SUPPLEMENTARY DATA

METHODS OF THE SUPPLEMENTARY DATA

Secondary outcome

A secondary outcome was established and defined as recurrent ACS and cardiovascular mortality. As in the primary outcome analysis, several Cox regression models were constructed, including an univariate model with all the interest variables, a multivariate clinical model and finally, the previous multivariate model with the addition of GRS terciles.

Statistical analysis

Comparison of the multivariate clinical model for improvement in reclassification with and without GRS information was performed by the Integrated Discrimination Improvement method (IDI) as described by Uno et al. This index compares the average difference in accurate prediction of risk for patients who have a recurrent event vs those who do not. 95% confidence interval for IDI was obtained by bootstrapping. The IDI index was calculated using the 'survIDINRI' package for R (R version 3.3.2). We calculated the C-statistic for both models with and without GRS using the 'survAUC' package, the ΔC-statistics between models using 'survC1' and the receiver operating curves using 'survivalROC' package for R. Graphics were generated with 'ggplot2' package for R.

RESULTS OF THE SUPPLEMENTARY DATA

In the univariate analysis of the secondary endpoint a previous history of CAD (HR 6.0; 95%CI 1.9-18.9, *P* = .002) or history of dyslipidaemia (HR 2.5; 95%CI 1.0-6.4, *P* = .049) were significantly associated with the secondary endpoint. Among clinical features at admission a Killip class (HR 2.1 per point increase; 95%CI 1.2-3.6, *P* = .009), suboptimal revascularization defined as final TIMI flow <3 (HR 8.5; 95%CI 2.3-31.0, *P* = 0.001), a low haemoglobin count (HR 1.4 per point decrease; 95%CI 1.1-1.6 *P* = .001) or need of diuretic drugs during index event (HR 7.7; 95%CI 2.6-22.8 *P* = .002) were also associated with recurrent events.

Table 1 of the supplementary data

Baseline clinical variables according to the occurrence of recurrent events during follow-up.

	Total	No Recurre	Recurrence	*P* (χ^2 t-St)	*P* (Cox)	HR	95%CI
Characteristic							
N	81	57	24				
GRS	7.2 ± 1.7	7.1 ± 1.8	7.5±1.7				
Age, years	48 ± 6	48 ± 6	48 ± 6	.99	.94	1.002	0.938-1.071
Sex, male	72 (89%)	51 (90%)	21 (88%)	.79	.70	0.8	0.2-2.6
BMI, kg/m^2	28.6 ± 5.3	27.9 ± 5.2	30.2 ± 5.2	.08	.06	1.06	0.99-1.13
Previous AMI	6 (7%)	2 (4%)	4 (17%)	.06	.02	3.3	1.1-9.9
Hypertension	31 (38%)	21 (37%)	10 (42%)	.68	.72	1.2	0.5-2.6
Dyslipidaemia	27 (33%)	19 (33%)	8 (33%)	1.00	.76	0.9	0.4-2.0
Current smoking	53 (65%)	40 (70%)	13 (54%)	.16	.20	0.6	0.3-1.3
History of cocaine abuse	5 (6%)	1 (2%)	4 (17%)	.03	.001	5.1	1.7-15.1
Family of premature CAD	23 (29%)	18 (32%)	5 (21%)	.30	.31	0.6	0.2-1.6
Laboratory parameters							
Haemoglobin, g/L	151 ± 16	155 ± 13	142 ± 19	.001	.001	0.7	0.6-0.9
GRF, mL/min per 1.73 m^{2,}	97 ± 24	97 ± 19	99 ± 33	.77	.75	1.00	0.99-1.02
Maximum Troponin I, ng/mL	48 ± 68	45 ± 72	55 ± 60	.58	.61	1.00	0.99-1.01
Total Cholesterol, mg/dL	188 ± 45	193 ± 39	175 ± 56	.11	.08	0.991	0.982-1.001
LDL-C, mg/dL	119 ± 41	124 ± 39	105 ± 43	.05	.03	0.989	0.978-0.999
LDL-C ≥110 mg/dL	43 (54%)	34 (60%)	9 (39%)	.10	.08	0.47	0.2 – 1.1
HDL-C, mg/dL	38 ± 11	38 ± 9	40 ± 13	.34	.31	1.022	0.980-1.066
Triglycerides, mg/dL	145 ± 96	142 ± 78	154 ± 130	.61	.54	1.00	0.997-1.005
MMP1	97 ± 12	96 ± 19	101 ± 9	.10	.09	1.036	0.994-1.080
MMP2	12 ± 8	11 ± 7	13 ± 11	.41	.24	1.031	0.980-1.085
MMP7	27 ± 3	27 ± 2	28 ± 4	.18	.04	1.149	1.001-1.319
MMP9	184 ± 77	182 ± 71	188 ± 91	.76	.69	1.001	0.996-1.007
MMP10	552 ± 431	500 ± 364	672 ± 548	.11	.03	1.001	1.000-1.001
TIMP1	190 ± 120	167 ± 75	241 ± 178	.01	.001	1.005	1.002-1.008

AMI Index Event							
ST-segment elevation MI	58 (72%)	40 (70%)	18 (75%)	.66	.66	1.2	0.5-3.0
Heart rate, bpm	78 ± 19	77 ± 17	80 ± 23	.47	.34	1.011	0.988-1.034
Successful revascularization[b]	77 (95%)	56 (98%)	21 (88%)	.08	.01	0.23	0.07-0.77
Killip class ≥ II	11 (14%)	5 (9%)	6 (25%)	.05	.01	3.1	1.2-7.9
GRACE risk score	117 ± 27	115 ± 23	121 ± 33	.31	.17	1.011	0.995-1.027
Cardiac CT findings							
CAC score	117 ± 27	286 ± 660	198 ± 253	.65	.70	1.000	0.998-1.001
CAC percentile above 90[c]	40%	36%	50%	.38	.35	1.7	0.5-5.2
Number of coronary plaques	5.5 ± 4.9	5.3 ± 5.2	5.9 ± 4.1	.74	.62	1.03	0.92-1.14
Multivessel disease[d]	71%	67%	83%	.27	.20	2.6	0.6-12.3
Echocardiographic findings							
LVEF at discharge, %	57 ± 11	58 ± 11	55 ± 12	.29	.20	0.978	0.944-1.013
Longitudinal strain	13.0 ± 3.4	12.7 ± 3.6	13.8 ± 3.1	.40	.42	1.085	0.886-1.328
Radial strain	27.7 ± 9.6	26.5 ± 9.3	30.9 ± 10.1	.22	.27	1.036	0.972-1.105
Circumferential strain	26.7 ± 6.1	25.8 ± 6.3	28.8 ± 5.1	.19	.26	1.064	0.953-1.189
Medications at discharge							
β-blocker	70 (86%)	51 (89%)	19 (79%)	.21	.08	0.4	0.2-1.1
ACEI inhibitor or ARB	61 (75%)	45 (79%)	16 (67%)	.24	.21	0.6	0.3-1.3
Diuretic	8 (10%)	3 (5%)	5 (21%)	.03	.002	4.2	1.5-11.2
High intensity statin	77 (95%)	55 (97%)	22 (92%)	.36	.16	0.4	0.1-1.5

n (%) is shown for categorical variables. Mean ± SD is shown for continuous variables. AMI, acute myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker, BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; CI, confidence interval; GFR, glomerular filtration rate; GRS, genetic risk score; HDL-C, high density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; PCI, percutaneous coronary intervention;

[a]GFR for each patient was estimated from serum creatinine using the modification of diet in renal disease study equation.
[b]Successful revascularization was defined as final TIMI flow 3.
[c]calcium percentile for each patient adjusted for age, sex and ethnicity according to Multi-Ethnic Study of Atherosclerosis (MESA).
[d]multivessel disease by cardiac CT was determined if an additional non-culprit stenosis >40% was identified.

Table 2 of the supplementary data

Genetic testing for familial hypercholesterolemia (FH) among patients with ‘possible FH’ according to the Dutch Lipid Clinic Network diagnostic criteria*

ID	Genetic testing FH				SNPs related with dyslipidaemia															
	Result	Gene	Nucleotide	Protein	rs11220462	rs1367117	rs1564348	rs1800562	rs2479409	rs3757354	rs429358	rs4299376	rs629301	rs6511720	rs7412	rs8017377	rs10455872	rs3798220	rs17244841	rs2032582
					ST3GAL4	APOB	SLC22A1	HFE	PCSK9	MYLIP	APOE	ABCG5-G8	CELSR2	LDLR	APOE	NYNRIN	LPA	LPA	HMGCR	ABCB1
1	negative	NA	NA	NA	GG	GG	CT	GG	AG	CC	CT	GT	TT	GG	CC	GG	AA	TT	AA	AC
2	VUS	APOB	c.13621A>C	p.Lys4541Gln	GG	GG	TT	GG	AA	CC	TT	TT	TT	GG	CC	GG	AA	TT	AA	CC
3	negative	NA	NA	NA	GG	AG	TT	GG	AG	CC	TT	TT	TT	GG	CC	GG	AA	TT	AA	AA
4	negative	NA	NA	NA	GG	AG	TT	GG	AA	CC	CT	GT	TT	GG	CC	AG	AA	TT	AA	AC
5	negative	NA	NA	NA	GG	GG	CT	GG	AA	CC	TT	TT	TT	GG	CC	AG	AA	TT	AA	AC
6	VUS	LDLR	c.2282C>T	p.Thr761Met	GG	AG	TT	GG	AG	CC	TT	GT	GT	GG	CC	GG	AA	TT	AA	CC
7	negative	NA	NA	NA	GG	AG	TT	GG	GG	CC	CT	GG	TT	GG	CC	GG	AG	CT	AA	AA
8	negative	NA	NA	NA	GG	GG	CT	GG	AG	CC	TT	TT	TT	GG	CC	GG	AA	TT	AA	AA

FH, familial hypercholesterolaemia; SNPs, single-nucleotide polymorphisms; VUS, variant of unknown significance.

* Genetic testing was limited to patients with ≥ 4 points; none of them reached the diagnosis of FH before or after genetic testing.

Table 3 of the supplementary data

Association of individual SNPs and risk of recurrences

Genetic variant	**HR**	**95%CI**	***P***
rs17465637	2.2	0.3-16.4	.48
rs6725887	1.4	0.6-3.2	.39
rs9818870	1.1	0.4-2.7	.84
rs10455872	1.0	0.4-3.0	.50
rs12526453	2.2	0.3-16.3	.37
rs1333049	1.1	0.3-3.7	.52
rs501120	1.6	0.2-11.8	.89
rs9982601	4.5	1.03-19.6	.04
rs10507391	1.1	0.5-2.5	.54
rs17222842	21.0	0->1000	.79
rs9315051	1.1	0.3-3.5	.84

Univariate Cox analysis for association between each risk allele and risk of recurrent event.

Table 4 of the supplementary data

Univariate and Multivariate Cox Regression Analysis using a secondary outcome (CV mortality or recurrent ACS)

	Univariate analysis			**Multivariate analysis[a]**		
GRS	HR (95%CI)	*P*			HR (95%CI)	*P**
Low GRS	1				1	
Intermediate GRS	1.2 (0.3-4.5)	.7		LDL-C ≤ 110 mg/dL (≤ 2.8 mmol/L)	0.7 (0.1- 3.8)	
				> 110 mg/dL (≥ 2.8 mmol/L)	**4.2 (0.3-57.6)**	**.28**
High GRS	2.1 (0.6- 8.0)	.2		LDL-C ≤ 110 mg/dL (≤ 2.8 mmol/L)	0.2 (0.1-2.4)	
				> 110 mg/dL (≥ 2.8 mmol/L)	**12.3 (1.3-117.3)**	**.029**

[a] The multivariate adjusted model included GRS, GRACE risk score, LDL-C and interaction between GRS and LDL-C. Interaction was noted between GRS terciles and LDL-cholesterol levels (*P* < .01). CI, confidence interval; HR, hazard ratio.

Table 5 of the supplementary data

Response to statin therapy at 6 months after myocardial infarction based on GRS terciles.

GRS	**LDL-C at baseline (mg/dL)**	***P*[a]**	**LDL-C after 6 months (mg/dL)**	**Change (mg/dL)**	**Change, %**	***P*[b]**
Low GRS	126 ± 40	.32	73 ± 19	-56 ± 42	-36 ± 29%	.37
Intermediate GRS	116 ± 44		67 ± 20	-48 ± 35	-35 ± 28%	
High GRS	113 ± 34		69 ± 20	-45 ± 41	-32 ± 30%	

[a] Regression model adjusted for age, sex and BMI; [b] Regression model adjusted for age, sex, BMI and baseline LDL-C level.

Figure 1 of the supplementary data. Risk Allele Frequency. In red, our cohort of non-diabetic patients < 55 years (n = 81); in blue, risk allele prevalence in the > 15,400 exome sequences from European (non-Finnish) population included in the Genome Aggregation Database (gnomAD). *P* < .005 for statistical significance.

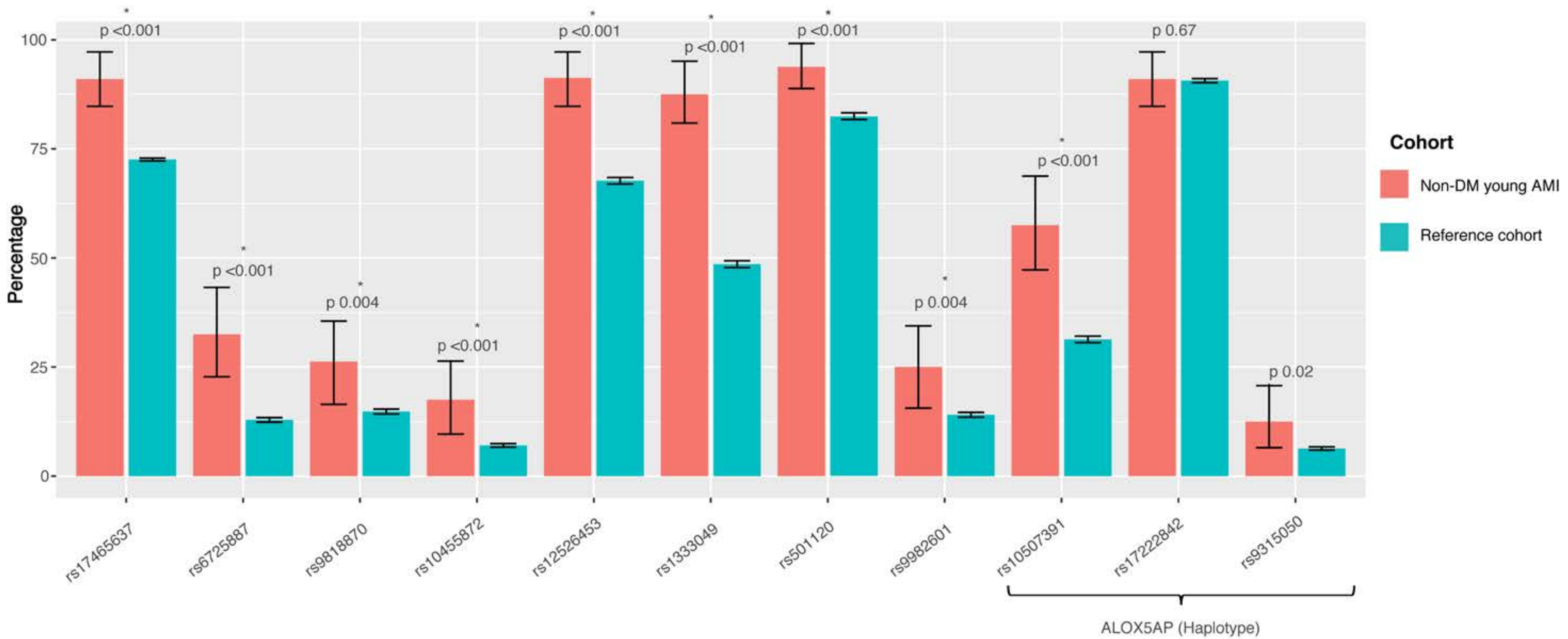
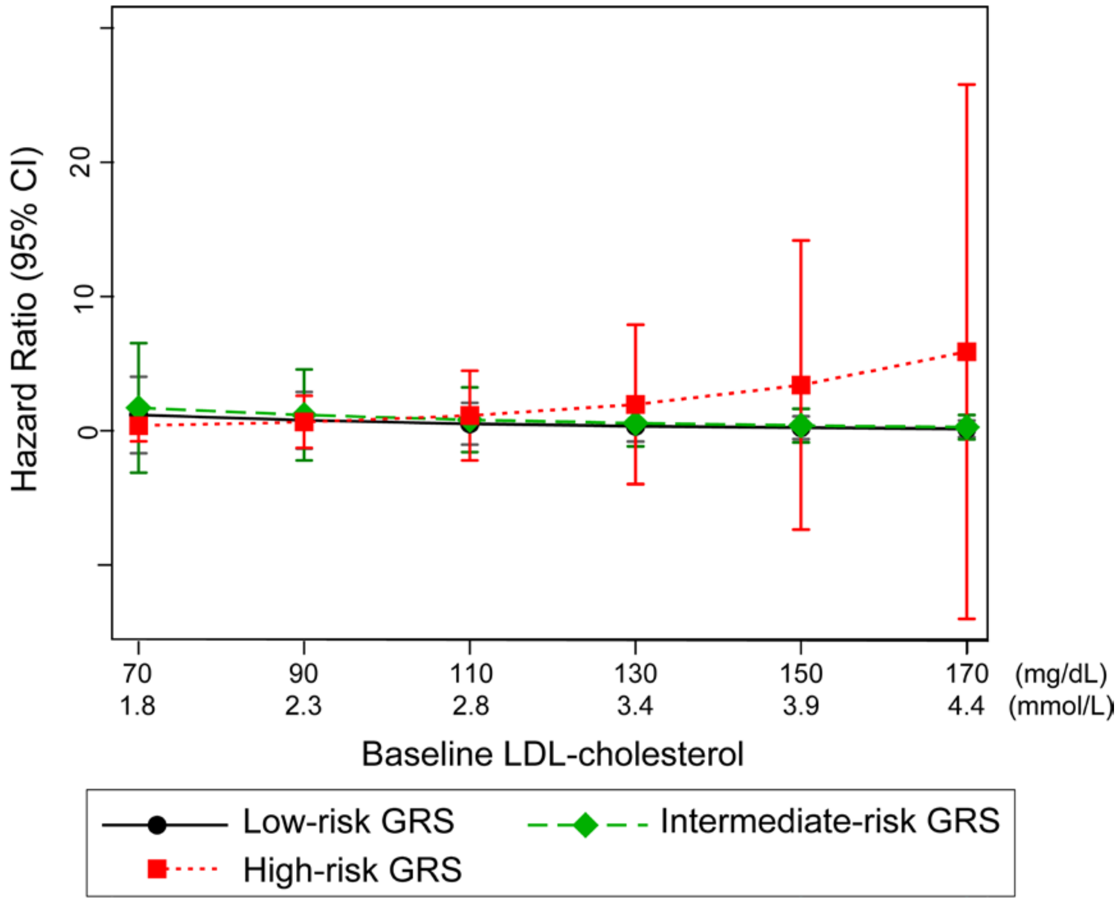


Figure 2 of the supplementary data. Interaction analysis between LDL-cholesterol levels and genetic risk score (GRS) terciles in the multivariate analysis.



For the high-risk GRS category:

$$HR_{(high-GRS)} = e^{(-4.493+(0.027*LDL-C))}$$

For the intermediate-risk GRS category:

$$HR_{(int-GRS)} = e^{(0.226-(0.019*LDL-C))}$$