SUPPLEMENTAL MATERIAL

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Table S1. Summary of Primary and Secondary Outcomes and the Percentage of Events Before the Diagnosis of FH.

	All patients (n=232)	Patients with *LDLR* gene variant (n=183)	Patients with *PCSK9* gene variant (n=35)	Patients with *LDLR/PCSK9* gene variants (n=14)
Primary outcome: Non-fatal MI				
Subjects who experienced events in lifetime, n (%)	39 (17)	30 (16)	3 (9)	6 (43)
Subjects who experienced events after FH diagnosis, n (%)	7 (3)	5 (3)	0 (0)	2 (14)
Subjects who experienced events before FH diagnosis, n (%)	32 (14)	25 (13)	3 (9)	4 (29)
Subjects who occurred events both before and after FH diagnosis, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
% of events before FH diagnosis in their lifetime, %	82	83	100	67
Secondary outcome: A composite of non-fatal MI and coronary revascularization				
Subjects who experienced events in lifetime, n (%)	69 (30)	55 (30)	7 (20)	7 (50)
Subjects who experienced events after FH diagnosis, n (%)	53 (23)	42 (23)	5 (14)	6 (43)
Subjects who experienced events before FH diagnosis, n (%)	27 (12)	21 (11)	3 (9)	3 (21)
Subjects who occurred events both before and after FH diagnosis, n (%)	11 (5)	8 (4)	1 (3)	2 (4)
% of events before FH diagnosis, %	39	38	43	43

Categorical variables were expressed as n (%).

FH = familial hypercholesterolemia, *LDLR* = low-density lipoprotein receptor, MI = myocardial infarction, *PCSK9* = proprotein convertase subtilisin/kexin type 9.

Table S2. Gene Variants Detected in Patients with *LDLR* and *PCSK9* Gene Variants.

LDLR		*PCSK9*		N
Nucleotide change	Effect of protein	Nucleotide change	Effect of protein	
ex 2-6 dup		c.94G > A	p.(Glu32Lys)	1
c.68-1G>C	Splicing error	c.10G > A	p.(Val4Ile)	1
c.418G>A	p.(Glu140Lys)	c.94G > A	p.(Glu32Lys)	1
c.478T>C	p.(Cys160Arg)	c.10G > A	p.(Val4Ile)	1
c.667_680dup	p.(Asp227Glufs*43)	c.10G > A	p.(Val4Ile)	1
c.888C>A	p.(Cys296*)	c.10G > A	p.(Val4Ile)	1
c.888C>A	p.(Cys296*)	c.94G > A	p.(Glu32Lys)	1
c.1124A>G	p.(Tyr375Cys)	c.10G > A	p.(Val4Ile)	1
c.1147T>G	p.(Phe383Val)	c.10G > A	p.(Val4Ile)	1
c.1297G>C	p.(Asp433His)	c.10G > A	p.(Val4Ile)	1
c.1502C>T	p.(Ala501Val)	c.94G > A	p.(Glu32Lys)	1
c.1618G>A	p.(Ala540Thr)	c.10G > A	p.(Val4Ile)	1
c.1845+2T>C	Splicing error	c.94G > A	p.(Glu32Lys)	1
c.2389G>A	p.(Val797Met)	c.10G > A	p.(Val4Ile)	1

LDLR = low-density lipoprotein receptor, N = number, *PCSK9* = proprotein convertase subtilisin/kexin type 9.

Table S3. Included *LDLR* Gene Variants.

Exon No.	Genomic location GRCh38 (Chr19)	Nucleotide change	Effect of protein	ClinVar	CADD score	rs number	Variant rating according to ACMG guideline	N
1	11089567	c.20_21del	p.(Lys7Ilefs*44)	N/A	N/A	N/A	Pathogenic	2
1	11100222	c.68-1G>C	Splicing error	Pathogenic	29.8	rs879254397	Pathogenic	4
2	11100249	c.94_111del	p.(Phe32_Gly37del)	N/A	N/A	N/A	Likely pathogenic	1
2	11100294	c.139G>A	p.(Asp47Asn)	Conflicting interpretations of pathogenicity	25.6	rs778284147	Uncertain significance	1
3	11102756	c.283T>G	p.(Cys95Gly)	Conflicting interpretations of pathogenicity	25.5	rs879254456	Likely pathogenic	2
3	11102757	c.284G>T	p.(Cys95Phe)	Pathogenic/ Likely pathogenic	25.7	rs879254457	Uncertain significance	1
3	11102758	c.285C>A	p.(Cys95*)	Pathogenic	21.3	rs139400379	Pathogenic	1
3	11102774	c.301G>A	p.(Glu101Lys)	Pathogenic/Likely pathogenic	25.2	rs144172724	Likely pathogenic	1
3	11102788	c.313+2dup	Splicing error	Pathogenic/Likely pathogenic	N/A	rs875989897	Pathogenic	1
4	11105250	c.344G>A	p.(Arg115His)	Conflicting interpretations of pathogenicity	22.5	rs201102461	Uncertain significance	4
4	11105295	c.389dup	p.(Asp131Argfs*49)	Pathogenic	N/A	rs879254510	Pathogenic	4
4	11105301	c.395G>A	p.(Arg132Gln)	N/A	0.044	rs751519676	Uncertain significance	1
4	11105314	c.408del	p.(Asp136Glufs*70)	N/A	N/A	N/A	Pathogenic	1
4	11105324	c.418G>A	p.(Glu140Lys)	Pathogenic/Likely pathogenic	26.6	rs748944640	Pathogenic	4
4	11105364	c.458T>C	p.(Phe153Ser)	N/A	25.5	N/A	Uncertain significance	1

4	11105384	c.478T>C	p.(Cys160Arg)	Pathogenic/Likely pathogenic	26.0	rs879254540	Likely pathogenic	3
4	11105406	c.500G>A	p.(Cys167Tyr)	Likely pathogenic	24.9	rs879254548	Uncertain significance	1
4	11105436	c.530C>T	p.(Ser177Leu)	Pathogenic/Likely pathogenic	24.7	rs121908026	Pathogenic	3
4	11105560	c.654_682del	p.(Pro220Lysfs*10)	N/A	N/A	N/A	Pathogenic	3
4	11105567	c.661G>T	p.(Asp221Tyr)	Pathogenic/Likely pathogenic	26.3	rs875989906	Likely pathogenic	1
4	11105573	c.667_680dup	p.(Asp227Glufs*43)	N/A	N/A	N/A	Pathogenic	1
4	11105576	c.670_682dup	p.(Glu228Glyfs*4)	N/A	N/A	N/A	Pathogenic	1
4	11105579	c.673_681dup	p.(Lys225_Asp227dup)	Likely pathogenic	N/A	rs1555803425	Likely pathogenic	2
4	11105587	c.681C>A	p.(Asp227Glu)	Pathogenic	18.28	rs121908028	Pathogenic	2
4	11105588	c.682G>A	p.(Glu228Lys)	Pathogenic/Likely pathogenic	27.0	rs121908029	Pathogenic	3
5	11106666	c.796G>A	p.(Asp266Asn)	Pathogenic/Likely pathogenic	27.5	rs875989907	Likely pathogenic	1
6	11107461	c.888G>A	p.(Cys296*)	Pathogenic	25.3	rs879254708	Pathogenic	6
7	11110685	c.974G>A	p.(Cys325Tyr)	Likely pathogenic	25.7	rs879254746	Uncertain significance	1
7	11110723	c.1012T>A	p.(Cys338Ser)	Pathogenic/Likely pathogenic	24.8	rs879254753	Pathogenic	19
7	11110766	c.1055G>A	p.(Cys352Tyr)	Pathogenic/Likely pathogenic	29.1	rs193922566	Likely pathogenic	1
8	11111515	c.1062dup	p.(Ile355Tyrfs*3)	Pathogenic	N/A	rs879254775	Pathogenic	1
8	11111519	c.1066G>C	p.(Asp356His)	Conflicting interpretations of pathogenicity	24.1	rs767767730	Uncertain significance	1
8	11111522	c.1069G>T	p.(Glu357*)	N/A	41	N/A	Pathogenic	1
8	11111577	c.1124A>G	p.(Tyr375Cys)	Pathogenic/Likely pathogenic	24.4	rs879254800	Likely pathogenic	1
8	11111600	c.1147T>G	p.(Phe383Val)	N/A	27.9	N/A	Uncertain significance	3
9	11113298	c.1207T>C	p.(Phe403Leu)	Likely pathogenic	26.7	rs879254831	Likely pathogenic	3
9	11113307	c.1216C>T	p.(Arg406Trp)	Pathogenic/Likely pathogenic	26.4	rs121908043	Likely pathogenic	2

9	11113343	c.1252G>A	p.(Glu418Lys)	Likely pathogenic	25.6	rs869320651	Uncertain significance	1
9	11113354	c.1263C>A	p.(Ser421Arg)	N/A	14.08	rs752942769	Uncertain significance	1
9	11113356	c.1265T>G	p.(Leu422Arg)	N/A	28.9	N/A	Uncertain significance	2
9	11113388	c.1297G>C	p.(Asp433His)	Pathogenic/Likely pathogenic	31	rs121908036	Pathogenic	8
10	11113571	c.1395T>G	p.(Tyr465*)	N/A	35	N/A	Pathogenic	1
10	11113645	c.1469G>A	p.(Trp490*)	Pathogenic	43	rs875989922	Pathogenic	1
10	11113653	c.1477_1488del	p.(Ser493_Gly496del)	N/A	N/A	N/A	Likely pathogenic	1
10	11113678	c.1502C>T	p.(Ala501Val)	Conflicting interpretations of pathogenicity	23.7	rs755667663	Uncertain significance	1
10	11113743	c.1567G>A	p.(Val523Met)	Pathogenic/Likely pathogenic	29.8	rs28942080	Likely pathogenic	1
10	11113763	c.1586+1G>A	Splicing error	Pathogenic/Likely pathogenic	34	rs755389753	Pathogenic	3
11	11116125	c.1618G>A	p.(Ala540Thr)	Pathogenic/Likely pathogenic	26.7	rs769370816	Uncertain significance	2
11	11116209	c.1702C>G	p.(Leu568Val)	Pathogenic/Likely pathogenic	24.3	rs746959386	Pathogenic	8
12	11116883	c.1730G>A	p.(Trp577*)	Pathogenic	49	rs138947766	Pathogenic	1
12	11116900	c.1747C>T	p.(His583Tyr)	Conflicting interpretations of pathogenicity	24.7	rs730882109	Uncertain significance	1
12	11116936	c.1783C>T	p.(Arg595Trp)	Conflicting interpretations of pathogenicity	24.6	rs373371572	Likely pathogenic	3
12	11117000	c.1845+2T>C	Splicing error	Pathogenic/Likely pathogenic	33	rs778408161	Pathogenic	20
13	11120117	c.1871_1873del	p.(Ile624del)	Pathogenic/Likely pathogenic	N/A	rs879255062	Likely pathogenic	1
14	11120408	c.2026G>A	p.(Gly676Ser)	Conflicting interpretations of pathogenicity	25.7	rs745753810	Uncertain significance	1

14	11120424	c.2042G>C	p.(Cys681Ser)	Likely pathogenic	26.1	rs201637900	Uncertain significance	1
14	11120436	c.2054C>T	p.(Pro685Leu)	Pathogenic/Likely pathogenic	24.9	rs28942084	Pathogenic	3
14	11120484	c.2102del	p.(Gly701Alafs*8)	N/A	N/A	N/A	Pathogenic	2
14	11123172	c.2141-2delA	Splicing error	N/A	N/A	N/A	Pathogenic	1
15	11128005	c.2312-3C>A	Splicing error	Pathogenic/Likely pathogenic	17.32	rs875989942	Pathogenic	5
16	11128085	c.2389G>A	p.(Val797Met)	Conflicting interpretations of pathogenicity	25.4	rs750518671	Likely pathogenic	4
17	11129539	c.2416dup	p.(Val806Glyfs*11)	Conflicting interpretations of pathogenicity	N/A	rs773618064	Pathogenic	3
17	11129539	c.2416_2418delinsAGAAG	p.(Val806Argfs*124)	N/A	N/A	N/A	Pathogenic	2
17	11129554	c.2431A>T	p.(Lys811*)	Pathogenic	43	rs879255211	Pathogenic	10
		ex1del		Pathogenic	N/A	N/A	Pathogenic	2
		ex2-3del		Pathogenic	N/A	N/A	Pathogenic	4
		ex2-6dup		N/A	N/A	N/A	Pathogenic	3
		ex5del		Pathogenic	N/A	N/A	Pathogenic	1
		ex7-18del		Pathogenic	N/A	N/A	Pathogenic	2
		ex13-14del		Pathogenic	N/A	N/A	Pathogenic	4
		ex13-14dup		Pathogenic	N/A	N/A	Likely pathogenic	1
		ex16-18del		N/A	N/A	N/A	Pathogenic	1
		ex17dup		N/A	N/A	N/A	Likely pathogenic	1
		ex17-18del		Pathogenic	N/A	N/A	Pathogenic	1

ACMG guideline = American College of Medical Genetics guideline, CADD score = Combined Annotation Dependent Depletion score, *LDLR* = low-density lipoprotein receptor, N = number, N/A = not applicable

Table S4. Included *PCSK9* Gene Variants.

Exon No.	Genomic location GRCh38 (Chr1)	Nucleotide change	Effect of protein	ClinVar	CADD score	rs number	Variant rating according to ACMG	N
1	55039847	c.10G > A	p.(Val4Ile)	Uncertain significance	6.659	rs186669805	Benign	16
1	55039931	c.94G > A	p.(Glu32Lys)	Conflicting interpretations of pathogenicity	22.3	rs564427867	Pathogenic	30
9	55058630	c.1486C > T	p.(Arg496Trp)	Uncertain significance	23.3	rs374603772	Likely pathogenic	3

ACMG guideline = American College of Medical Genetics guideline, CADD score = Combined Annotation Dependent Depletion score, N = number, N/A = not applicable *PCSK9* = proprotein convertase subtilisin/kexin type 9.

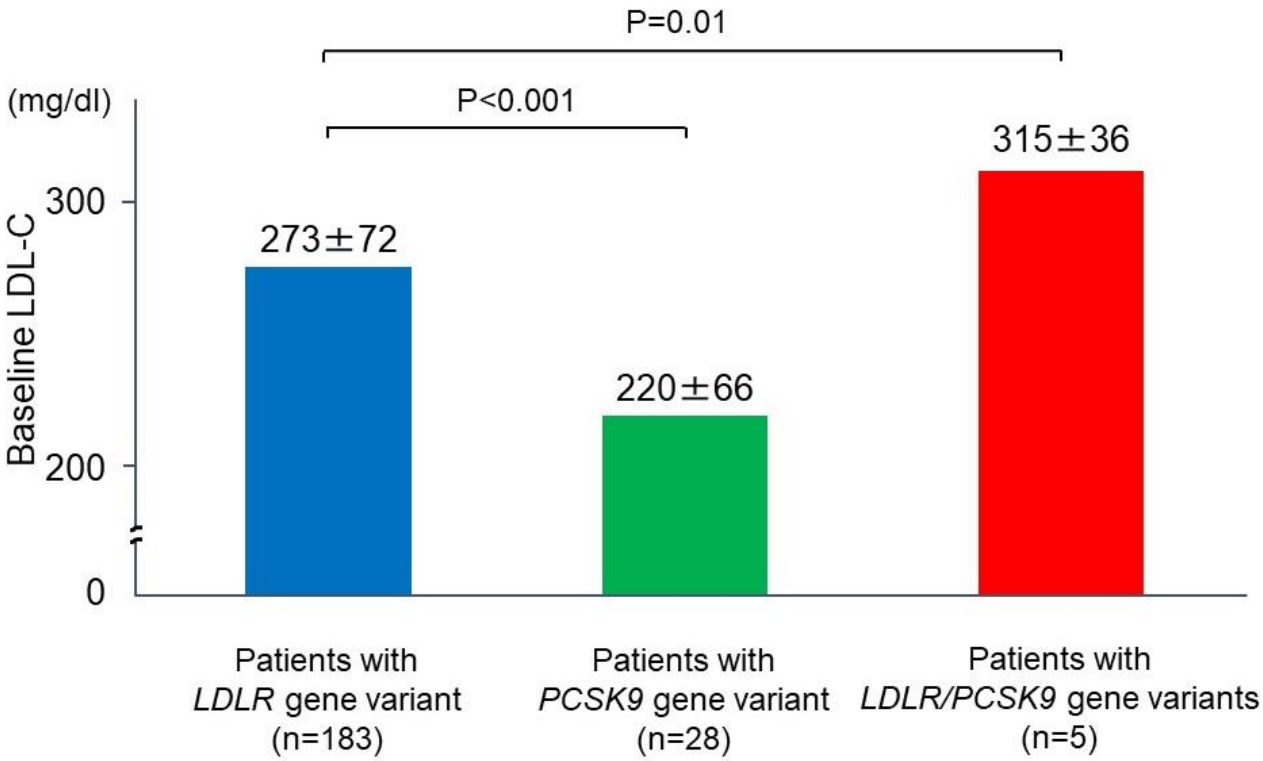
Table S5. Details of MACE.

Case No.	Age, y	Sex	Genotype	MACE	Cause of death	Culprit artery	Culprit site	Treatment Option
1	46	M	*LDLR/PCSK9*	Non-fatal MI	-	LAD	#7	PCI
2	37	M	*LDLR/PCSK9*	Non-fatal MI	-	LAD	#7	PCI
3	36	M	*LDLR/PCSK9*	Non-fatal MI	-	LCX	#14	MT
4	64	M	*LDLR/PCSK9*	Non-fatal MI	-	RCA	#2	PCI
5	53	M	*LDLR/PCSK9*	Non-fatal MI	-	RCA	#1	PCI
6	41	M	*LDLR/PCSK9*	Non-fatal MI	-	RCA	#1	PCI
7	40	M	*LDLR*	Non-fatal MI	-	RCA	#3	PCI
8	51	F	*LDLR*	Non-fatal MI	-	LAD	#6	PCI
9	71	F	*LDLR*	Non-fatal MI	-	LAD	#7	PCI
10	62	F	*LDLR*	Non-fatal MI	-	LAD	#6	PCI
11	32	F	*LDLR*	Non-fatal MI	-	RCA	#2	PCI
12	48	M	*LDLR*	Non-fatal MI	-	LAD	#7	CABG
13	42	M	*LDLR*	Non-fatal MI	-	RCA	#1	PCI
14	39	M	*LDLR*	Non-fatal MI	-	RCA	#1	MT
15	59	M	*LDLR*	Non-fatal MI	-	RCA	#2	CABG
16	39	M	*LDLR*	Non-fatal MI	-	LAD	N/A	MT
17	55	F	*LDLR*	Non-fatal MI	-	LAD	#7	MT
18	48	M	*LDLR*	Non-fatal MI	-	RCA	#2	PCI
19	45	M	*LDLR*	Non-fatal MI	-	RCA	#1, #13	CABG
20	54	M	*LDLR*	Non-fatal MI	-	LCX	#13	MT
21	45	M	*LDLR*	Non-fatal MI	-	LCX	#14	CABG

22	46	M	*LDLR*	Non-fatal MI	-	RCA	#2	PCI
23	36	M	*LDLR*	Non-fatal MI	-	LAD	#7	PCI
24	69	F	*LDLR*	Non-fatal MI	-	RCA	#2	PCI
25	63	M	*LDLR*	Non-fatal MI	-	LCX	#13	PCI
26	38	M	*LDLR*	Non-fatal MI	-	RCA	#3	PCI
27	66	M	*LDLR*	Non-fatal MI	-	RCA	#3	PCI
28	41	M	*LDLR*	Non-fatal MI	-	N/A	N/A	MT
29	64	M	*LDLR*	Non-fatal MI	-	N/A	#6, #13, #3	CABG
30	32	M	*LDLR*	Non-fatal MI	-	LAD	#6	PCI
31	30	F	*LDLR*	Non-fatal MI	-	RCA	#3	PCI
32	31	F	*LDLR*	Non-fatal MI	-	LAD	#7	PCI
33	43	M	*LDLR*	Non-fatal MI	-	LAD	#6	PCI
34	75	M	*LDLR*	Non-fatal MI	-	RCA	#2	MT
35	44	M	*LDLR*	Non-fatal MI	-	RCA	#1	PCI
36	44	M	*LDLR*	Non-fatal MI	-	LAD	#7	PCI
37	50	M	*PCSK9*	Non-fatal MI	-	LAD	#6	PCI
38	53	M	*PCSK9*	Non-fatal MI	-	RCA	#4AV	PCI
39	60	M	*PCSK9*	Non-fatal MI	-	RCA	#3	PCI

AV = atrioventricular, CABG = coronary artery bypass grafting, F = female, LAD = left anterior descending artery, LCX = left circumflex artery, *LDLR* = low-density lipoprotein receptor, M = male, MACE = major adverse cardiac events, MI = myocardial infarction, MT = medical treatment, No = number, RCA = right coronary artery, PCI = percutaneous coronary intervention, *PCSK9* = proprotein convertase subtilisin/kexin type 9

Figure S1. Comparison of LDL-C in Patients with *LDLR* Gene Variants and/or *PCSK9* (p.Glu32Lys, p.Arg496Trp) Gene Variant.

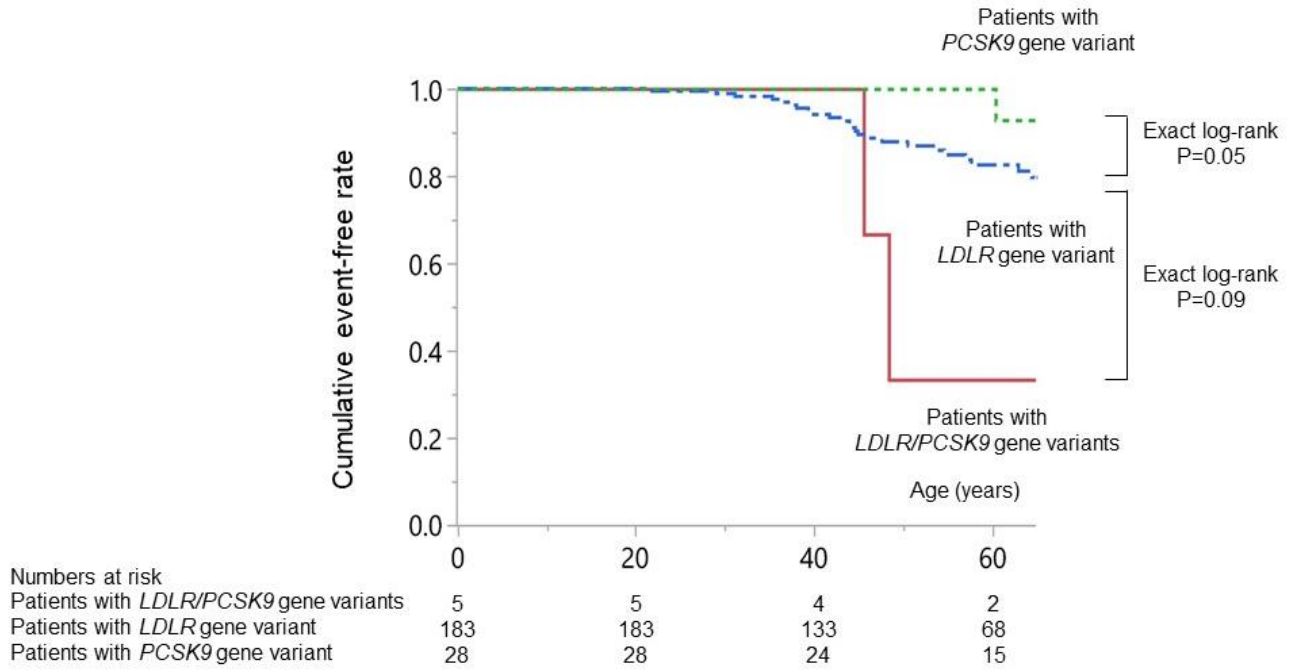


The levels of baseline LDL-C were shown. Blue, green, and red bars indicate the levels of baseline LDL-C in patients with *LDLR* gene variant, those with *PCSK9* gene variant, and those with *LDLR/PCSK9* gene variants, respectively.

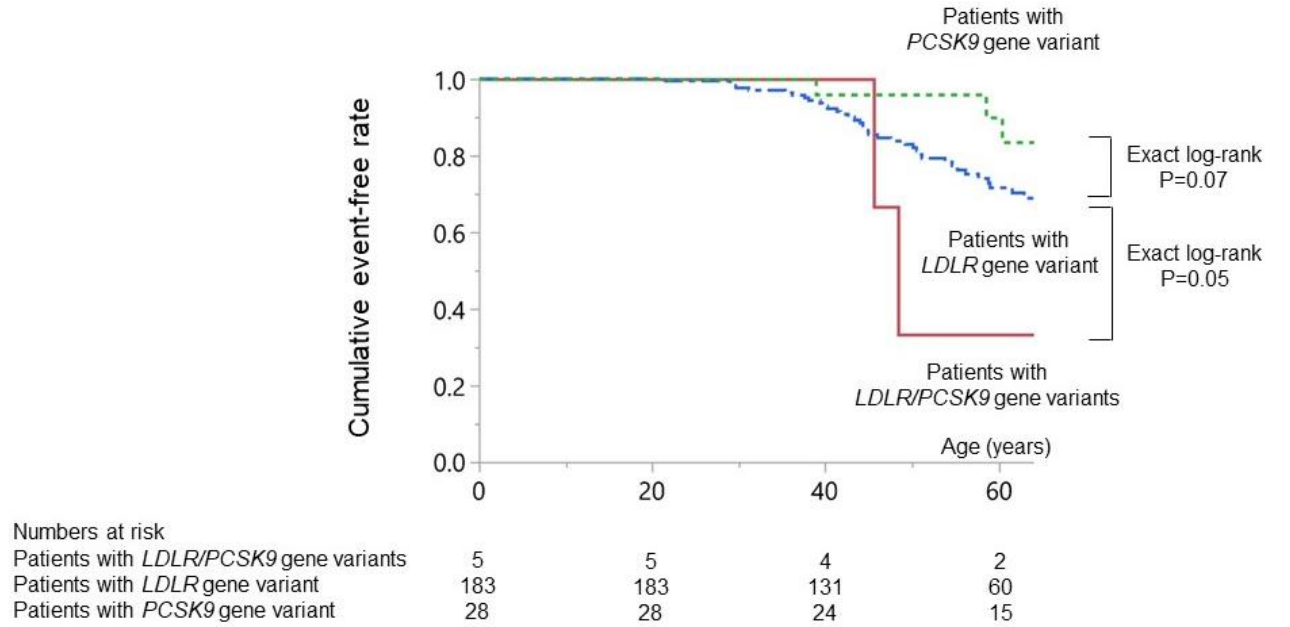
LDL-C = low-density lipoprotein cholesterol, *LDLR* = low-density lipoprotein receptor, *PCSK9* = proprotein convertase subtilisin/kexin type 9.

Figure S2. Comparison of Prognostic Influence of Genotype in Patients with *LDLR* Gene Variants and/or *PCSK9* (p.Glu32Lys, p.Arg496Trp) Gene Variant.

a.



b.



Prognostic influence of genotype in FH patients on primary outcome (non-fatal MI) (a) and

secondary outcome (non-fatal MI, and coronary revascularization) (b). Solid red, blue dash-dotted, and green dotted lines indicate event-free survival curves for patients with *LDLR/PCSK9* gene variants, patients with *LDLR* gene variant, and patients with *PCSK9* gene variant, respectively.

FH = familial hypercholesterolemia, *LDLR* = low-density lipoprotein receptor, MI = myocardial infarction, *PCSK9* = proprotein convertase subtilisin/kexin type 9