**<0.001**	**0.69**	**<0.001**
	ATV	**0.75**	**<0.001**	**0.73**	**<0.001**	**0.65**	**<0.001**	**0.63**	**<0.001**	**1.00**	**<0.001**	**0.84**	**<0.001**
	ATVLAC	**0.53**	**<0.001**	**0.79**	**<0.001**	**0.46**	**<0.001**	**0.69**	**<0.001**	**0.84**	**<0.001**	**1.00**	**<0.001**
Renal Function	Sodium (mmol/L)	0.01	0.837	0.04	0.414	0.04	0.424	-0.06	0.238	0.03	0.541	0.07	0.197
	Potasssium (mmol/L)	-0.06	0.216	0.05	0.333	0.02	0.664	0.06	0.257	0.01	0.836	0.09	0.051
	Urea (mmol/L)	0.08	0.136	**0.16**	**0.002**	**0.10**	**0.040**	**0.15**	**0.002**	**0.19**	**<0.001**	**0.22**	**<0.001**
	Creatinine (mmol/L)	0.04	0.451	**0.16**	**0.001**	**0.11**	**0.024**	**0.13**	**0.006**	**0.14**	**0.003**	**0.20**	**<0.001**
	eGFR (mL/min/1.73m^2)	0.06	0.186	**0.18**	**<0.001**	**0.14**	**0.004**	**0.15**	**0.002**	**0.17**	**<0.001**	**-0.21**	**<0.001**
Lipid Profile	Total Cholesterol (mmol/L)	-0.05	0.313	-0.01	0.831	-0.06	0.225	0.05	0.335	0.02	0.636	0.04	0.409
	Triglycerides (mmol/L)	0.02	0.755	0.02	0.745	0.00	0.983	0.01	0.865	0.07	0.162	0.07	0.140
	HDL (mmol/L)	0.04	0.397	0.01	0.878	0.04	0.428	0.10	0.054	0.02	0.727	0.07	0.168
	LDL (mmol/L)	0.05	0.364	0.01	0.795	0.05	0.353	0.01	0.825	0.02	0.631	0.06	0.249
	Cholesterol / HDL Ratio	0.07	0.164	0.00	0.952	0.04	0.441	0.02	0.625	0.04	0.375	0.10	0.052
Liver Function	AST (U/L)	0.00	0.961	0.07	0.186	0.04	0.466	0.08	0.128	0.00	0.987	0.06	0.297
	ALT (U/L)	0.04	0.420	0.02	0.714	0.02	0.755	0.07	0.196	0.06	0.244	0.01	0.870
	ALP (U/L)	0.09	0.141	0.11	0.059	0.04	0.460	**0.13**	**0.025**	0.07	0.244	0.07	0.249
Misc	Creatine Kinase (U/L)	0.10	0.111	0.01	0.877	0.10	0.111	0.01	0.883	0.10	0.106	0.01	0.937
	Age	**0.19**	**<0.001**	**0.22**	**<0.001**	**0.22**	**<0.001**	**0.25**	**<0.001**	**0.18**	**<0.001**	**0.16**	**0.001**
	Female Gender	0.00	0.944	-0.01	0.911	0.02	0.664	0.00	0.976	-0.01	0.870	-0.05	0.259
	BMI	**0.10**	**0.035**	**0.17**	**<0.001**	0.02	0.678	0.06	0.225	0.03	0.550	0.03	0.595
Race	Malay	-0.03	0.533	-0.01	0.852	-0.02	0.685	-0.02	0.750	-0.04	0.363	-0.02	0.599
	Chinese	0.07	0.143	0.01	0.853	0.07	0.122	0.05	0.305	0.05	0.254	-0.01	0.788
	Indian	-0.04	0.382	0.01	0.896	-0.06	0.215	-0.03	0.549	-0.01	0.834	0.05	0.326
	Others	-0.03	0.510	-0.02	0.602	-0.03	0.588	-0.04	0.350	-0.03	0.553	-0.02	0.722

Table S3. Correlation Table of Atorvastatin (ATV) Metabolites. Significant correlations in bold, defined as $p<0.05$. BMI – Body-Mass Index; eGFR – estimated Glomerular Filtration Rate; HDL – High-Density Lipoprotein; LDL – Low-Density Lipoprotein; AST – Aspartate Aminotransferase; ALT – Alanine Transaminase; ALP – Alkaline Phosphatase

Table S4 (related to Figure 4) - Spearman's Correlation of SMV metabolites with restricted to patients with dose of 40mg

Class	Variables	SMV Metabolites			
		SMVLAC		SMV	
		ρ	p-value	ρ	p-value
SMV Metabolites	SMVLAC	**1.00**	**<0.001**	0.738	**<0.001**
	SMV	0.738	**<0.001**	**1.00**	**<0.001**
Renal Function	Sodium (mmol/L)	0.215	0.083	0.282	0.022
	Potasssium (mmol/L)	-0.229	0.058	-0.083	0.499
	Urea (mmol/L)	0.180	0.15	0.318	0.01
	Creatinine (mmol/L)	0.180	0.138	0.206	0.09
	eGFR (mL/min/1.73m^s)	-0.186	0.126	-0.188	0.121
Lipid Profile	Total Cholesterol (mmol/L)	-0.223	0.068	-0.247	0.042
	Triglycerides (mmol/L)	-0.243	0.046	-0.335	0.005
	HDL (mmol/L)	-0.044	0.723	0.138	0.261
	LDL (mmol/L)	-0.174	0.155	-0.190	0.121
	Cholesterol / HDL Ratio	-0.103	0.402	-0.284	0.019
Liver Function	AST (U/L)	0.182	0.156	0.083	0.522
	ALT (U/L)	-0.026	0.839	-0.097	0.442
	ALP (U/L)	0.033	0.821	0.085	0.56
Misc	Creatine Kinase (U/L)	-0.076	0.582	-0.055	0.69
	Age	0.094	0.422	0.058	0.619
	BMI	-0.086	0.462	-0.086	0.462
Race	Malay	0.050	0.669	-0.053	0.652
	Chinese	-0.080	0.498	-0.049	0.674
	Indian	-0.022	0.853	0.034	0.775
	Others	0.081	0.491	0.004	0.971

Table S4**.** Simvastatin (SMV) Metabolite Correlation Table. Significant correlations in bold. Significance defined as $p<0.05$.

Table S5 (related to Figures 2 and 4) – Third Tertile Threshold summary statistics.

	ATVLAC (ng/mL) (n%)			SMVLAC (ng/mL) (n%)		
Variables	All (n=703)	<3.9 (n=465)	>3.9 (n=238)	All (n=190)	<0.16 (n=126)	>0.16 (n=64)
MACE, n (%)	109 (16%)	50 (11%)	59 (25%)	36 (19%)	17 (13%)	19 (30%)
MACE, HR (95%CI)	2.45 (CI=1.60-3.44), P<0.001			2.61 (CI=1.36-5.02), P=0.004		
Death, n (%)	69 (10%)	27 (6%)	42 (18%)	24 (13%)	12 (10%)	12 (19%)
Death, HR (95%CI)	3.18 (CI=1.96-5.16), P<0.001			2.20 (CI=0.99-4.91), P=0.053		

Table S5. Threshold summary statistics. Death = all-cause mortality; SMVLAC = Simvastatin Lactone; ATVLAC = Atorvastatin Lactone; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event. The cohort included all patients with full outcome records on (5-60mg) doses SMV (n=190) and 5-80mg ATV doses (n = 703) and were used to analyze time to MACE and time to death, HR (95% CI). Plasma ATVLAC were normalized to 10h and 13h post-dose.

Table S6 (related to Figure 5) – Prevalence of co-prescriptions

Co-medications	NUH Cohort (N=668)	SGH Cohort (N=648)	Total (N=1316)	P-Value
Aspirin	437 (65.4)	440 (67.9)	877 (66.6)	0.340
Omeprazole	331 (49.6)	379 (58.5)	710 (54.0)	0.001
Bisoprolol	209 (31.3)	377 (58.2)	586 (44.5)	<0.001
Metformin	200 (29.9)	210 (32.4)	410 (31.2)	0.334
Clopidogrel	87 (13.0)	225 (34.7)	312 (23.7)	<0.001
Frusemide	75 (11.2)	169 (26.1)	244 (18.5)	<0.001
Enalapril	147 (22.0)	92 (14.2)	239 (18.2)	<0.001
Glyceryl Trinitrate	54 (8.1)	170 (26.2)	224 (17.0)	<0.001
Isosorbide	51 (7.6)	165 (25.5)	216 (16.4)	<0.001
Glipizide	110 (16.5)	104 (16.0)	214 (16.3)	0.837
Warfarin	121 (18.1)	76 (11.7)	197 (15.0)	0.001
Carvedilol	157 (23.5)	32 (4.9)	189 (14.4)	<0.001
Amlodipine	103 (15.4)	75 (11.6)	178 (13.5)	0.041
Spironolactone	56 (8.4)	99 (15.3)	155 (11.8)	<0.001
Losartan	80 (12)	73 (11.3)	153 (11.6)	0.688
Lisinopril	77 (11.5)	49 (7.6)	126 (9.6)	0.015
Famotidine	37 (5.5)	84 (13.0)	121 (9.2)	<0.001
Atenolol	64 (9.6)	55 (8.5)	119 (9.0)	0.489
Perindopril	19 (2.8)	78 (12.0)	97 (7.4)	<0.001
Neurobion	20 (3.0)	62 (9.6)	82 (6.2)	<0.001
Insulin	27 (4.0)	53 (8.2)	80 (6.1)	0.002
Valsartan	44 (6.6)	35 (5.4)	79 (6.0)	0.365
Digoxin	30 (4.5)	44 (6.8)	74 (5.6)	0.070
Ezetimibe	41 (6.1)	32 (4.9)	73 (5.5)	0.342
Ticagrelor	32 (4.8)	33 (5.1)	65 (4.9)	0.800
Fenofibrate	38 (5.7)	27 (4.2)	65 (4.9)	0.203
Nifedipine	19 (2.8)	44 (6.8)	63 (4.8)	0.001
Trimetazidine	16 (2.4)	44 (6.8)	60 (4.6)	<0.001
Plavix	54 (8.1)	0 (0)	54 (4.1)	<0.001
Ivabradine	9 (1.3)	38 (5.9)	47 (3.6)	<0.001
Glucosamine	22 (3.3)	24 (3.7)	46 (3.5)	0.685

Allopurinol	27 (4.0)	15 (2.3)	42 (3.2)	0.075
Sitagliptin	17 (2.5)	24 (3.7)	41 (3.1)	0.226
Metoprolol	38 (5.7)	1 (0.2)	39 (3.0)	<0.001
Gliclazide	15 (2.2)	23 (3.5)	38 (2.9)	0.158
Imdex	35 (5.2)	0 (0)	35 (2.7)	<0.001
Sangobion	5 (0.7)	30 (4.6)	35 (2.7)	<0.001
Folic acid	5 (0.7)	28 (4.3)	33 (2.5)	<0.001
Hydrochlorothiazide	18 (2.7)	10 (1.5)	28 (2.1)	0.148
Linagliptin	11 (1.6)	17 (2.6)	28 (2.1)	0.220
Gabapentin	4 (0.6)	23 (3.5)	27 (2.1)	<0.001
Lasix	23 (3.4)	0 (0)	23 (1.7)	<0.001
Mecobalamin	7 (1.0)	16 (2.5)	23 (1.7)	0.049
Telmisartan	8 (1.2)	13 (2.0)	21 (1.6)	0.242
Acarbose	7 (1.0)	14 (2.2)	21 (1.6)	0.107
Salbutamol	7 (1.0)	13 (2.0)	20 (1.5)	0.155
Prasugrel	18 (2.7)	1 (0.2)	19 (1.4)	<0.001
Levothyroxine	2 (0.3)	17 (2.6)	19 (1.4)	<0.001
Rivaroxaban	2 (0.3)	13 (2.0)	15 (1.1)	0.004
Irbesartan	6 (0.9)	7 (1.1)	13 (1.0)	0.739
Ramipril	1 (0.1)	2 (0.3)	3 (0.2)	0.546
Enoxaparin	0 (0)	1 (0.2)	1 (0.1)	0.310
Ferrous Fumarate	0 (0)	1 (0.2)	1 (0.1)	0.310

Table S6 – Common co-prescriptions taken alongside statin. Chi-square P-values are reported. NUH – National University Hospital; SGH – Singapore General Hospital.

Table S7 (related to Figure 5) – No association between SMVLAC and co-prescriptions

Co-Prescription	Fold Change	P-Value	Takers	Prevalence (n%)
Atenolol	2.02	0.123	24	12.6
Omeprazole	1.34	0.463	84	44.2
Bisoprolol	0.73	0.463	46	24.2
Carvedilol	1.41	0.463	44	23.2
Nifedipine	2.16	0.463	6	3.2
Allopurinol	2.65	0.463	5	2.6
Salbutamol	0.36	0.463	4	2.1
Ezetimibe	4.03	0.463	2	1.1
Levothyroxine	4.13	0.463	2	1.1
Metformin	1.21	0.624	56	29.5
Warfarin	0.86	0.624	46	24.2
Losartan	1.24	0.624	26	13.7
Frusemide	1.45	0.624	25	13.2
Glyceryl Trinitrate	1.31	0.624	22	11.6
Isosorbide	1.33	0.624	18	9.5
Hydrochlorothiazide	1.81	0.624	9	4.7
Insulin	1.71	0.624	8	4.2
Trimetazidine	0.6	0.624	7	3.7
Neurobion	1.65	0.624	6	3.2
Lasix	1.56	0.624	6	3.2
Metoprolol	1.7	0.624	5	2.6
Irbesartan	3.08	0.624	2	1.1
Mecobalamin	0.5	0.624	2	1.1
Prasugrel	3.51	0.624	1	0.5
Rivaroxaban	2.95	0.624	1	0.5
Plavix	1.35	0.652	10	5.3
Ivabradine	1.67	0.652	4	2.1

Spironolactone	1.27	0.691	23	12.1
Lisinopril	1.22	0.738	15	7.9
Aspirin	1.1	0.75	100	52.6
Enalapril	0.93	0.812	36	18.9
Famotidine	0.84	0.812	13	6.8
Fenofibrate	1.26	0.812	9	4.7
Sitagliptin	0.7	0.812	6	3.2
Telmisartan	0.81	0.812	5	2.6
Acarbose	1.31	0.812	4	2.1
Sangobion	0.7	0.812	2	1.1
Linagliptin	1.58	0.812	2	1.1
Ticagrelor	1.32	0.822	3	1.6
Gabapentin	1.53	0.844	1	0.5
Clopidogrel	1.14	0.871	19	10
Perindopril	0.57	0.871	2	1.1
Valsartan	1.03	0.913	20	10.5
Gliclazide	0.95	0.913	5	2.6
Folicacid	1.32	0.913	3	1.6
Glipizide	1.05	0.953	35	18.4
Amlodipine	1.01	0.959	32	16.8
Digoxin	1.09	0.959	17	8.9
Imdex	1.03	0.959	12	6.3
Glucosamine	1	0.959	11	5.8

Table S7 – Associations of co-prescriptions with SMVLAC in subjects taking SMV with outliers in quantitation removed (n=190). Fold Change is calculated by taking the difference of the mean of log-transformed plasma ATVLAC concentrations of takers and subtracting the non-takers, then transforming back. Mann-Whitney U Test P-Value adjusted by Benjamini-Hochberg correction is reported. Medications are sorted by P-value.

Variable	Lasso Coefficient
Sodium..mmol.L.	-0.157
Potasssium..mmol.L.	0.000
Urea..mmol.L.	0.000
Creatinine..umol.L.	0.000
eGFR	-0.001
Glucose..mmol.L.	0.000
HBA1c....	0.000
Total.Cholesterol..mmol.L.	0.084
Triglycerides..mmol.L.	0.000
HDL.C..mmol.L.	0.000
LDL.C..mmol.L.	0.190
Chol.HDL.Ratio	0.000
AST..U.L.	0.000
ALT..U.L.	0.000
ALP..U.L.	0.000
Creatine.Kinase..U.L.	0.000
Age	0.000
GenderCode	0.000
Height	0.000
Weight	0.000
BMI	0.000
StatinDose	0.000
Hx_Smoker_Code	0.000
MI	0.000
Renal_Problems	0.000
Liver_Problems	0.000
Hypertension	0.000
Diabetes_Mellitus	0.000
Hypercholesterolemia	0.000

Table S8 - Lasso Coefficients of variables regressed against 5-year MACE

	rs11891311	rs4663969	rs10929302	rs3755319	rs887829	rs6742078	rs4148324	rs4148325	rs929596	rs1042640	rs8330	rs4148323	rs4124874	rs12052787	rs2003569	rs3771342	rs1018124	rs10929303	rs2269352	rs3806598	rs2741049	rs7586110	rs4261716	rs10173355	rs6759892	rs2070959	rs1105879
rs11891311	1.00	0.59	0.98	-0.60	0.97	0.96	0.96	0.96	0.98	0.15	0.15	0.00	-0.02	0.01	0.01	0.01	-0.01	-0.04	-0.26	-0.09	-0.25	0.48	0.52	0.47	0.52	0.47	0.51
rs4663969	0.59	1.00	0.59	-0.97	0.58	0.58	0.57	0.57	0.59	0.14	0.14	0.04	0.01	0.01	0.01	0.01	0.01	-0.02	-0.31	-0.20	-0.60	0.16	0.24	0.15	0.24	0.15	0.23
rs10929302	0.98	0.59	1.00	-0.60	0.98	0.97	0.97	0.97	0.99	0.15	0.15	0.00	-0.03	0.02	0.02	0.02	0.01	-0.04	-0.25	-0.08	-0.25	0.47	0.52	0.47	0.52	0.47	0.52
rs3755319	-0.60	-0.97	-0.60	1.00	-0.61	-0.60	-0.60	-0.60	-0.60	-0.12	-0.12	-0.04	-0.01	-0.01	-0.01	-0.01	-0.01	0.00	0.33	0.19	0.60	-0.18	-0.27	-0.18	-0.27	-0.18	-0.26
rs887829	0.97	0.58	0.98	-0.61	1.00	0.99	0.99	0.99	0.98	0.13	0.13	0.00	-0.03	0.03	0.02	0.02	0.01	-0.04	-0.26	-0.09	-0.25	0.47	0.53	0.48	0.53	0.48	0.53
rs6742078	0.96	0.58	0.97	-0.60	0.99	1.00	1.00	1.00	0.98	0.13	0.12	0.00	-0.04	0.03	0.03	0.03	0.02	-0.03	-0.25	-0.09	-0.25	0.46	0.52	0.46	0.52	0.46	0.52
rs4148324	0.96	0.57	0.97	-0.60	0.99	1.00	1.00	1.00	0.98	0.12	0.12	0.00	-0.04	0.03	0.03	0.03	0.02	-0.03	-0.26	-0.09	-0.25	0.46	0.52	0.46	0.52	0.46	0.52
rs4148325	0.96	0.57	0.97	-0.60	0.99	1.00	1.00	1.00	0.98	0.12	0.12	0.00	-0.04	0.03	0.03	0.03	0.02	-0.03	-0.25	-0.08	-0.25	0.47	0.52	0.47	0.52	0.47	0.52
rs929596	0.98	0.59	0.99	-0.60	0.98	0.98	0.98	0.98	1.00	0.15	0.15	-0.01	-0.03	0.03	0.03	0.03	0.02	-0.04	-0.25	-0.08	-0.25	0.46	0.51	0.46	0.51	0.46	0.51
rs1042640	0.15	0.14	0.15	-0.12	0.13	0.13	0.12	0.12	0.15	1.00	0.99	-0.02	0.06	-0.02	-0.01	-0.01	-0.02	-0.04	0.24	0.09	-0.10	0.14	0.16	0.14	0.16	0.15	0.16
rs8330	0.15	0.14	0.15	-0.12	0.13	0.12	0.12	0.12	0.15	0.99	1.00	-0.02	0.06	-0.02	-0.02	-0.02	-0.03	-0.03	0.25	0.09	-0.10	0.13	0.15	0.14	0.15	0.14	0.15
rs4148323	0.00	0.04	0.00	-0.04	0.00	0.00	0.00	0.00	-0.01	-0.02	-0.02	1.00	0.33	-0.14	-0.15	-0.15	-0.15	-0.10	-0.02	-0.05	0.00	-0.05	-0.03	-0.05	-0.03	-0.05	-0.04
rs4124874	-0.02	0.01	-0.03	-0.01	-0.03	-0.04	-0.04	-0.04	-0.03	0.06	0.06	0.33	1.00	-0.56	-0.56	-0.56	-0.55	0.12	0.07	-0.05	-0.01	-0.04	-0.04	-0.04	-0.04	-0.04	-0.04
rs12052787	0.01	0.01	0.02	-0.01	0.03	0.03	0.03	0.03	0.03	-0.02	-0.02	-0.14	-0.56	1.00	0.99	0.99	0.98	-0.03	-0.02	0.02	0.04	0.01	0.01	0.01	0.01	0.01	0.01
rs2003569	0.01	0.01	0.02	-0.01	0.02	0.03	0.03	0.03	0.03	-0.01	-0.02	-0.15	-0.56	0.99	1.00	1.00	0.98	-0.03	-0.02	0.03	0.03	0.01	0.01	0.01	0.01	0.01	0.01
rs3771342	0.01	0.01	0.02	-0.01	0.02	0.03	0.03	0.03	0.03	-0.01	-0.02	-0.15	-0.56	0.99	1.00	1.00	0.98	-0.03	-0.02	0.03	0.03	0.01	0.01	0.01	0.01	0.01	0.01
rs1018124	-0.01	0.01	0.01	-0.01	0.01	0.02	0.02	0.02	0.02	-0.02	-0.03	-0.15	-0.55	0.98	0.98	0.98	1.00	-0.03	-0.01	0.03	0.05	0.00	0.00	0.00	0.00	0.00	0.00
rs10929303	-0.04	-0.02	-0.04	0.00	-0.04	-0.03	-0.03	-0.03	-0.04	-0.04	-0.03	-0.10	0.12	-0.03	-0.03	-0.03	-0.03	1.00	0.00	0.04	0.01	0.02	0.00	0.02	0.00	0.02	0.00
rs2269352	-0.26	-0.31	-0.25	0.33	-0.26	-0.25	-0.26	-0.25	-0.25	0.24	0.25	-0.02	0.07	-0.02	-0.02	-0.02	-0.01	0.00	1.00	-0.30	0.57	-0.51	-0.55	-0.50	-0.55	-0.50	-0.55
rs3806598	-0.09	-0.20	-0.08	0.19	-0.09	-0.09	-0.09	-0.08	-0.08	0.09	0.09	-0.05	-0.05	0.02	0.03	0.03	0.03	0.04	-0.30	1.00	-0.34	0.61	0.55	0.61	0.55	0.61	0.56
rs2741049	-0.25	-0.60	-0.25	0.60	-0.25	-0.25	-0.25	-0.25	-0.25	-0.10	-0.10	0.00	-0.01	0.04	0.03	0.03	0.05	0.01	0.57	-0.34	1.00	-0.56	-0.61	-0.55	-0.61	-0.55	-0.61
rs7586110	0.48	0.16	0.47	-0.18	0.47	0.46	0.46	0.47	0.46	0.14	0.13	-0.05	-0.04	0.01	0.01	0.01	0.00	0.02	-0.51	0.61	-0.56	1.00	0.91	0.99	0.91	0.99	0.91
rs4261716	0.52	0.24	0.52	-0.27	0.53	0.52	0.52	0.52	0.51	0.16	0.15	-0.03	-0.04	0.01	0.01	0.01	0.00	0.00	-0.55	0.55	-0.61	0.91	1.00	0.91	1.00	0.91	0.99
rs10173355	0.47	0.15	0.47	-0.18	0.48	0.46	0.46	0.47	0.46	0.14	0.14	-0.05	-0.04	0.01	0.01	0.01	0.00	0.02	-0.50	0.61	-0.55	0.99	0.91	1.00	0.91	1.00	0.92
rs6759892	0.52	0.24	0.52	-0.27	0.53	0.52	0.52	0.52	0.51	0.16	0.15	-0.03	-0.04	0.01	0.01	0.01	0.00	0.00	-0.55	0.55	-0.61	0.91	1.00	0.91	1.00	0.91	0.99
rs2070959	0.47	0.15	0.47	-0.18	0.48	0.46	0.46	0.47	0.46	0.15	0.14	-0.05	-0.04	0.01	0.01	0.01	0.00	0.02	-0.50	0.61	-0.55	0.99	0.91	1.00	0.91	1.00	0.91
rs1105879	0.51	0.23	0.52	-0.26	0.53	0.52	0.52	0.52	0.51	0.16	0.15	-0.04	-0.04	0.01	0.01	0.01	0.00	0.00	-0.55	0.56	-0.61	0.91	0.99	0.92	0.99	0.91	1.00

Table S9 - Pearson's Correlation between all 27 *UGT1A* SNPs

SNP	Block
rs8330	1
rs4148323	2
rs2070959	3
rs1018124	4
rs3755319	5
rs10929303	6

These SNPs survived caret's findCorrelation cutoff at 0.2 using the caret package