Supplemental Materials

for

A Model-Based Cost-Effectiveness Analysis of Pharmacogenomic Panel Testing in Cardiovascular Disease Management: Preemptive, Reactive or None?

Contents

Supplemental Materials I – eTables and eFigures

eTable 1. Diseases treated with drugs of the study interest recommended by clinical practice guidelines

Disease Dx	Subcategory	Drug	Genes	ref.	Early Hospital Care	Long-Term Care
Myocardial Infarction (MI)	Non-ST-elevated MI (NSTEMI) assum8	Clopidogrel	*CYP2C19*	[1,2]	Options: Clopidogrel: 300-mg or 600-mg loading dose, Ticagrelor: 180-mg loading dose	A P2Y12 inhibitor (either clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications Options: Clopidogrel: 75 mg daily Ticagrelor: 90 mg twice daily (293,294) (Level of Evidence: B)
		Statin	*SLCO1B1, KIF6, CETP*	[1,2]	high-intensity stain therapy should be initiated or continued in all patients with no contraindications (Atorvastatin (40 mg‡) 80mg, Rosuvastatin 20 mg (40 mg))	continue as an outpatient regiment
	ST-elevated MI (STEMI)	Clopidogrel	*CYP2C19*	[1,3]	Loading dose (as early as possible or at time of PCI): Clopidogrel: 600 mg; Prasugrel: 60 mg; Ticagrelor: 180 mg.	maintenance doses: Clopidogrel: 75 mg qd; Prasugrel: 10 mg qd; Ticagrelor: 90 mg bid (post-PCI only), for 1 year
		Statin	*SLCO1B1, KIF6, CETP*	[1,3]	high-intensity stain therapy should be initiated or continued in all patients with no contraindications (Atorvastatin (40 mg‡) 80mg, Rosuvastatin 20 mg (40 mg))	continue as an outpatient regiment
Coronary Heart Disease (CHD)	-	Clopidogrel	*CYP2C19*	[4]	Loading dose: Clopidogrel: 600 mg; Prasugrel: 60 mg; Ticagrelor: 180 mg.	Maintenance doses: Clopidogrel: 75 mg qd; Prasugrel: 10 mg qd; Ticagrelor: 90 mg bid.
Atrial Fibrillation (AF)	-	Warfarin, Phenprocoumon	*CYP2C9, VKORC1*	[5]	-	Dose adjusted for INR 2.0–3.0
Valvular Heart Disease (VHD)	Mitral valve stenosis (MS)	Warfarin, Phenprocoumon	*CYP2C9, VKORC1*	[6]	-	Dose adjusted for INR 2.0–3.1
	Other valves + CHA2DS2>=2	Warfarin, Phenprocoumon	*CYP2C9, VKORC1*	[6]	-	Dose adjusted for INR 2.0–3.2
	Prosthetic	Warfarin,	*CYP2C9,*	[6]	-	Dose adjusted for INR 2.0–3.0

	Health Valves	Phenprocoumon	*VKORC1*			
Hyperlipidemia (HLP)	-	Statin	*SLCO1B1, KIF6, CETP*	[7]	-	High intensity: Atorvastatin (40 mg‡) 80mg,Rosuvastatin 20 mg (40 mg); moderate intensity: Atorvastatin 10 mg (20 mg), Rosuvastatin (5 mg) 10 mg, Simvastatin 20–40 mg; low intensity: simvastatin 10mg
Peripheral Artery Disease (PAD)	Lower extremity	Clopidogrel	*CYP2C19*	[8]	-	Clopidogrel (75 mg per day), or aspirin
		Statin	*SLCO1B1, KIF6, CETP*	[8]	-	simvastatin 40 mg daily
	Carotid and/or vertebral	Clopidogrel	*CYP2C19*	[9]	-	Clopidogrel (75 mg per day), or aspirin
		Statin	*SLCO1B1, KIF6, CETP*	[8]	-	simvastatin 40 mg daily
Stroke (STR)	-	Clopidogrel	*CYP2C19*	[10]	Aspirin+clopidogrel for 21 days	Clopidogrel 90 days

* Only Class I and IIa are considered recommended and adopted in this study.

eTable 2. Genetic polymorphism included in the proposed pharmacogenomic panel.

Gene	Medication	Genotype Variants[a]	Alt. Med.	Ref.
CYP2C19	Clopidogrel	*2, *3, *4, *5, *6, *7, and *8	Ticagrelor	[11-14]
CYP2C9	Warfarin	*2, *3	NOAC	[12,15,16]
VKORC1	Warfarin	1639G>A, 1173C>T, 1542G>C, 2255T>C, and 3730G>A	NOAC	[15-21]
SLCO1B1	Statin	*5, *15	PCSK 9 inhibitor	[22,23]

[a] Individual with heterozygous variants genotypes were considered variants in the model.
PCSK 9 inhibitor, proprotein convertase subtilisin/kexin type 9 inhibitor.

eTable 3. Summary of key model parameter inputs

Variable	Root Definition	Low	High	Distribution	Ref.
Cost Values (2019 USD)					
Genetic Testing					
Cost of genetic testing, *CYP2C19*	260.95	106.00	578.00	Gamma	[24]
Cost of genetic testing, *CYP2C9/VKORC1*	242.24	55.00	761.00	Gamma	[25]
Cost of PGx panel testing, *CYP2C19, SLCO1B1, CYP2C9, VKORC1*	209.96	54.64	761.33	Gamma	assumption
Monthly Costs of Health States					
Monthly cost of treatment free	0	0	0	Constant	assumption
Monthly cost of medications, Clopidogrel	34.84	4.50	202.04	Gamma	[24]
Monthly cost of medications, NOAC	231.13	73.72	339.13	Gamma	[26]
Monthly cost of medications, PCSK9 inhibitor	487.50	487.50	487.50	Constant	[27,28]
Monthly cost of medications, statin	4.17	4.17	31.60	Gamma	[29,30]
Monthly cost of medications, ticagrelor	190.47	116.14	376.16	Gamma	[31]
Monthly cost of medications, warfarin	24.60	4.41	158.01	Gamma	[25]
Monthly cost of Treatment without ADE, AF	137.82	126.79	143.34	Gamma	[32]
Monthly cost of Treatment without ADE, CHD	413.46	181.18	1287.98	Gamma	[24]
Monthly cost of Treatment without ADE, HLP	0	0	0	Constant	assumption
Monthly cost of Treatment without ADE, MI	320.02	240.06	400.7	Gamma	[33]
Monthly cost of Treatment without ADE, PAD	34.20	23.17	39.72	Gamma	[32]
Monthly cost of Treatment without ADE, STR	433.84	273.49	433.84	Gamma	[32]
Monthly cost of Treatment without ADE, VHD	34.20	23.17	39.72	Gamma	[32]
Event Costs					
Event cost, STR	66214.19	9528.03	114455.37	Gamma	[25]
Event cost, MI	33896.47	10830.56	70084.05	Gamma	[25]
Event costs, CVD death	24567.40	14850.24	42803.50	Gamma	[34]
Event costs, non-CVD death	13501.37	6185.3	19795.73	Gamma	[34]
Additional Monthly Costs for Treatment Adverse Events					
Monthly additional cost of Tx ADE, AF warfarin (bleeding)	725.00	276.99	1897.52	Gamma	[24]
Monthly additional cost of Tx ADE, CHD clopidogrel (bleeding, Rash, Diarrhea, nausea/vomiting, Hepatic toxicity)	725.00	276.99	1897.52	Gamma	[24]
Monthly additional cost of Tx ADE, HLP statin (muscle-related complains, rhabdomyolysis)	0	0	0	Constant	assumption

Monthly additional cost of Tx ADE, MI clopidogrel (bleeding, Rash, Diarrhea, nausea/vomiting, Hepatic toxicity)	725.00	276.99	1897.52	Gamma	[24]
Monthly additional cost of Tx ADE, MI statin (muscle-related complains, rhabdomyolysis)	353.32	339.57	3000.58	Gamma	[34]
Monthly additional cost of Tx ADE, PAD clopidogrel (bleeding, Rash, Diarrhea, nausea/vomiting, Hepatic toxicity)	725.00	276.99	1897.52	Gamma	[24]
Monthly additional cost of Tx ADE, PAD statin (muscle-related complains, rhabdomyolysis)	353.32	339.57	3000.58	Gamma	[34]
Monthly additional cost of Tx ADE, STR clopidogrel (bleeding, Rash, Diarrhea, nausea/vomiting, Hepatic toxicity)	725.00	276.99	1897.52	Gamma	[24]
Monthly additional cost of Tx ADE, VHD warfarin (bleeding)	725.00	276.99	1897.52	Gamma	[24]
Heath State Utility Values (QALY)					
Utilities of Health States					
CVD death	0	0	0	Constant	assumption
CVD death	0.2355	0.1905	0.2805	Gamma	[31,35]
Tx free	1	1	1	Constant	assumption
Tx without ADE, AF	0.786	0.761	0.844	Gamma	[25,36]
Tx without ADE, CHD	0.724	0.597	0.827	Gamma	[37]
Tx without ADE, HLP	0.81	0.788	1	Gamma	[37]
Tx without ADE, MI	0.704	0.575	0.843	Gamma	[37]
Tx without ADE, PAD	0.746	0.708	0.833	Gamma	[37]
Tx without ADE, STR	0.63695	0.4479	0.76586	Gamma	[38]
Tx without ADE, VHD	0.781	0.708	1	Gamma	[37]
Disutilities of Events and Adverse Events					
Event disutility, MI	-0.300	-0.440	-0.160	Gamma	[34]
Event disutility, Stroke	-0.640	-0.890	-0.360	Gamma	[37]
Tx with ADE, AF (disutility)	-0.547	-0.729	-0.155	Gamma	[34,37,39]
Tx with ADE, CHD (disutility)	-0.547	-0.729	-0.155	Gamma	[34,37,39]
Tx with ADE, HLP (disutility)	-0.140	-0.142	-0.137	Gamma	[37]
Tx with ADE, MI clopidogrel (disutility)	-0.547	-0.729	-0.155	Gamma	[34,37,39]
Tx with ADE, MI statin (disutility)	-0.367	-0.412	-0.115	Gamma	[34,37]
Tx with ADE, PAD clopidogrel (disutility)	-0.547	-0.729	-0.155	Gamma	[34,37,39]
Tx with ADE, PAD statin (disutility)	-0.367	-0.412	-0.115	Gamma	[34,37]
Tx with ADE, STR (disutility)	-0.547	-0.729	-0.155	Gamma	[34,37,39]

Tx with ADE, VHD (disutility)	-0.547	-0.729	-0.155	Gamma	[34,37,39]
Transition Probability					
Genetic Variants					
Freq. of CYP2C19+SLCOB+CYP2C9/VKORC1 variants	0.37	0.3	0.4	Beta	[40]
Freq. of CYP2C19+CYP2C9+SLCOB1+VKORC1 variants	0.18	0.1	0.3	Beta	[40]
Freq. of CYP2C19 variants	By race	0.03	0.46	Beta	[11,12,41]
Freq. of CYP2C9 variant (*2 or *3)	By race	0.004	0.238	Beta	[12,41]
Freq. of CYP2C9 variant (*2 or *3) and VKORC1	By race	0.37	0.37	Beta	[40,41]
Freq. of SLCO1B1 (*5, or *15)	By race	0.06	0.48	Beta	[22,23,41]
Freq. of VKORC1 variants	By race	0	0.86	Beta	[20,21]
Disease Free and Disease Development					
Tx free to non-CVD death	By race, gender and age	0	0.000022	Table*	[42]
Tx free to AF Tx	By race, gender and age	0	0.0003289	Table*	[43,44]
Tx free to CHD Tx	By race, gender and age	0	0.0005591	Table*	[45]
Tx free to HLP Tx	By race, gender and age	0	0.0131623	Table*	[46,47]
Tx free to MI Tx	By race, gender and age	0	0.000278	Table*	[45]
Tx free to PAD Tx	By race, gender and age	0	0.0017331	Table*	[48,49]
Tx free to STR Tx	By race, gender and age	0	0.0008393	Table*	[50]
Tx free to VHD Tx	By race, gender and age	0	0.0014794	Table*	[50]
Treatment without Adverse Events to CVD Death					
Tx without ADE to CVD death, AF (no variant)	0.00177	0.00117	0.00296	Beta	[51-56]
Tx without ADE to CVD death, CHD (no variant)	0.00168	0.00168	0.00168	Beta	[4,57]
Tx without ADE to CVD death, HLP (no variant)	0.00247	0.00085	0.00499	Beta	[58-60]
Tx without ADE to CVD death, MI clopidogrel (no variant)	0.00307	0.00161	0.00439	Beta	[57,61-63]
Tx without ADE to CVD death, MI statin (no variant)	0.00144	0.000461	0.00283	Beta	[64-67]
Tx without ADE to CVD death, PAD clopidogrel (no variant)	0.00138	0.00138	0.00138	Beta	[57]
Tx without ADE to CVD death, PAD statin (no variant)	0.00165	0	0.00399	Beta	[68,69]
Tx without ADE to CVD death, STR (no variant)	0.000554	0.0000640	0.000868	Beta	[57,70]
Tx without ADE to CVD death, VHD (no variant)	0.0180	0.00972	0.0461	Beta	[71]
Tx without ADE to CVD death, CHD (with variant)	0.00134	0.00109	0.00160	Beta	[22,23]
Tx without ADE to CVD death, AF (usual care)	0.00193	0.00113	0.00361	Beta	[51-56]
Tx without ADE to CVD death, CHD (usual care)	0.00168	0.00168	0.00168	Beta	[4,57]
Tx without ADE to CVD death, HLP (usual care)	0.00247	0.000851	0.00499	Beta	[58-60]
Tx without ADE to CVD death, MI clopidogrel (usual care)	0.00307	0.00161	0.00439	Beta	[57,61-63]

Tx without ADE to CVD death, MI statin (usual care)	0.00144	0.000461	0.00283	Beta	[64-67]
Tx without ADE to CVD death, PAD clopidogrel (usual care)	0.00138	0.00138	0.00138	Beta	[57]
Tx without ADE to CVD death, PAD statin (usual care)	0.00165	0.00165	0.00165	Beta	[68,69]
Tx without ADE to CVD death, STR (usual care)	0.000743	0.0000704	0.00141	Beta	[57,70]
Tx without ADE to CVD death, VHD (usual care)	0.00873	0.00873	0.00873	Beta	[71]
Treatment without Adverse Events to Death					
Tx without ADE to death, AF (no variant)	0.00313	0.00124	0.00725	Beta	[51,52,72-75]
Tx without ADE to death, HLP, CHD (no variant),	0.00258	0.00258	0.00258	Beta	[4,57]
Tx without ADE to death, HLP (no variant)	0.00333	0.00217	0.00448	Beta	[59,60]
Tx without ADE to death, MI clop (no variant)	0.00514	0.00293	0.00811	Beta	[61-63,76]
Tx without ADE to death, PAD clop (no variant)	0.00442	0.00287	0.00559	Beta	[57,69]
Tx without ADE to death, PAD statin (no variant)	0.00721	0	0.0251	Beta	[68,69,77]
Tx without ADE to death, STR (no variant)	0.000642	0.000115	0.00139	Beta	[70]
Tx without ADE to death, VHD (no variant)	0.0193	0.00232	0.0492	Beta	[71,78,79]
Tx without ADE to death, CHD (with variant)	0.00134	0.00109	0.00160	Beta	[22,23]
Tx without ADE to death, AF (usual care)	0.00341	0.00151	0.00703	Beta	[51,52 72-75 ,]
Tx without ADE to death, CHD (usual care)	0.00258	0.00258	0.00258	Beta	[4,57]
Tx without ADE to death, HLP (usual care)	0.00333	0.00217	0.00448	Beta	[59,60]
Tx without ADE to death, MI clopidogrel (usual care)	0.00514	0.00293	0.00811	Beta	[61-63,76]
Tx without ADE to death, MI statin (usual care)	0.003971	0.000926	0.0106	Beta	[65,66,80,81]
Tx without ADE to death, PAD clopidogrel (usual care)	0.00442	0.00287	0.00559	Beta	[57,69]
Tx without ADE to death, PAD statin (usual care)	0.00721	0	0.0251	Beta	[68,69,77]
Tx without ADE to death, STR (usual care)	0.000860	0.000188	0.00153	Beta	[70]
Tx without ADE to death, VHD (usual care)	0.00933	0.00209	0.00933	Beta	[71,78,79]
Treatment without Adverse Events to Adverse Events					
Tx without ADE to Tx with ADE, CHD (no variants)	0.0395	0.0395	0.0395	Beta	[4,57]
Tx without ADE to Tx with ADE, AF (no variants)	0.0203	0.0106	0.0338	Beta	[51-54,72-75,82,83]
Tx without ADE to Tx with ADE, MI statin (no variants)	0.00397	0.000926	0.0106	Beta	[65,66,80,81]
Tx without ADE to Tx with ADE, HLP (no variants)	0.00689	0.0000252	0.0157	Beta	[59,60]
Tx without ADE to Tx with ADE, MI clopidogrel (no variants)	0.0418	0.0345	0.0493	Beta	[57,62,63,76]
Tx without ADE to Tx with ADE, MI statin (no variants)	0.000100	0.000997	0.00100	Beta	[67,80]
Tx without ADE to Tx with ADE, PAD clopidogrel (no variants)	0.0396	0.0395	0.0395	Beta	[57,69]
Tx without ADE to Tx with ADE, PAD statin (no variants)	0.000250	0.000250	0.000250	Beta	[77]
Tx without ADE to Tx with ADE, STR (no variants)	0.0347	0.0298	0.0395	Beta	[57,69,70]

Tx without ADE to Tx with ADE, VHD (no variants)	0.0185	0.00510	0.0307	Beta	[71,78,79,84]
Tx without ADE to Tx with ADE , AF (usual care)	0.0203	0.0106	0.0338	Beta	[51-54,72-75,82,83]
Tx without ADE to Tx with ADE, CHD (usual care)	0.0395	0.0395	0.0395	Beta	[4,57]
Tx without ADE to Tx with ADE , HLP (usual care)	0.00689	0.0000252	0.0157	Beta	[59,60]
Tx without ADE to Tx with ADE, MI clopidogrel (usual care)	0.0418	0.0345	0.0493	Beta	[57,62,63,76]
Tx without ADE to Tx with ADE, MI statin (usual care)	0.000100	0.0009968	0.00100	Beta	[67,80]
Tx without ADE to Tx with ADE, PAD clopidogrel (usual care)	0.0395	0.0395	0.0395	Beta	[57,69]
Tx without ADE to Tx with ADE, PAD statin (usual care)	0.000250	0.000250	0.000250	Beta	[77]
Tx without ADE to Tx with ADE, STR (usual care)	0.0347	0.0298	0.0395	Beta	[57,69,70]
Tx without ADE to Tx with ADE, VHD (usual care)	0.0177	0.00306	0.0307	Beta	[71,78,79,84]
Second Disease Developed					
MI after PAD with clopidogrel (no variant)	0.000722	0.000722	0.000722	Beta	[57]
STR after PAD with clopidogrel (no variant)	0.00101	0.00101	0.00101	Beta	[57]
MI after PAD with clopidogrel (usual care)	0.000722	0.000722	0.000722	Beta	[57]
STR after PAD with clopidogrel (usual care)	0.00101	0.00101	0.00101	Beta	[57]
MI after PAD with statin (usual care)	0.00192	0.00192	0.00192	Beta	[85]
STR after PAD with statin (usual care)	0.00250	0.00192	0.00480	Beta	[85]
MI after CHD (no variant)	0.00107	0.00107	0.00107	Beta	[4,57]
STR after CHD (no variant)	0.00193	0.00193	0.00193	Beta	[4,57]
MI after CHD (usual care)	0.00107	0.00107	0.00107	Beta	[4,57]
STR after CHD (usual care)	0.00193	0.00193	0.00193	Beta	[4,57]
MI after PAD with statin (no variant)	0.00192	0.00192	0.00192	Beta	[85]
STR after PAD with statin (no variant)	0.00250	0.00192	0.00480	Beta	[85]
MI after VHD (no variant)	0.00255	0.00255	0.00255	Beta	[71]
STR after VHD (no variant)	0.00191	0.000840	0.00324	Beta	[71,78,79,84]
STR after AF (no variant)	0.00145	0.000343	0.00335	Beta	[51,72-74,83,86]
STR after AF (usual care)	0.00145	0.000343	0.00335	Beta	[51,58,72-74,83,86]
MI after VHD (usual care)	0.00255	0.00255	0.00255	Beta	[71]
STR after VHD (usual care)	0.00183	0.000528	0.00324	Beta	[71,78,79,84]
Risk Ratios of Alternative Medicine					
Relative risk of MI ticagrelor vs clopidogrel	0.830	0.74	0.92	Lognormal	[87]
Relative risk of MI NOAC vs warfarin	0.970	0.78	1.2	Lognormal	[26]
Relative risk of major bleeding ticagrelor vs clopidogrel	1.090	0.96	1.23	Lognormal	[87]
Relative risk of major bleeding NOAC vs warfarin	0.860	0.73	1	Lognormal	[26]

Relative risk of stroke ticagrelor vs clopidogrel	1.060	0.88	1.26	Lognormal	[87]
Relative risk of stroke NOAC vs warfarin	0.810	0.73	0.91	Lognormal	[26]
Risk reduction for major CHD event using PSCK9 inhibitor	0.780	0.58	1.04	Lognormal	[88]
Relative risk of death carriers in PAD	2.075	1.114	5.376	Lognormal	[87]
Hazard ratio of CHD to MI (nonfatal) ticagrelor vs clopidogrel	0.830	0.59	1.16	Lognormal	[87]
Hazard ratio of CHD to STR (nonfatal) ticagrelor vs clopidogrel	1.010	0.44	2.32	Lognormal	[87]
Hazard ratio of death alter vs warfarin in AF	0.835	0.73	0.955	Lognormal	[26]
Hazard ratio of death ticagrelor vs clopidogrel in CHD	0.770	0.51	1.17	Lognormal	[87]
Hazard ratio of death ticagrelor vs clopidogrel in MI	0.770	0.51	1.17	Lognormal	[87]
Hazard ratio of death alter vs warfarin in VHD	0.835	0.73	0.955	Lognormal	[26]
Hazard ratio of ADE ticagrelor vs clopidogrel in MI	1.020	0.70	1.49	Lognormal	[87]
Odds ratio of myopathy using statin (per SLCO1B1 risk allele)	4.300	2.50	7.20	Lognormal	[23]
Population Parameters					
Age	Distribution	45	95	Table[a]	[42]
Gender Male	Distribution	0	1	Table[b]	[42]
Race	Distribution	0	0	Table[c]	[42]
Risk adjustment for developing CVD	4%	4%	8%	Lognormal	assumption

CVD, cardiovascular disease
NOAC, novel oral anticoagulant
PSCK9, Proprotein convertase subtilisin/kexin type 9 inhibitor
ADE, adverse drug events
AF, atrial fibrillation
CHD, coronary heart disease
HLP, hyperlipidemia
MI, myocardial infarction
PAD, peripheral artery disease
STR, stroke
VHD, valvular heart disease
Tx, treatment
QALY, quality-adjusted life-year
a. Attached excel spreadsheet: eTable 6
b. Age distribution: eFigure 4
c. Sex distribution: male 49%
d. Race distribution: 80% White, 14% African American, 6% Asian

eTable 4. Model assumptions

	Genetic variants
1	Heterozygotes have much higher prevalence in the population than homozygotes, therefore if didn't mentioned, homozygotes were not separated from heterozygotes. However, homozygotes patients have much higher Odds to developed side effects. Therefore, in the sensitivity analysis, the input values from homozygotes patients were tested.
2	We assumed that individuals carrying 1 or 2 minor alleles were abnormal metabolizers and, thus, would be treated with alternative medications. The minor alleles were genetic variants that would lead to changes in drug metabolism or transport. The rest of the individuals were assumed to carry wild-type alleles or minor alleles that don't lead to changes in drug metabolism or transport, therefore would be treated with same medications used in usual care.
3	Values from race-based data were used if available. For the parameters based on the population data with mixed races, the mean value was used for all races.
4	VKORC1 variants (Asp36Tyr or D36Y) can cause warfarin resistance. But the case is rare (<0.1%) and require large dosage (>70mg/week). Therefore, this scenario was omitted from the model.
5	VKORC1 genetic variants are referred with different names, such as VKORC1AB, VKORC1BB, VKORC1AG, VKORC1GG, VKORC1 SNP -1639G>A, etc. In this analysis, VKORC1AA (homozygotes, more severe) and VKORC1AG (heterozygotes, mild) were used as the warfarin sensitive genotypes.
6	The frequecies of KIF6 for ACS vs general population are similar among Caucasian population. So we assumed that other races share the same pattern as the Caucasian population.
7	All the minor allele frequencies are independent of others. No evidence was found that two of them were associated.
8	The minor allele frequencies were the same for general population and the disease groups if not separate in the model (e.g., CYP2C9, CYP2C19, SLO1B1).
9	Genetic minor allele doesn't change an individual's life expectancy, and only disease statuses can change a person's life expectancy.
10	Alternative treatment for minor allele carriers shares the same time frame with majority allele carriers.
	Population Selection
1	Individuals with congenital heart diseases were not specified in the study population, and this group of individuals followed the background probabilities for different disease states.
2	Individuals entered the model with treatment free status.
3	According to the most recent definition, MI includes STEMI, NSTEMI. However, unstable angina (UA) was usually studied together with NSTEMI, therefore, was included in the NSTEMI in the study model.
4	Individuals who developed CVD were not comorbid with other chronic diseases (single disease status) or pregnancy.
	Treatment selection
1	According to the ACC/AHA, no evidence available on safety or efficacy of immediate switching patients from one P2Y12 inhibitor to a different one. Therefore, this study assumes that there are no negative effects on the outcomes for if patient switch medications immediately.
2	Patients with PAD were recommended to take aspirin or clopidogrel as routine treatment. In this study, only clopidogrel cases were discussed. We assume all the patients took aspirin, same as those in clinical trials.
3	Primary prevention of cardiovascular diseases (treatment started before diseases actually developed) using theses 3 types of drugs were not included in the model. Secondary prevention of diseases (reduced the disease comorbidities after disease developed and treatment started) were included and compared in the model.

4	The drug alternative for clopidogrel is ticagrelor or pasugrel. Ticagrelor is less sensitive to genetic variants. Pasugrel was not recommended NSTEMI, and coronary anatomy has be to defined by angiography before initiating pasugrel. Therefore, ticagrelor was selected in all diseases as an alternative to clopidogrel.
5	The drug alternatives for statin are additional PCSK9 inhibitors or ezetimibe. Since studies reported that the effectiveness of ezetimibe is not significantly different from placebo, therefore PSCK9 was selected.
6	Patients with VKORC1 variants can be benefit from dosage reduce, but since NOAC has been used more frequently recently, and was reported to be more effective to all the population. Also, warfarin-PGx treatment was found to be not effective compared to warfarin alone. Therefore, NOAC was selected as an alternative, including dabigatran 150 mg twice daily, rivaroxaban 20 mg daily or apixaban 5 mg twice daily. The base-case analysis used the average value for these medications, and sensitivity analysis examined different medications separately.
	Disease States
1	Patient with the PGx-guided treatments develop drug side effects at a different rate.
2	The study population, although with higher risk of CVD development, share the same probabilities of genetic distribution as the general population. No information was reported that disease risk will affect the drug response.
3	Development of HLP was screening based, which means they were diagnosed of hyperlipidemia through the health check-ups. Since the check-ups are once per year, the annual rate was converted into monthly rate in order to be insistent with monthly-cycles of the Markov model. The development of other diseases were symptoms based, which means only when patients have onset of symptoms and sought for medical care, they can be diagnosed of diseases and initiated treatment if they need.
4	The incidence of AF in Medicare sample has 91% of white, 55% female. The study used the overall incidence rate in the US as the incidence rate for all the races.
5	The disease free to death rate was estimated from the non-cardiovascular death rate.
6	According to the guidelines, the treatments (except for MI-clopidogrel and stroke) are unfortunately cannot be stopped unless physical function decline (physically or cognitively due to comorbidities) or pregnancy (which was not included in the study). Therefore, the transition from treatment to disease free state is not included in this study.
7	Treatment will not lead to side effects of the study interest. The treatments could still lead to other side effects, which were not related to genetic variants, which were very likely shared between genetic variant group and non-variant group.
8	Once treatment developed side effects, it is not possible to convert back to without side effects state since side effects were caused by different metabolism determined by genetic variant. However, it is still possible that with the same genetic variant, some patients could still transit from originally treatment state without side effects into side effects.
9	Stroke history didn't change the risk of bleeding from clopidogrel.
10	If not reported by study, ADEs included the side effects reported by studies different from adverse outcomes (stroke, MI). The adverse outcomes were considered as disease states.
11	Stroke state included in the model is ischemic stroke. Hemorrhage stroke is included in the "ADE/hemorrhage" state to avoid confusion.
12	Patients without other adverse outcomes (stroke, MI, hemorrhage) and death will continue treatments throughout the life.
13	Treatment side effects can be managed by medications, and would not affect the MI and stroke management timeframe (MI-clopidogrel 1 year, stroke-clopidogrel 90 days).
14	There is a 30-day (1 month) turn-around time for reactive testing results. The one-month assumption is

	required by the length of the model cycle. Patients went under usual care while they were waiting for the results and providers make decision upon receiving test results. However, clinically, providers may not necessarily wait until results to come back and prescribe or switch medications.
15	There is no turnaround time for preemptive testing group. Genotype information is known when individuals enter the Markov cycles.
	Limited Information
1	All the patients started and were adherent to the indicated treatment once disease was diagnosed, and the quality of care were consistently as high as clinical trials regardless of patient characteristics and practice variants.
2	If only mean values were found, the high and low value was calculated by +/-2SD values in one-way sensitivity analysis and probabilistic sensitivity analysis.
3	Gender differences were considered as population differences if no information was found.
4	If alternative treatment effectiveness was not found in some diagnosis, such as VHD-warfarin, the general effectiveness of NOAC vs warfarin was used as it is a pooled result from all the diseases.
5	If study/report for Mortality rate for multiple CVD were not found, the sum number of each mortality rate was used. Example: CHD/STR death=CHD death + STR death
6	Unless the direct evidence was found, the disutilities of multiply disease status were calculated from multiplication of disutility of single disease status, plus disutility of 2 chronic conditions.
7	If no ADE costs were identified through studies, the cost value for “survive after 1 event” was used as estimation.
8	The disutility of STR and MI developed after primary diseases, were calculated regardless of whether patients had clopidogrel or statin ADE, or with genetic variant or not in order to simply the model, since the disutilities of STR and MI were relatively big.
9	The disutilities of ADEs were calculated using the QALY of the diseases * (1-the disutility of the ADE).
10	The QALYs for muscle-related complaints were estimated from the values for rheumatoid arthritis and related diseases.
11	The QALYs for rhabdomyolysis were estimated from the values for "other disease of the kidney and ureters".
12	CHD costs were estimated from ACS costs. Some other costs were similarly estimated from diseases that share similar characteristics and treatments.

eTable 5. Simulation outcomes of the base-case cohort and the scenario analysis by diagnosis, death and adverse events (in proportion of patients). UC, usual care; Rea, reactive testing; Pre, preemptive testing.

Base-Case Analysis		Disease Diagnosis							Death		Adverse Events			
		HLP	CHD	MI	STR	PAD	VHD	AF	CVD	Non-CVD	Any	Clopidogrel[a]	Statin[b]	Warfarin[c]
	UC	0.111	0.395	0.510	0.167	0.067	0.002	0.005	0.485	0.512	0.763	0.725	0.032	0.006
	Rea	0.111	0.395	0.508	0.172	0.067	0.002	0.005	0.464	0.532	0.442	0.727	0.043	0.005
	Pre	0.113	0.394	0.508	0.172	0.066	0.003	0.005	0.398	0.532	0.807	0.754	0.049	0.004
age														
44-54	UC	0.152	0.367	0.511	0.212	0.084	0.001	0.009	0.624	0.373	0.755	0.706	0.041	0.009
	Rea	0.152	0.367	0.505	0.215	0.084	0.001	0.009	0.586	0.412	0.457	0.707	0.060	0.007
	Pre	0.156	0.360	0.505	0.218	0.082	0.001	0.007	0.501	0.412	0.807	0.737	0.065	0.005
55-64	UC	0.096	0.398	0.517	0.171	0.063	0.002	0.005	0.487	0.513	0.781	0.745	0.029	0.006
	Rea	0.096	0.398	0.522	0.170	0.063	0.002	0.005	0.463	0.537	0.456	0.751	0.039	0.006
	Pre	0.094	0.401	0.522	0.174	0.065	0.003	0.004	0.405	0.537	0.828	0.781	0.043	0.003
65-74	UC	0.064	0.428	0.520	0.129	0.051	0.004	0.002	0.386	0.614	0.810	0.782	0.024	0.005
	Rea	0.064	0.428	0.519	0.134	0.051	0.004	0.002	0.368	0.632	0.444	0.782	0.032	0.004
	Pre	0.060	0.435	0.519	0.135	0.045	0.005	0.003	0.299	0.632	0.841	0.806	0.030	0.005
75 above	UC	0.051	0.431	0.512	0.075	0.031	0.005	0.004	0.191	0.809	0.694	0.670	0.019	0.005
	Rea	0.051	0.431	0.507	0.082	0.031	0.005	0.004	0.193	0.807	0.388	0.668	0.022	0.004
	Pre	0.052	0.431	0.507	0.077	0.030	0.005	0.003	0.150	0.807	0.717	0.694	0.021	0.002
Sex														
Male	UC	0.107	0.399	0.503	0.161	0.067	0.002	0.006	0.450	0.548	0.757	0.719	0.032	0.005
	Rea	0.107	0.399	0.504	0.163	0.067	0.002	0.006	0.430	0.568	0.436	0.720	0.043	0.004
	Pre	0.107	0.397	0.504	0.164	0.069	0.002	0.005	0.369	0.568	0.800	0.749	0.048	0.003
Female	UC	0.176	0.350	0.476	0.199	0.095	0.005	0.007	0.525	0.471	0.724	0.669	0.047	0.008
	Rea	0.176	0.350	0.477	0.201	0.095	0.005	0.007	0.492	0.504	0.448	0.673	0.069	0.007
	Pre	0.176	0.353	0.477	0.207	0.093	0.005	0.007	0.432	0.504	0.785	0.699	0.080	0.006
Race														
Caucasian	UC	0.124	0.411	0.528	0.170	0.022	0.002	0.006	0.503	0.494	0.760	0.720	0.035	0.006
	Rea	0.124	0.411	0.528	0.175	0.022	0.002	0.006	0.482	0.515	0.426	0.722	0.048	0.005
	Pre	0.126	0.409	0.528	0.175	0.022	0.002	0.005	0.416	0.515	0.805	0.747	0.055	0.004
Asian	UC	0.074	0.446	0.539	0.147	0.009	0.003	0.002	0.470	0.528	0.790	0.759	0.028	0.004

	Rea	0.074	0.446	0.540	0.151	0.009	0.003	0.002	0.440	0.558	0.424	0.762	0.036	0.003
	Pre	0.074	0.448	0.540	0.154	0.009	0.003	0.002	0.388	0.558	0.827	0.788	0.036	0.003
African	UC	0.049	0.287	0.399	0.147	0.347	0.002	0.001	0.396	0.602	0.767	0.749	0.017	0.002
	Rea	0.049	0.287	0.392	0.150	0.347	0.002	0.001	0.376	0.622	0.546	0.756	0.022	0.001
	Pre	0.050	0.285	0.392	0.152	0.350	0.002	0.001	0.300	0.622	0.810	0.785	0.024	0.001
Risk Level														
Risk X 1.5	UC	0.109	0.402	0.510	0.168	0.065	0.002	0.005	0.490	0.507	0.765	0.729	0.031	0.005
	Rea	0.109	0.402	0.506	0.174	0.065	0.002	0.005	0.464	0.533	0.439	0.732	0.042	0.005
	Pre	0.112	0.399	0.506	0.174	0.065	0.002	0.005	0.397	0.533	0.811	0.756	0.051	0.003
Risk X 2	UC	0.110	0.398	0.511	0.167	0.065	0.002	0.004	0.486	0.512	0.765	0.731	0.031	0.004
	Rea	0.110	0.398	0.508	0.174	0.065	0.002	0.004	0.464	0.533	0.442	0.733	0.043	0.004
	Pre	0.112	0.399	0.508	0.175	0.065	0.002	0.005	0.399	0.533	0.810	0.756	0.051	0.003
Time frame														
5 years	UC	0.104	0.398	0.465	0.077	0.068	0.002	0.004	0.147	0.116	0.709	0.679	0.027	0.004
	Rea	0.104	0.398	0.463	0.077	0.068	0.002	0.004	0.140	0.121	0.413	0.685	0.036	0.003
	Pre	0.105	0.400	0.463	0.078	0.067	0.002	0.005	0.107	0.121	0.748	0.705	0.042	0.002
14 years	UC	0.107	0.406	0.491	0.139	0.067	0.002	0.005	0.334	0.275	0.766	0.730	0.031	0.005
	Rea	0.107	0.406	0.490	0.142	0.067	0.002	0.005	0.312	0.282	0.439	0.734	0.043	0.004
	Pre	0.106	0.401	0.490	0.138	0.069	0.002	0.004	0.258	0.282	0.810	0.759	0.048	0.003
30 years	UC	0.109	0.400	0.507	0.163	0.066	0.002	0.006	0.461	0.455	0.765	0.727	0.032	0.006
	Rea	0.109	0.400	0.505	0.167	0.066	0.002	0.006	0.438	0.469	0.438	0.729	0.043	0.005
	Pre	0.111	0.399	0.505	0.166	0.066	0.002	0.005	0.373	0.469	0.808	0.756	0.049	0.003

HLP, hyperlipidemia; CHD, coronary heart disease; MI, myocardial infarction; STR, stroke; PAD, peripheral artery disease; VHD, valvular heart disease; AF, atrial fibrillation; CVD, cardiovascular disease.

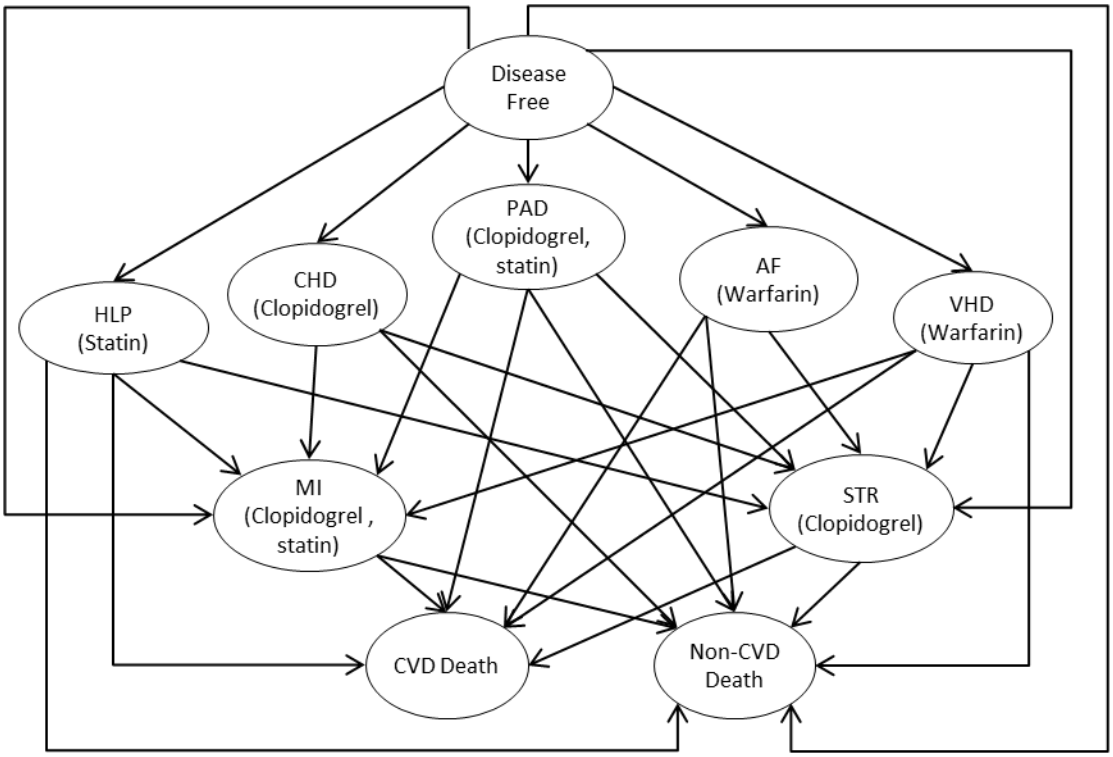
a. The adverse events were from clopidogrel for usual care group or no genetic variant patients, from ticagrelor for genetic variant patients.

b. The adverse events were from statin for usual care group or no genetic variant patients, from PSCK 9 inhibitor for genetic variant patients.

c. The adverse events were from warfarin for usual care group or no genetic variant patients, from NOAC for genetic variant patients.

Note: the proportion of disease diagnosis and adverse events could be overlapped, since one patient could develop two different diagnoses, or treatment adverse events.

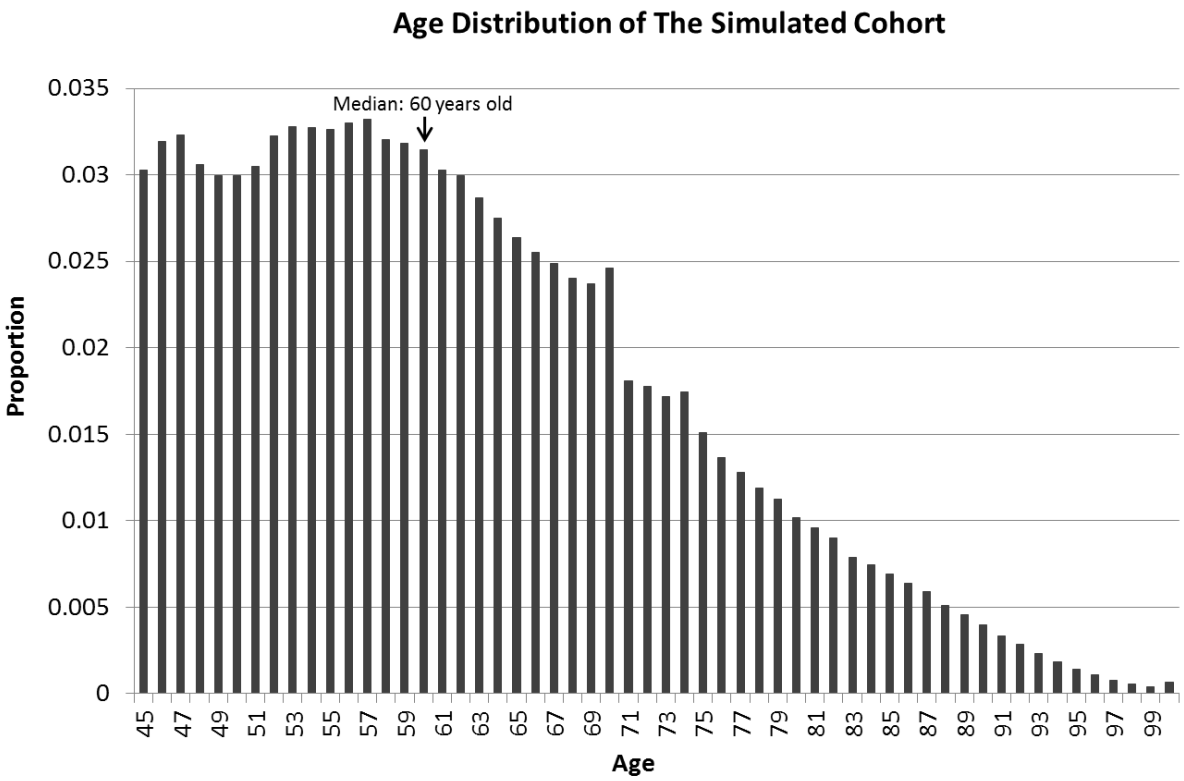
Note: The preemptive testing group had higher adverse events than the reactive and usual care patients, because ticagrelor yield higher bleeding rates than clopidogrel.



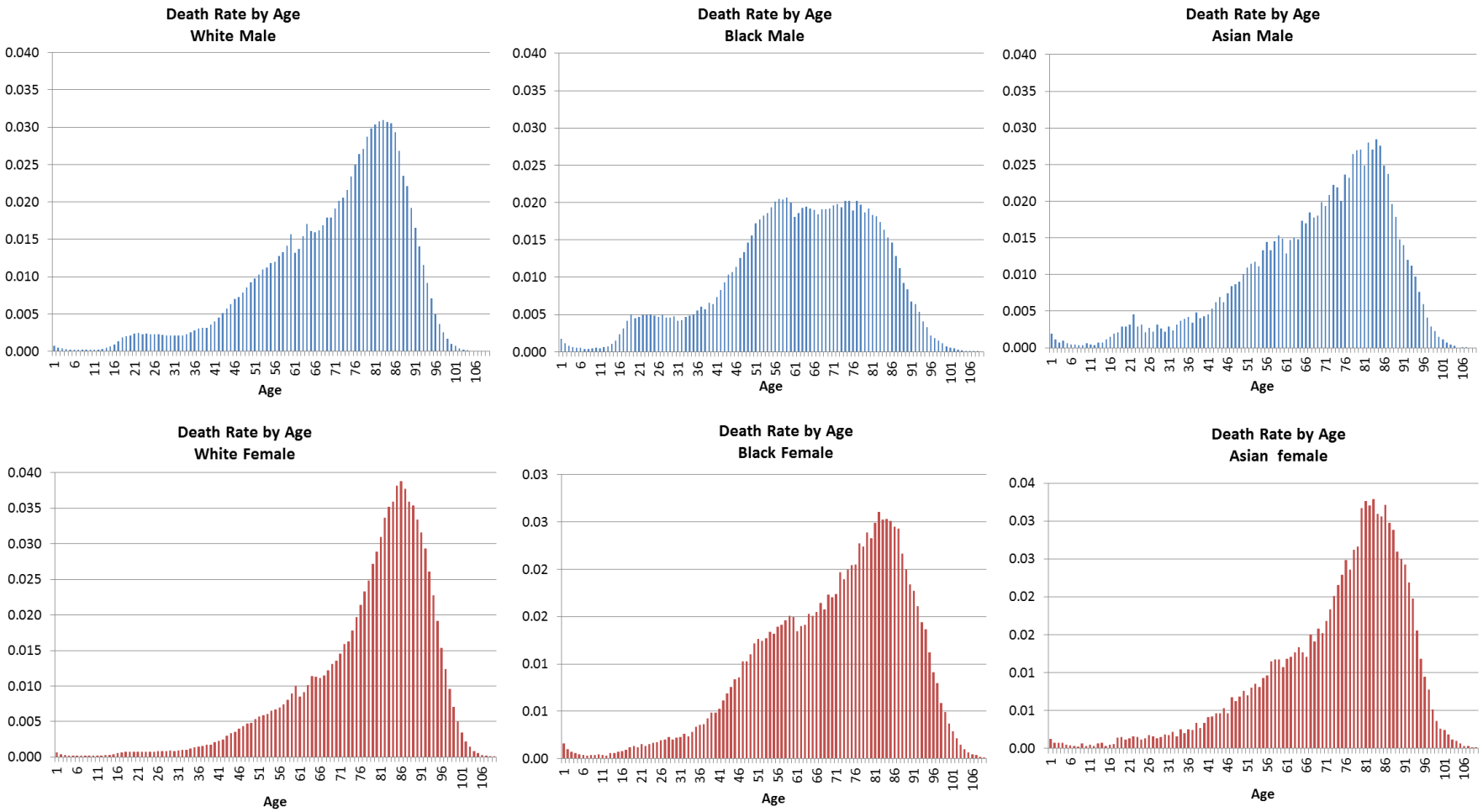
Medication	Adverse Events
Statin	muscle-related complains, Rhabdomyolysis, All adverse events*
Clopidogrel	Rash; Diarrhea, Nausea/vomiting, Bleeding, Hemorrhage, Hepatic toxicity, All adverse events*
Warfarin	Hemorrhage, Bleeding (minor: skin, joint, etc.)

* Cost or utility value reported by literature as a whole value.

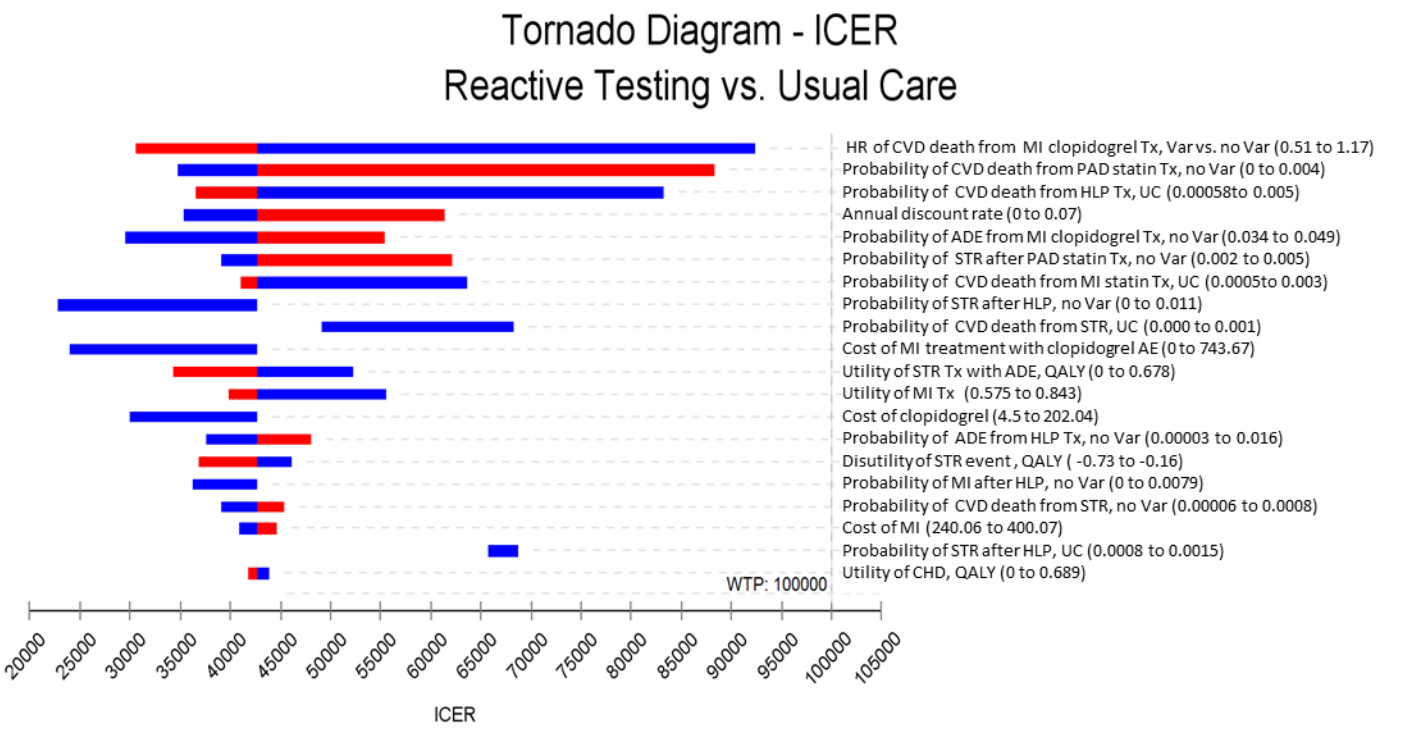
eFigure 1. Disease states and medications



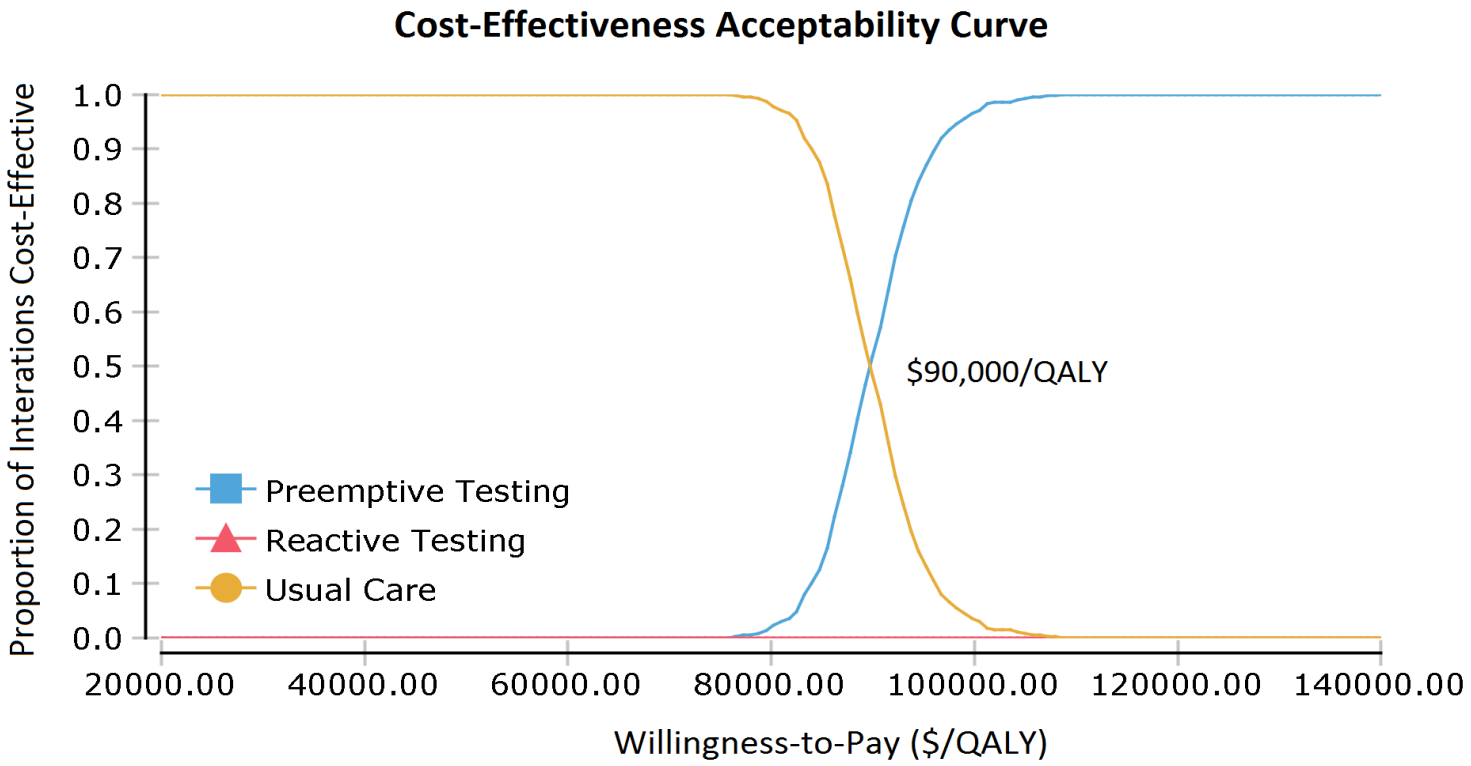
eFigure 2. Age distribution of the simulated cohort



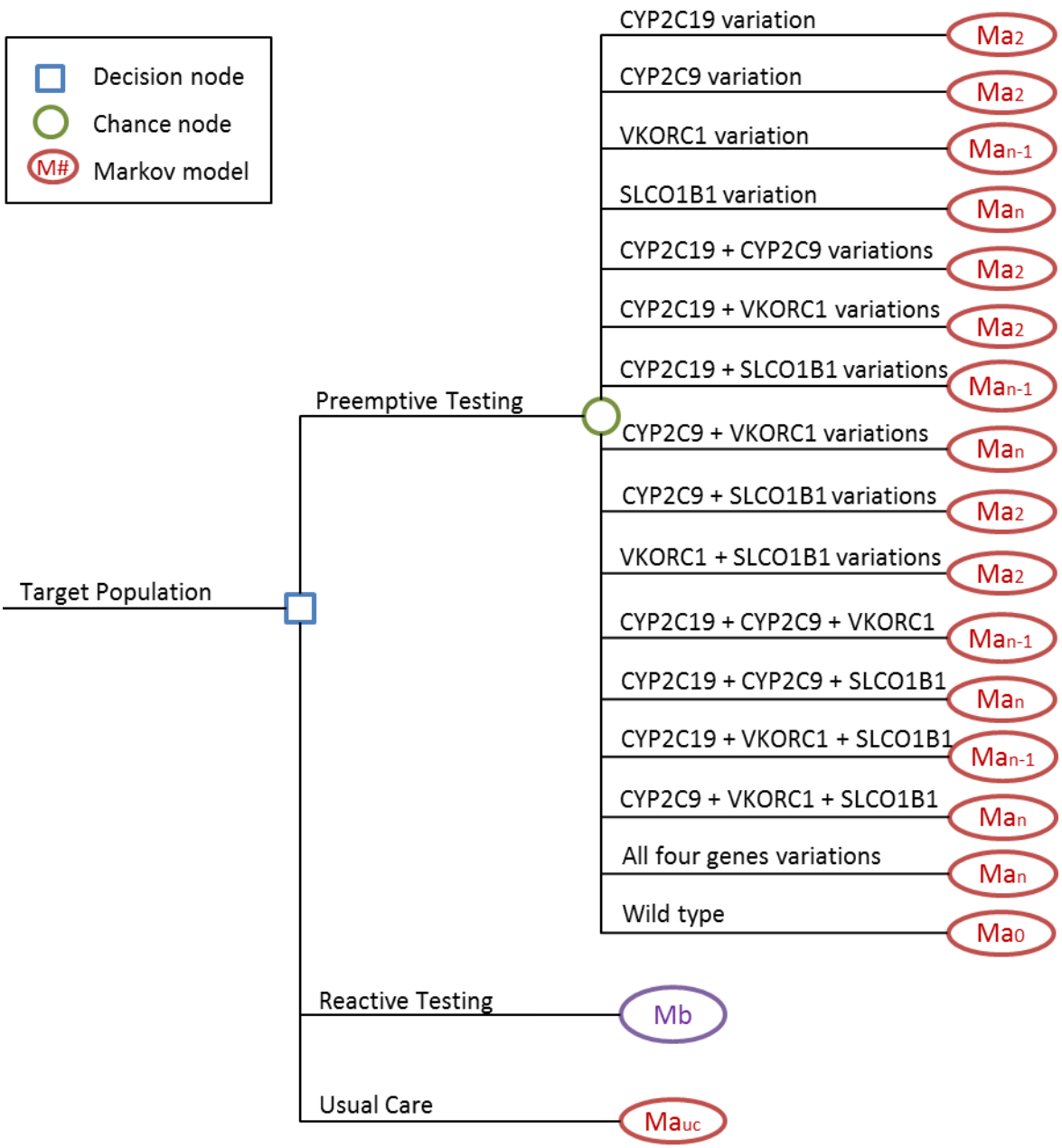
eFigure 3. Distributions of death rates in the US adopted in simulation by age and race



eFigure 4. Tornado diagram for incremental cost-effectiveness ratio (ICER) of reactive pharmacogenomic panel testing vs. usual care. Each horizontal bar represents the change in ICER when the value of the corresponding parameter is varied from its lower to upper limit. Red color suggested negative correlation, and blue suggested positive correlation. The top 20 parameters that impacted the ICER most are listed. Cost and probability values were reported on a monthly basis, while utility was reported on a yearly basis. CHD, coronary artery disease; ADE, adverse events; STR, stroke; MI, myocardial infarction; PAD; peripheral artery disease; AF, atrial fibrillation; VHD, valvular heart disease; Tx, treatment; RR, relative risk; HR, hazard ratio; Var, genetic variant; UC, usual care.

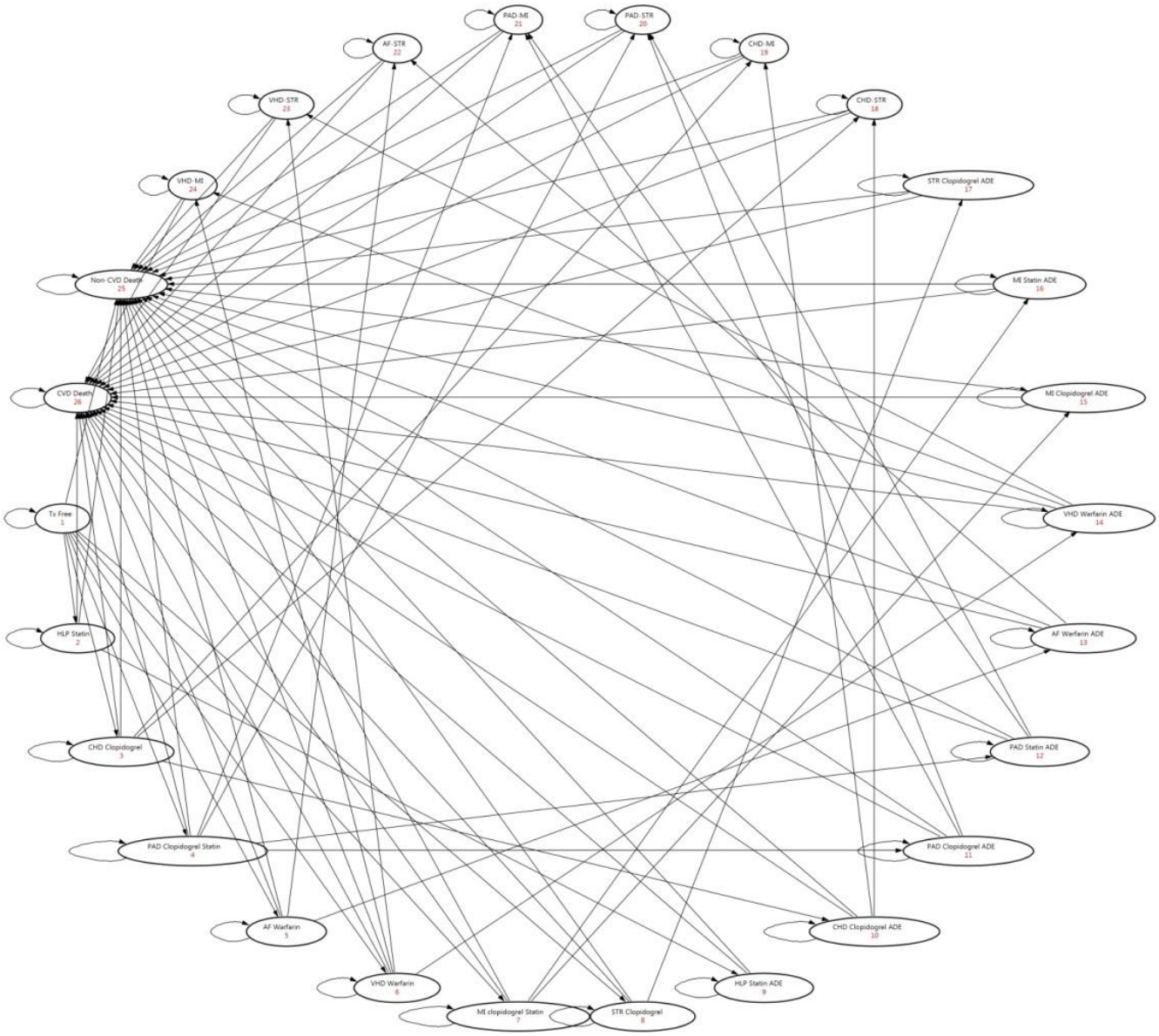


eFigure 5. Cost-effectiveness acceptability curve**.** Each of the curves represents the probability of corresponding strategy to be preferred against the willingness-to-pay level per QALY (in 2019 US dollars). QALY, quality-adjusted life year.



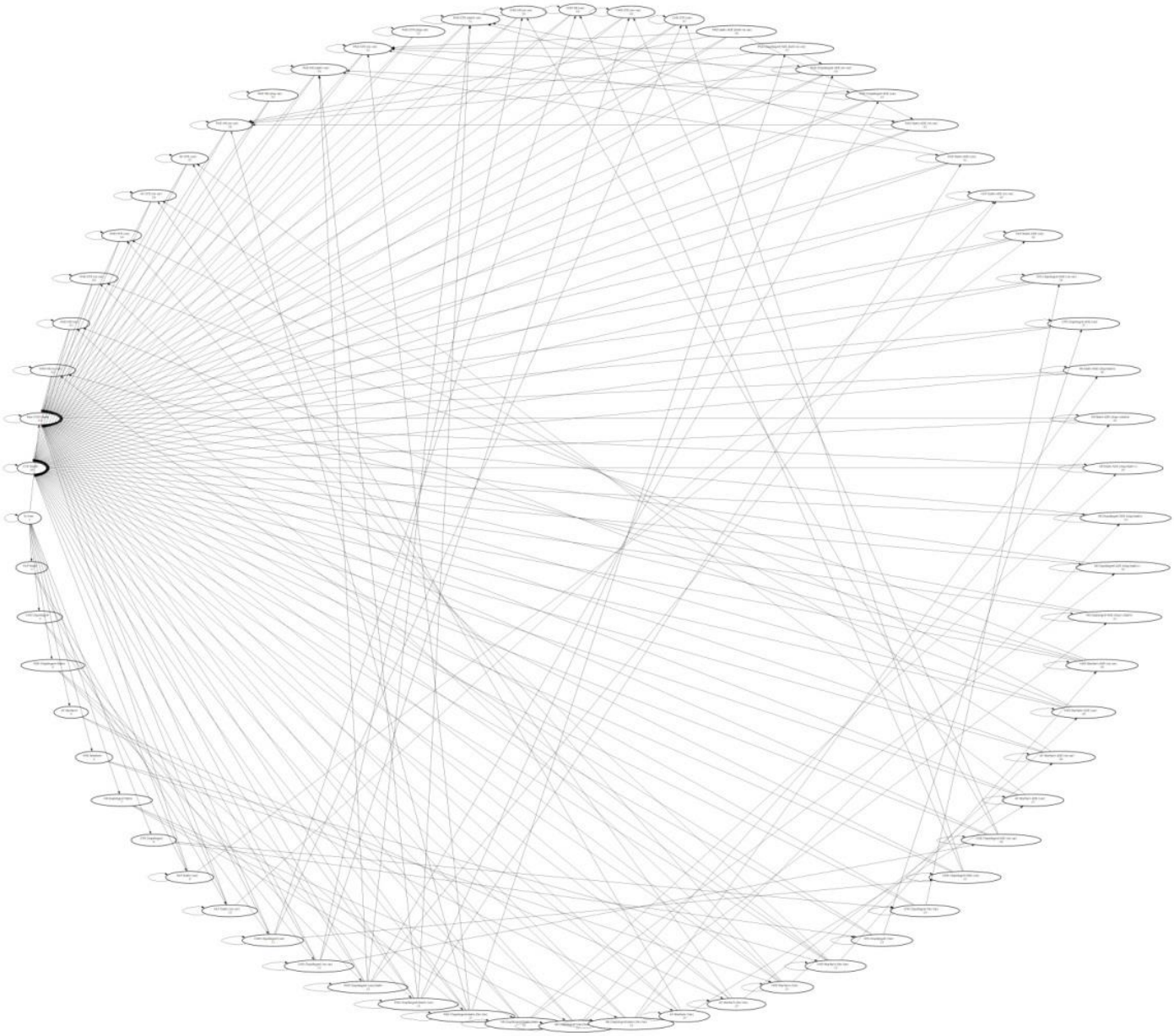
eFigure 6. Decision tree structure in detail

a. Markov Disease State for Preemptive PGx Testing Strategy and Usual Care study arms



eFigure 7. Markov models in details

b. Markov Disease States for Reactive PGx Testing Strategy



eFigure 7. Markov models in details (cont.)

Supplemental Material II– Cost Calculation

Step 1: Values were captured from literatures for a parameter.

Step 2: Compare the original studies to identify if the disease diagnosis and population were close to the model settings. If there was one study fit the model best, its values were captured as base-case value, and its ranges were used as the range in the model. Then skip to Step 4.

Step 3: If none of the studies were satisfied enough regarding the disease diagnosis and population, multiple values were captured and average values will be calculated as a base-case value. The minimum values reported in these studies were captured as minimum values, and the maximum values were used as the maximum in the modeling.

Step 4: Examine the cost for whether it was time-dependent or event-based. If it was event-based, capture the amount and skip to Step 7.

Step 5: If the cost was identified depend on time, convert all the study time into month. If study was reported in years, 12 months per year were used in calculating, and if study was in days, 30 days per month were used.

Step 6: Divide the values by study time in month.

Step 7: We adopted the U.S. gross domestic product deflator (https://apps.bea.gov/iTable/iTable.cfm?reqid=19&step=2#reqid=19&step=2&isuri=1&1921=survey) to convert all the costs from study year to 2019. The price index for each year was listed below:

For example, if the costs were $1,000 in 2012, then the costs in 2019 would be:

C_{2019}= (1000 /100)*112.348=1123.48 USD

year	Price Index
1997	74.446
2003	82.567
2007	92.498
2008	94.264
2009	94.999
2010	96.109
2011	98.112
2012	100
2013	101.773
2014	103.687
2015	104.757
2016	105.899
2017	107.932
2018	110.331
2019	112.348

References

1. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Journal of the American College of Cardiology 2018;72:2231-64.
2. Anderson JL, Adams CD, Antman EM, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;123:e426-e579.
3. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2013;61:e78-e140.
4. Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. Journal of the American college of cardiology 2011;58:2432-46.
5. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Journal of the American College of Cardiology 2014;64:e1-e76.
6. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology 2017;70:252-89.
7. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology 2018:25709.
8. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology 2017;69:e71-e126.
9. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neurointerventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery developed in collaboration with the American Academy of Neurology and Society of Cardiovascular Computed Tomography. Journal of the American College of Cardiology 2011;57:e16-e94.
10. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46-e99.

11. Niu X, Mao L, Huang Y, et al. CYP2C19 polymorphism and clinical outcomes among patients of different races treated with clopidogrel: a systematic review and meta-analysis. Journal of Huazhong University of Science and Technology [Medical Sciences] 2015;35:147-56.
12. Hirota T, Eguchi S, Ieiri I. Impact of genetic polymorphisms in CYP2C9 and CYP2C19 on the pharmacokinetics of clinically used drugs. Drug metabolism and pharmacokinetics 2013;28:28-37.
13. Scott S, Sangkuhl K, Stein C, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clinical Pharmacology & Therapeutics 2013;94:317-23.
14. Members WC, Holmes Jr DR, Dehmer GJ, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "Boxed Warning" a report of the american college of cardiology foundation task force on clinical expert consensus documents and the american heart association. Circulation 2010;122:537-57.
15. Flockhart DA, O'Kane D, Williams MS, et al. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. Genetics in Medicine 2008;10:139-50.
16. Lund K, Gaffney D, Spooner R, Etherington AM, Tansey P, Tait RC. Polymorphisms in VKORC 1 have more impact than CYP2C9 polymorphisms on early warfarin I nternational N ormalized R atio control and bleeding rates. British journal of haematology 2012;158:256-61.
17. Sinxadi P, Blockman M. Warfarin resistance: cardiovascular prescriber. Cardiovascular Journal of Africa 2008;19:215-7.
18. Deng J, Vozmediano V, Rodriguez M, Cavallari LH, Schmidt S. Genotype-guided dosing of warfarin through modeling and simulation. European Journal of Pharmaceutical Sciences 2017;109:S9-S14.
19. Kaye JB, Schultz LE, Steiner HE, Kittles RA, Cavallari LH, Karnes JH. Warfarin pharmacogenomics in diverse populations. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2017;37:1150-63.
20. Perera MA, Cavallari LH, Limdi NA, et al. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. The Lancet 2013;382:790-6.
21. Moyer TP, O'kane DJ, Baudhuin LM, et al. Warfarin sensitivity genotyping: a review of the literature and summary of patient experience. Mayo Clinic Proceedings; 2009: Elsevier. p. 1079-94.
22. Voora D, Shah SH, Spasojevic I, et al. The SLCO1B1* 5Genetic variant is associated with statin-induced side effects. Journal of the American College of Cardiology 2009;54:1609-16.
23. Group SC. SLCO1B1 variants and statin-induced myopathy—a genomewide study. New England Journal of Medicine 2008;359:789-99.
24. Crespin DJ, Federspiel JJ, Biddle AK, Jonas DE, Rossi JS. Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: a cost-effectiveness analysis. Value in Health 2011;14:483-91.
25. Meckley LM, Gudgeon JM, Anderson JL, Williams MS, Veenstra DL. A policy model to evaluate the benefits, risks and costs of warfarin pharmacogenomic testing. Pharmacoeconomics 2010;28:61-74.
26. You JH. Universal versus genotype-guided use of direct oral anticoagulants in atrial fibrillation patients: a decision analysis. Pharmacogenomics 2015;16:1089-100.
27. Amgen Announces 60% Reduction in List Price of PCSK9 Inhibitor Evolocumab. 2019. (Accessed August 7, 2019, at https://www.ajmc.com/newsroom/amgen-announces-60-reduction-in-list-price-of-pcsk9-inhibitor-evolocumab.)
28. Second Price Cut for PCSK9 Inhibitor Alirocumab (Praluent). 2019. (Accessed August 7, 2019, at https://www.medscape.com/viewarticle/908990.)
29. Parthan A, Leahy KJ, O'Sullivan AK, et al. Cost effectiveness of targeted high-dose atorvastatin therapy following genotype testing in patients with acute coronary syndrome. Pharmacoeconomics 2013;31:519-31.

30. Odden MC, Pletcher MJ, Coxson PG, et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States. Annals of internal medicine 2015;162:533-41.
31. Coleman CI, Limone BL. Cost-effectiveness of universal and platelet reactivity assay-driven antiplatelet therapy in acute coronary syndrome. The American journal of cardiology 2013;112:355-62.
32. You JH, Tsui KK, Wong RS, Cheng G. Cost-effectiveness of dabigatran versus genotype-guided management of warfarin therapy for stroke prevention in patients with atrial fibrillation. PloS one 2012;7:e39640.
33. Johnson SG, Gruntowicz D, Chua T, Morlock RJ. Financial analysis of CYP2C19 genotyping in patients receiving dual antiplatelet therapy following acute coronary syndrome and percutaneous coronary intervention. Journal of managed care & specialty pharmacy 2015;21:552-7.
34. Lala A, Berger J, Sharma G, Hochman J, Scott Braithwaite R, Ladapo J. Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a cost‐effectiveness analysis. Journal of thrombosis and haemostasis 2013;11:81-91.
35. Jiang M, You JH. CYP2C19 genotype plus platelet reactivity-guided antiplatelet therapy in acute coronary syndrome patients: a decision analysis. Pharmacogenetics and genomics 2015;25:609-17.
36. Patrick AR, Avorn J, Choudhry NK. Cost-effectiveness of genotype-guided warfarin dosing for patients with atrial fibrillation. Circulation: Cardiovascular Quality and Outcomes 2009;2:429-36.
37. Sullivan PW, Lawrence WF, Ghushchyan V. A national catalog of preference-based scores for chronic conditions in the United States. Medical care 2005:736-49.
38. Yu R, Chau P, McGhee S, et al. Trends of disease burden consequent to stroke in older persons in Hong Kong: Implications of population ageing. The Hong Kong Jockey Club; 2012.
39. O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. Jama 2005;293:699-706.
40. Ji Y, Skierka JM, Blommel JH, et al. Preemptive pharmacogenomic testing for precision medicine: a comprehensive analysis of five actionable pharmacogenomic genes using next-generation DNA sequencing and a customized CYP2D6 genotyping cascade. The Journal of Molecular Diagnostics 2016;18:438-45.
41. Scott SA, Sangkuhl K, Stein C, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clinical Pharmacology & Therapeutics 2013;94:317-23.
42. CDC. Deaths by Single Years of Age, Race, and Sex: United States, 1999-2007. https://www.cdc.gov/nchs/nvss/mortality/gmwk310.htm.
43. Amponsah MK, Benjamin EJ, Magnani JW. Atrial fibrillation and race–a contemporary review. Current cardiovascular risk reports 2013;7:336-45.
44. Rodriguez CJ, Soliman EZ, Alonso A, et al. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the Multi-Ethnic Study of Atherosclerosis. Annals of epidemiology 2015;25:71-6. e1.
45. D'Agostino Sr RB, Pencina MJ, Massaro JM, Coady S. Cardiovascular disease risk assessment: insights from Framingham. Global heart 2013;8:11-23.
46. Crawford AG, Cote C, Couto J, et al. Prevalence of obesity, type II diabetes mellitus, hyperlipidemia, and hypertension in the United States: findings from the GE Centricity Electronic Medical Record database. Population health management 2010;13:151-61.
47. Wong ND, Lopez V, Tang S, Williams GR. Prevalence, treatment, and control of combined hypertension and hypercholesterolemia in the United States. The American journal of cardiology 2006;98:204-8.

48. Ostchega Y, Paulose‐Ram R, Dillon CF, Gu Q, Hughes JP. Prevalence of peripheral arterial disease and risk factors in persons aged 60 and older: data from the National Health and Nutrition Examination Survey 1999–2004. Journal of the American Geriatrics Society 2007;55:583-9.
49. Collins TC, Petersen NJ, Suarez-Almazor M, Ashton CM. The prevalence of peripheral arterial disease in a racially diverse population. Archives of internal medicine 2003;163:1469-74.
50. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017;135:e146-e603.
51. Agarwal S, Hachamovitch R, Menon V. Current trial-associated outcomes with warfarin in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis. Archives of Internal Medicine 2012;172:623-31.
52. Site HG. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006;367:1903-12.
53. Executive Steering Committee on Behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. The Lancet 2003;362:1691-8.
54. Oldgren J, Alings M, Darius H, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. Annals of internal medicine 2011;155:660-7.
55. Investigators A. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. The Lancet 2008;371:315-21.
56. Mant J, Hobbs FR, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. The Lancet 2007;370:493-503.
57. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). The Lancet 1996;348:1329-39.
58. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Elsevier; 2010.
59. Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. Cochrane database of systematic reviews 2011.
60. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. New England Journal of Medicine 2016;374:2021-31.
61. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 2010;122:2131-41.
62. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. New England Journal of Medicine 2009;361:1045-57.
63. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. The Lancet 2009;373:723-31.
64. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. New England Journal of Medicine 1996;335:1001-9.
65. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. New England journal of medicine 2004;350:1495-504.

66. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. Journal of the American College of Cardiology 2006;48:438-45.
67. Cholesterol Treatment Trialists, Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010;376:1670-81.
68. Kumbhani DJ, Steg PG, Cannon CP, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. European heart journal 2014;35:2864-72.
69. Aung PP, Maxwell H, Jepson RG, Price J, Leng GC. Lipid‐lowering for peripheral arterial disease of the lower limb. Cochrane Database of Systematic Reviews 2007.
70. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. New England Journal of Medicine 2013;369:11-9.
71. Breithardt G, Baumgartner H, Berkowitz SD, et al. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. European heart journal 2014;35:3377-85.
72. Investigators* BAATfAF. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. New England Journal of Medicine 1990;323:1505-11.
73. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. The Lancet 1996;348:633-8.
74. Investigators SPiAF. Stroke prevention in atrial fibrillation study: final results. Circulation 1991;84:527-39.
75. Group EAFTS. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993;342:1255-62.
76. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. New England Journal of Medicine 2007;357:2001-15.
77. Ramos R, García-Gil M, Comas-Cufí M, et al. Statins for prevention of cardiovascular events in a low-risk population with low ankle brachial index. Journal of the American College of Cardiology 2016;67:630-40.
78. Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Circulation 2015;132:624-32.
79. Ezekowitz MD, Nagarakanti R, Noack H, et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy). Circulation 2016;134:589-98.
80. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. Jama 2004;292:1307-16.
81. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. Jama 2001;285:1711-8.
82. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine 2011;365:981-92.
83. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian atrial fibrillation anticoaguiation (CAFA) study. Journal of the American College of Cardiology 1991;18:349-55.
84. Noseworthy PA, Yao X, Shah ND, Gersh BJ. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease. International journal of cardiology 2016;209:181.

85. Group HPSC. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. Journal of Vascular Surgery 2007;45:645-54. e1.
86. Petersen P, Godtfredsen J, Boysen G, Andersen E, Andersen Br. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. The Lancet 1989;333:175-9.
87. Kang H-J, Clare RM, Gao R, et al. Ticagrelor versus clopidogrel in Asian patients with acute coronary syndrome: A retrospective analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. American heart journal 2015;169:899-905. e1.
88. Iakoubova OA, Sabatine MS, Rowland CM, et al. Polymorphism in KIF6 gene and benefit from statins after acute coronary syndromes: results from the PROVE IT-TIMI 22 study. Journal of the American College of Cardiology 2008;51:449-55.