

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 Δ C-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 | <i>P</i> (χ^2 t-St) | <i>P</i> (Cox) | HR | 95%CI |
|-------------------------------------|------------|------------|------------|---------------------------------|----------------|-------|-------------|
| <i>Characteristic</i> | | | | | | | |
| 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 |
| <i>Laboratory parameters</i> | | | | | | | |
| 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 |

| | | | | | | | |
|-------------------------------------------|------------|------------|-------------|-----|------|-------|-------------|
| <i>AMI Index Event</i> | | | | | | | |
| 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 |
| <i>Echocardiographic findings</i> | | | | | | | |
| 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 |
| <i>Medications at discharge</i> | | | | | | | |
| 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;

^aGFR for each patient was estimated from serum creatinine using the modification of diet in renal disease study equation.

^bSuccessful revascularization was defined as final TIMI flow 3.

^ccalcium percentile for each patient adjusted for age, sex and ethnicity according to Multi-Ethnic Study of Atherosclerosis (MESA).

^dmultivessel 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)

| GRS | Univariate analysis | | Multivariate analysis ^a | | |
|------------------|---------------------|----------|----------------------------------------------------------------|------------------------------------------|-------------|
| | HR (95%CI) | <i>P</i> | | HR (95%CI) | <i>P</i> * |
| Low GRS | 1 | | | 1 | |
| Intermediate GRS | 1.2 (0.3-4.5) | .7 | LDL-C ≤ 110 mg/dL (≤ 2.8 mmol/L) > 110 mg/dL (≥ 2.8 mmol/L) | 0.7 (0.1- 3.8) 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) > 110 mg/dL (≥ 2.8 mmol/L) | 0.2 (0.1-2.4) 12.3 (1.3-117.3) | .029 |

^aThe 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) | <i>p</i>^a | LDL-C after 6 months: (mg/dL) | Change (mg/dL) | Change, % | <i>p</i>^b |
|-------------------------|------------------------------------------|-----------------------------|----------------------------------------------|---------------------------|------------------|-----------------------------|
| <i>Low GRS</i> | 126 ± 40 | .32 | 73 ± 19 | -56 ± 42 | -36 ± 29% | .37 |
| <i>Intermediate GRS</i> | 116 ± 44 | | 67 ± 20 | -48 ± 35 | -35 ± 28% | |
| <i>High GRS</i> | 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.

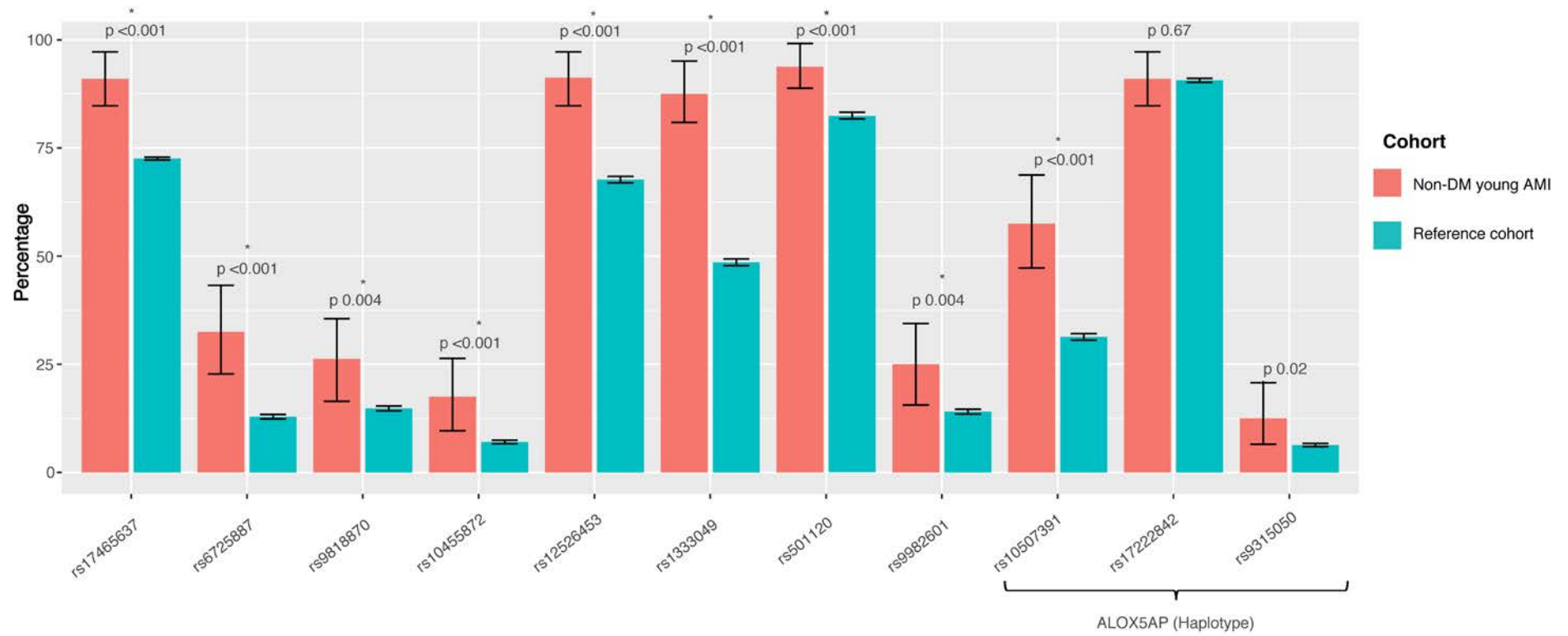
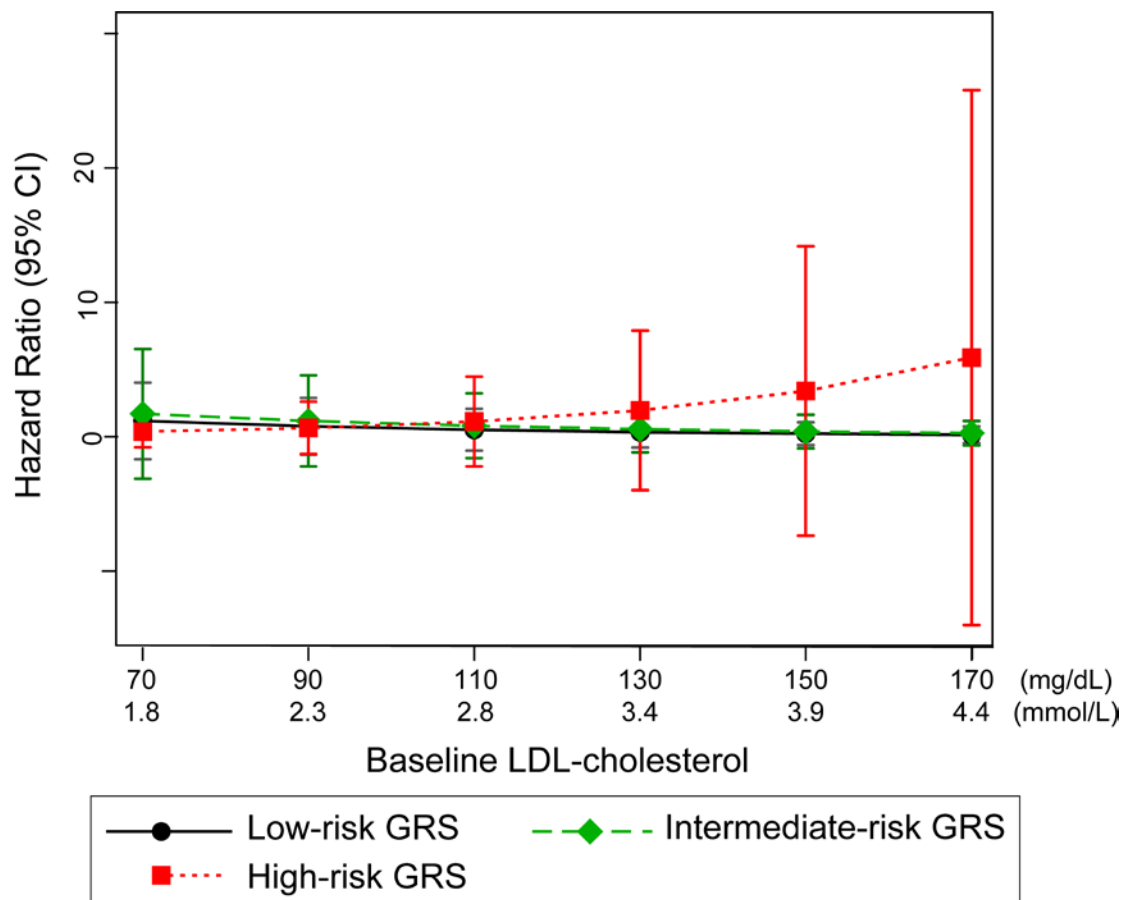


Figure 2 of the supplementary data. Interaction analysis between LDL-cholesterol levels and genetic risk score (GRS) tertiles in the multivariate analysis.



For the high-risk GRS category:

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

For the intermediate-risk GRS category:

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