Table S4. Summary table of *CYBA* gene polymorphisms and their association with CAD.

rs number (previous name)	Functional evidence	Association with CAD/MI	GWAS Catalog / CAD-GWAS	Overall interpretation
rs4673 (214C>T; C242T; His72Tyr)	- may ↓ enzymatic activity by altering the heme-binding site [61], - A allele reduce [63] and GG genotype increase NADPH oxidase activity [64], - no effect on p22phox mRNA or protein level [63], - GG carriers: ↓ endothelium-dependent dilation of epicardial coronary arteries [65], - ↑ stimulated superoxide production in neutrophils of A carriers and in HL-60 cells transfected with the variant [66], - no significant single-SNP association with ROS generation in this study; part of haplogroup C (rs4673 G, rs1049254 G, rs1049255 T) associated with reduced ROS production [69], - cis-eQTL for CYBA [51].	- A allele not associated with CAD - overall population (allelic odds ratio (OR) 0.93, 0.82-1.05; I^2 67.9%), in Asians ↓ risk of CAD allelic OR 0.75 (0.67-0.84) and dominant OR 0.69 (0.61-0.79) [72], and ACS: allelic OR 0.73 (0.64-0.83), I^2 39%, $p < 0.001$ [74], no effect in Caucasians [72,74], - marginal risk of CAD in Caucasian under a recessive model (AA vs GA + GG: OR 1.21, 95% CI 1.00-1.46, $p = 0.05$ $I^2 = 29.1\%$) [73], - AA genotype was protective against all-cause mortality but associated with elective revascularisation [75].	CAD GWAS: effect allele A; $\beta = 0.0083$ (SE = 0.0053); OR = 1.01 (95% CI 1.00-1.02); P = 0.118 (NS) [49]. GWAS Catalog: no genome-wide-significant variant-CAD association reported.	Meta-analyses suggest lower CAD risk in A-allele carriers in Asian populations. European-ancestry results are largely null.
rs1049255 (*24A>G, A640G)	- predicted to strengthen microRNA binding [293], - no effect on superoxide production in neutrophils [62] - CC genotype - 28% ↓ superoxide production [67], - C allele - ↓ NADPH oxidase activity and ↓ *CYBA* mRNA and protein expression [77], - no significant effect on *CYBA* mRNA expression [67]. - Associated with ↓ ROS generation in single-SNP analyses, largely explained by haplogroup C [69].	- ↓ CHD risk in Caucasians for TC versus TT (OR = 0.77, 95% CI 0.66-0.91) [79], - C allele protective against CAD in the overall population (after sensitivity analysis OR = 0.84, 95% CI 0.75-0.93) [72], - no association with death, MACE or revascularisation [75].	CAD GWAS: effect allele T; $\beta = 0.0066$ (SE = 0.0051); OR = 1.01 (95% CI 1.00-1.02); P = 0.196 (NS) [49]. GWAS Catalog: no genome-wide-significant variant-CAD association reported.	A modest protective association with CAD, particularly for the C allele in meta-analyses.
rs7195830 (*49A>G)	- may influence transcription factor binding and *CYBA* expression [81], - eQTL for *CYBA* in terminal ileum ($p = 0.027$);[81] - may interfere with microRNA binding activity and p22phox expression [80].	- G allele ↑ CAD risk in Polish case-control study (OR = 1.40, 95% CI 1.08-1.83), with a stronger effect among women (OR = 4.35, 95% CI 1.50-13.20) [82]; - diplotypes CG (rs9932581, rs7195830) and AG (rs72811418, rs7195830) - ↑ CAD risk in Polish subjects [83]	CAD GWAS: effect allele A; $\beta = -0.0063$ (SE = 0.0052); OR = 0.99 (95% CI 0.98-1.00); P = 0.220 (NS) [49]. GWAS Catalog: no genome-wide-significant variant-CAD association reported.	Association with CAD reported in a single population with no replication of the CAD association.
rs9932581 (−930A>G)	- C allele - 30% ↑ expression [84], - CC genotype - ↑ p22phox mRNA and protein level and NADPH oxidase activity [85], - no effect on superoxide production [62,63,67].	- C allele ↑ CAD risk in Polish population (OR = 2.03, 95% CI 1.21-3.44) [88], - C allele - protective effect in Austrian ≤40 years (OR = 0.50, 95% CI 0.30-0.81) [90],	CAD GWAS: effect allele T; $\beta = -0.0018$ (SE = 0.0056); OR = 1.00 (95% CI 0.99-1.01); P = 0.741 (NS) [49]. GWAS Catalog: no genome-wide-significant variant-	Functional effect demonstrated, epidemiological direction inconsistent: a risk allele in one population and

rs number (previous name)	Functional evidence	Association with CAD/MI	GWAS Catalog / CAD-GWAS	Overall interpretation
		- diplotype CA (rs9932581, rs72811418) - ↑ CAD risk in Polish subjects [83].	CAD association reported.	protective in another.
rs72811418 (−675A>T)	- A allele: ↑ reporter gene expression in response to HIF-1α [93], - AA genotype - ↑ superoxide production and greater carotid IMT [93].	- no association with CAD as a single variant [83], - CA (rs9932581 C / rs72811418 A) associated with ↑ CAD risk; AG (rs72811418 A / rs7195830 G) - sex-dependent association with CAD [83] - TA heterozygotes: ↑ risk of cardiovascular death at 5 and 10 years (prospective Polish cohort with CAD) HR 3.27 and HR 2.37) [94]	CAD GWAS: effect allele A; β = 0.0037 (SE = 0.0095); OR = 1.00 (95% CI 0.99-1.02); P = 0.698 (NS) [49]. GWAS Catalog: no genome-wide-significant variant-CAD association reported.	No independent CAD association.
rs13306296 (−536C>T)	- A allele: ↓ CYBA expression in aorta, tibial artery, atrial appendage, left ventricle and whole blood (GTEx) [51].	- lack of data about association with CAD, - GG genotype more frequently observed in patients with peripheral artery disease (Polish) [83].	CAD GWAS: effect allele A; β = −0.0044 (SE = 0.0054); OR = 1.00 (95% CI 0.99-1.01); P = 0.412 (NS) [49]. GWAS Catalog: no genome-wide-significant variant-CAD association reported.	No direct evidence for CAD association was identified.
rs16966671 (−852C>G)	- G allele: ↑ CYBA expression in aorta, tibial artery and left ventricle (GTEx) [51].	- lack of data about association with CAD, - G allele associated with multivessel stenosis (Polish) [83].	CAD GWAS: effect allele C; β = −0.0055 (SE = 0.0053); OR = 0.99 (95% CI 0.98-1.00); P = 0.298 (NS) [49]. GWAS Catalog: no genome-wide-significant variant-CAD association reported.	The reported association concerns CAD extent (multivessel stenosis), rather than CAD.
rs1049254 (521T>C; 549C>T; p.Val174Ala)	- as part of haplogroup C (rs4673 G, rs1049254 G, rs1049255 T), associated with ↓ NOX2-dependent ROS generation, as a single variant effect in rescued cells only [69] - ↓ NOX2-dependent ROS production in blood myeloid cells of carriers of the rs1049254/G allele [91].	- AA or GA vs. GG ↑ risk of CAD (Chinese) [92].	CAD GWAS: effect allele A; β = −0.0062 (SE = 0.0056); OR = 0.99 (95% CI 0.98-1.00); P = 0.264 (NS) [49]. GWAS Catalog: no genome-wide-significant variant-CAD association reported.	Functional associations vary between experimental systems. The CAD association has been reported in a single study.

Legend: ACS - acute coronary syndrome; CAD - coronary artery disease; CHD - coronary heart disease; CI - confidence interval; eQTL - expression quantitative trait locus; GTEx - Genotype-Tissue Expression project; GWAS - genome-wide association study; HIF-1α - hypoxia-inducible factor 1α; HR- hazard ratio; I^2 - proportion of total variability due to between-study heterogeneity; IMT - intima-media thickness; MACE- major adverse cardiovascular events; MI - myocardial infarction; mRNA - messenger RNA; NADPH - nicotinamide adenine dinucleotide phosphate; NOX2 - NADPH oxidase 2; NS- non-significant; OR- odds ratio; ROS -reactive oxygen species; SNP - single-nucleotide polymorphism. CAD-GWAS [49] values are from full summary statistics. The 95% CIs were calculated from β and SE as exp[β ± 1.96 × SE]. GWS, $P < 5 \times 10^{-8}$; NS, $P \geq 0.05$; EA, effect allele.