

Supplementary Table 2. “Repurposed” randomized clinical trials examining treatment-by-genotype pharmacogenetic interactions. This list was created by exploring the basic biomedical research literature (272 studies: candidate gene and genome-wide association studies) for “repurposed” or “effect modification” randomised trials—that is, studies that genotyped stored samples of participants in placebo controlled trials of cardiovascular drugs and thus enabled a test of the interaction between genotype and treatment that provides a higher level of evidence than conventional treatment only analyses. Genes with statistically significant results are shown in bold. Genes with “confirmed” pharmacogenetic associations based on our literature review criteria are denoted with an asterisk. As shown below, we identified 20 studies stemming from 13 unique trials; of 11 significant associations based on interaction tests, only one (*LDLR* pravastatin) met our criteria for “confirmation.”

Drug	RCT acronym	Reference	Gene	Intended use	Result
Bucindolol	BEST	18953265	<b><i>EDN1</i></b>	Efficacy: prevention of heart failure hospitalization or all-cause death	2 <i>EDN1</i> SNPs (rs2071942 and rs5370) with significant treatment–genotype interactions for the combined outcome of first heart failure hospitalization or all-cause death
	BEST	19880803	<b><i>ADRA2A</i></b>	Efficacy: sympatholytic response; all-cause mortality, time to all-cause mortality or cardiac transplantation, and left ventricular ejection fraction change measured at 12 months.	Significant interaction test for the Del322-325 polymorphism for sympatholytic response at 3 months. No significant findings for the clinical endpoints
	BEST	16844790	<i>ADRB1</i> *	Efficacy: prevention of heart failure hospitalization or all-cause death	Non-significant test for interaction
Isosorbide/Hydralazine	GRAHF (A-HeFT)	19327620	<i>NOS3</i>	Efficacy: event-free survival and composite score of survival, hospitalization, and quality of life	Non-significant tests for interaction for 3 SNPs

Losartan	GENRES	19593208	<i>CYP2C9</i>	Efficacy: blood pressure response	Non-significant test for interaction
Perindopril	PERGENE	19082699	<i>AGT, REN, ACE, AGTR1, AGTR2, CYP11B, KLK, KNG, BDKR1, BDKR2, NOS3</i>	Efficacy: prevention of composite outcome of cardiovascular mortality, myocardial infarction, or cardiac arrest	Significant interaction tests for <i>AGTR1</i> and <i>BDKR1</i> SNPs
Pravastatin	GISSI-Prevenzione study	17567623	<i>APOE*</i>	Efficacy: mortality	Non-significant test for interaction
	GenHAT (ALLHAT)	17174637	<i>ACE</i>	Efficacy: reduction in mortality and in composite cardiovascular outcome	Non-significant test for interaction
	CARE, WOSCOPS	18174457	<b><i>ADAMTS1</i></b>	Efficacy: prevention of fatal coronary disease and non-fatal myocardial infarction	Significant interaction test for 1 SNP (rs428785)
	PROSPER	18262190	<i>PCSK9</i>	Efficacy: lipid response, prevention of coronary heart disease development	Non-significant test for interaction
	PROSPER	18261733	<b><i>LDLR*</i></b> , <i>HMGCR</i>	Efficacy: lipid response, prevention of coronary heart disease development	Significant test for interaction for 1 <i>LDLR</i> SNP (C44857T) for lipid response
	GenHAT (ALLHAT)	19415820	<i>F2, F5, F7, F12, F13</i>	Efficacy: reduction in mortality and in composite cardiovascular outcome	Significant tests for interaction with the composite cardiovascular outcome for 2 <i>F5</i> SNPs (rs6025, rs6046)
	PROSPER	19752398	<b><i>NPC1L1</i></b>	Efficacy: lipid response, prevention of coronary heart disease development	Significant test for interaction for 1 <i>NPC1L1</i> SNP (rs17655652) for lipid response
	CARE, WOSCOPS	17008591	<b><i>FCAR</i></b>	Efficacy: prevention of fatal coronary disease and non-fatal myocardial infarction	Significant test for interaction for 1 SNP (Asp92Asn)
	CARE	20403483	<b><i>KIF6</i></b>	Efficacy: prevention of fatal coronary disease and non-fatal myocardial infarction	Significant test for interaction for 1 SNP (rs20455)
Fluvastatin	ALERT	17563401	<i>ABCB1, ACE, ADRB2, AGER, AGT, AGTR1, BCL2, BCL2L1, CCL2, CETP, CYP2C9,</i>	Efficacy: lipid response	Non-significant tests for interaction

			<i>HMGCR, HMOX1, IL6, IL6R, LPL, MMP3, SLC01B1</i>		
ximelagatran	THRIVE III	16512831	<i>F5, F2</i>	Efficacy: prevent thromboembolism; Safety: bleeding	Non-significant tests for interaction
Clopidogrel	CHARISMA	NA	<i>CYP2C19*</i>	Efficacy: composite cardiovascular outcome Safety: major bleeding	Non-significant tests for interaction
	CLARITY	NA	<i>CYP2C19*</i>	Efficacy: composite cardiovascular outcome	Non-significant tests for interaction
	ACTIVE-A, CURE	20979470	<i>CYP2C19*</i>	Efficacy: composite cardiovascular outcome Safety: major bleeding	Non-significant tests for interaction

Abbreviations: SNP, single nucleotide polymorphism; NA, non-available.