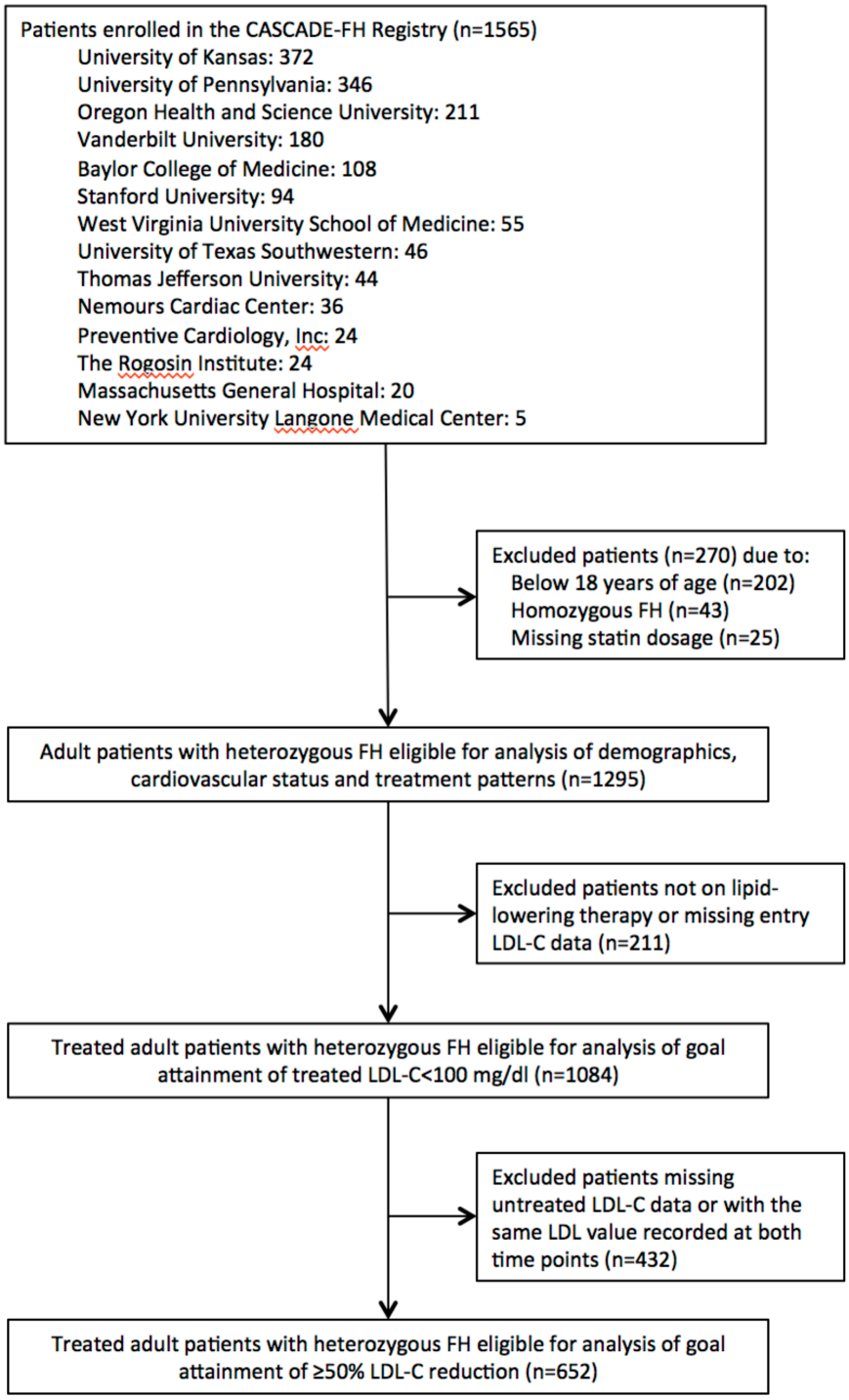
SUPPLEMENTAL MATERIAL

Supplementary Figure: Flow chart for analysis of patients enrolled in the CASCADE-FH Registry.



Supplementary Table 1: Demographics, clinical, and lipid/lipoprotein characteristics of adults with heterozygous familial hypercholesterolemia enrolled in the CASCADE-FH Registry.

	All subjects
Demographics	
Age at enrollment, years, median (IQR)	57 (43-66)
Female, %	59.3
Ethnicity, %	
White	80.0
Black	7.0
Hispanic	2.9
Other	10.2
FH history	
Age at FH diagnosis, years, median (IQR), n=1232	47 (31-59)
FH diagnosis before age 30 years, %	22.0
FH diagnosis before age 18 years, %	9.4
Age at initiation of LDL-lowering therapy, years, median (IQR), n=677	39 (25-50)
LDL-lowering therapy before age 30 years, %	16.6
LDL-lowering therapy before age 18 years, %	6.4
Family history of premature MI, %, n=938	45.0
Lipids, mg/dl, median (IQR)	
Untreated	
Total cholesterol, n=949	329 (297-389)
LDL-C, n=888	239 (211-294)
Treated	
Total cholesterol, n=1097	215 (178-268)
LDL-C, n=1084	134 (100-183)
Triglycerides, n=1092	113 (78-160)
HDL-C, n=1096	52 (42-64)
Entry	
Total cholesterol, n=1292	224 (182-281)
LDL-C, mg/dl, n=1278	141 (103-197)
Triglycerides, n=1286	113 (79-164)
HDL-C, n=1291	52 (42-64)
Cholesterol-years score, mg/dl*years, n=862	27121 (19812-35178)
Cardiovascular risk factors	
Number of additional modifiable cardiovascular risk factors, %*	
0	38.8
1	37.8
2	16.1
3	6.6
4	0.8
Diabetes, %, n=1280	13.0
Body-mass index among diabetics, kg/m^2, median (IQR)	30.4 (27.6-35.5)
Current smoker, %, n=1272	6.9
Hypertension, %, n=1283	42.8
Low HDL-C (<40 mg/dl in men, <50 mg/dl in women), %, n=1285	31.0
Obesity (body-mass index>30 kg/m2), %, n=1223	31.5
Body-mass index, kg/m^2, median (IQR), n=1223	27.3 (24.2-31.0)
Cardiovascular disease	

ASCVD, %, n=1273[†]	37.9
Age at onset, years, median (IQR)	52 (42-61)
CHD, overall cohort, %	35.9
Age at onset, years, median (IQR)	51 (42-61)
CHD, men, %	46.6
Age at onset, years, median (IQR)	47 (40-56)
CHD with onset <30 years of age, men, %	2.3
CHD, women, %	28.9
Age at onset, years, median (IQR)	55 (47-63)
CHD with onset <30 years of age, women, %	0.1
Stroke or TIA, %, n=1282	4.8
Aortic valve disease, %, n=1284	3.0

Sample size for calculation of prevalence rates and medians is 1295 unless otherwise noted.

* Additional modifiable cardiovascular risk factors defined as diabetes, current smoker, hypertension, and low HDL-C.

† ASCVD includes any history of CHD, stroke, TIA, peripheral artery disease.

Supplementary Table 2: Prevalence of prevalent coronary heart disease at baseline by age groups.

Age	N	CHD, n (%)
<30	140	0 (0.0%)
30-39	120	24 (20.0%)
40-49	191	52 (27.2%)
50-59	292	99 (33.9%)
60-69	332	170 (51.2%)
70-79	179	91 (50.8%)
≥80	41	29 (70.7%)
All	1295	465 (35.9%)

Supplementary Table 3: Overview of studies in the US reporting characteristics of ≥200 adults with heterozygous familial hypercholesterolemia.

Reference	CASCADE-FH 2015	Stone 1974[1]	Hopkins 2001[2]	Elis 2011[3]
Cohort	• n=1295 • 10 lipid centers • Clinical and/or genetic diagnosis of heFH*	• N=284 heFH, 5 hoFH • 1 lipid center • Clinical diagnosis of heFH/hoFH	• N=262 • MEDPED registry • Clinical diagnosis of heFH (MEDPED)	• N=327 • 1 lipid center • Clinical diagnosis of heFH (SB)
Demographics				
Age, years	57	40	50	45
Female, %	59	47	57	40
FH history				
Confirmed FH mutation	3	-	-	-
Age at FH diagnosis, years	47	-	-	38
Age at initiation of therapy, years	39	-	-	-
Lipids				
Untreated lipid values or, when unavailable, lipid values at initial clinic visit or at time of inclusion into registry†				
Total cholesterol, mg/dl	329	402	-	340
LDL-C, mg/dl	239	-	224	256
Treated lipid values or, when unavailable, most recent lipids‡				
Total cholesterol, mg/dl	215	-	-	195
LDL-C, mg/dl	134	-	172	116
LDL-C<100 mg/dl, %	25	-	-	30
≥50% LDL-C reduction, %	41	-	-	-
Statin, %	75	-	44	98
High-intensity statin, %	42	-	-	-
Statin + ezetimibe, %	34	-	-	44
Cardiovascular risk factors				
Diabetes, %	13	-	3	-
Current/ever smoker, %	7/31	-/44	-/16	10/28
Hypertension, %	43	-	16	-
Body-mass index, kg/m^2	27	24	28	-
Cardiovascular disease				
CVD or CHD, %	CHD 36	CHD 30	CHD 26	CVD 35
Age at onset, years	M 47, W 55	M 42, W 62	M 44, W 50	54

* Diagnosis using DLCN, MEDPED, SB, or other clinical criteria and/or genetic testing.
† CASCADE-FH 2015 highest untreated; Stone 1974 at time of inclusion into registry; Hopkins 2001 not on drug(s); Elis 2011 initial untreated; Allard 2014 first clinic visit; Benn 2012 off-treatment; Beliard 2014 at diagnosis; Harada-Shiba 2012 at time of inclusion into registry; Pijlman 2010 baseline; Mundal 2014 at time of inclusion into registry; Mata 2011 at time of inclusion into registry; Hadfield 2008 pre-treatment.
‡ CASCADE-FH 2015 most recent treated; Hopkins 2001 on drug(s); Elis 2011 most recent treated; Benn 2012 on-treatment; Beliard 2014 under medical care; Pijlman 2010 recent; Mundal 2014 during lipid-lowering treatment; Hadfield 2008 post-treatment.
Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; DLCN, Dutch Lipid Clinic Network; heFH, heterozygous familial hypercholesterolemia; hoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MEDPED, Make Early Diagnoses - Prevent Early Deaths; SB, Simon Broome

Supplementary Table 4: Overview of contemporary registries worldwide reporting characteristics of ≥200 adults with heterozygous FH.

Country	US	Canada	Denmark	France	Japan
Reference	CASCADE-FH 2015	Allard 2014[4]	Benn 2012[5]	Beliard 2014[6]	Harada-Shiba 2012[7]
Cohort	• n=1295 • 10 lipid centers • Clinical and/or genetic diagnosis of heFH*	• N=409 • 1 lipid center • Clinical diagnosis of heFH (DLCN, definite)	• N=502 • Population registry • Clinical diagnosis of FH (DLCN, probable or definite)	• N=1669 • 5 lipid centers • Clinical and/or genetic diagnosis of FH (DLCN, SB)	• N=419 • 6 lipid centers • Clinical and/or genetic diagnosis of heFH (Japanese)
Demographics					
Age, years	57	61	59	46	53
Female, %	59	55	59	51	57
FH history					
Confirmed FH mutation	3	-	20	39	53
Xanthoma documented	19	-	-	46	64
Age at FH diagnosis, years	47	-	-	-	-
Age at initiation of therapy	39	-	-	-	-
Lipids					
Untreated lipid values or, when unavailable, lipid values at initial clinic visit or at time of inclusion into registry†					
Total cholesterol, mg/dl	329	343	333	389	339
LDL-C, mg/dl	239	262	251		257
Treated lipid values or, when unavailable, most recent lipid values‡					
Total cholesterol, mg/dl	215	-	271	270	-
LDL-C, mg/dl	134	-	182	194	-
LDL-C<100 mg/dl, %	25	-	-	10	-
≥50% LDL-C reduction, %	41	-	-	-	-
Statin, %	75	-	-	79	-
High-intensity statin, %	42	-	-	-	-
Statin + ezetimibe, %	34	-	-	35	-
Cardiovascular risk factors					
Diabetes, %	13	6	5	4	-
Current/ever smoker, %	7/31	-/43	27/-	19/-	-
Hypertension, %	43	23	76	11	-
Body-mass index, kg/m^2	27	26	27	25	-
Cardiovascular disease					
CVD or CHD, %	CHD 36	CVD 27	CHD 33	CVD 12	-
Age at onset, years	M 47, W 55	M 50, W 57	-	-	-

Supplementary Table 4 (cont.): Overview of contemporary registries worldwide reporting characteristics of ≥200 adults with heFH.

Country	Netherlands	Norway	Spain	UK
Reference	Pijlman 2010[8]	Mundal 2014[9]	Mata 2011[10]	Hadfield 2008[11]
Cohort	• N=1249 • 5 lipid centers • Clinical diagnosis of heFH (DLCN, probable or definite)	• N=4688 • 1 coordinating center • Genetic diagnosis of heFH/hoFH	• N=1262 • 19 lipid centers • Genetic diagnosis of heFH/hoFH	• N=733 • 11 lipid centers • Clinical and/or genetic diagnosis of heFH (SB)
Demographics				
Age, years	50	55	46	51
Female, %	52	52	52	55
FH history				
Confirmed FH mutation	54	100	100	-
Xanthoma documented	-	-	15	21
Age at FH diagnosis, years	-	-	-	-
Age at initiation of therapy	-	-	-	-
Lipids				
Untreated lipid values or, when unavailable, lipid values at initial clinic visit or at time of inclusion into registry[†]				
Total cholesterol, mg/dl	350	437	262	-
LDL-C, mg/dl	258	348	192	259
Treated lipid values or, when unavailable, most recent lipid values[‡]				
Total cholesterol, mg/dl	196	259	-	-
LDL-C, mg/dl	124	182	-	128
LDL-C<100 mg/dl, %	21	-	3	30[§]
≥50% LDL-C reduction, %	60	-	-	64[‖]
Statin, %	96	-	80	89
High-intensity statin, %	34	-	13	-
Statin + ezetimibe, %	53	-	26	-
Cardiovascular risk factors				
Diabetes, %	2	-	3	-
Current/ever smoker, %	-/26	-	28/-	-
Hypertension, %	20	-	15	-
Body-mass index, kg/m^2	25	-	27	-
Cardiovascular disease				
CVD or CHD, %	CVD 17	-	CVD 14	CHD 18

Age at onset, years	-	CV death M 57, W 67	48	-

Means shown for continuous variables except for CASCADE-FH data where medians are shown.

* Diagnosis using DLCN, MEDPED, SB, or other clinical criteria and/or genetic testing.

† CASCADE-FH 2015 highest untreated; Stone 1974 at time of inclusion into registry; Hopkins 2001 not on drug(s); Elis 2011 initial untreated; Allard 2014 first clinic visit; Benn 2012 off-treatment; Beliard 2014 at diagnosis; Harada-Shiba 2012 at time of inclusion into registry; Pijlman 2010 baseline; Mundal 2014 at time of inclusion into registry; Mata 2011 at time of inclusion into registry; Hadfield 2008 pre-treatment.

‡ CASCADE-FH 2015 most recent; Hopkins 2001 on drug(s); Elis 2011 most recent treated; Benn 2012 on-treatment; Beliard 2014 under medical care; Pijlman 2010 recent; Mundal 2014 during lipid-lowering treatment; Hadfield 2008 post-treatment.

§ Estimated from figure

|| >45% LDL-C reduction

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; DLCN, Dutch Lipid Clinic Network; heFH, heterozygous familial hypercholesterolemia; hoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MEDPED, Make Early Diagnoses - Prevent Early Deaths; SB, Simon Broome

Supplementary Table 5: Overview of studies with ≥200 subjects reporting factors associated with cardiovascular outcomes in adults with heterozygous familial hypercholesterolemia.

Country	Reference	Factor	Risk ratio (95% CI)
Cross-sectional studies			**Odds ratio**
US	CASCADE-FH 2015* n=1282	Age, per 10-year increment	1.53 (1.35-1.73)
		Male	2.68 (1.91-3.78)
		Family history of premature MI	1.83 (1.25-2.70)
		Diabetes	1.66 (1.01-2.72)
		Hypertension	2.68 (1.91-3.76)
		Low HDL-C (<40 mg/dl for men, <50 mg/dl for women)	1.53 (1.09-2.14)
		Untreated total cholesterol, per 10-mg/dl increment	1.02 (1.00-1.04)
	Hopkins 2001[2†] n=262	Age, per 10-year increment	2.24 (1.63-3.08)
		Male	5.64 (2.62-12.1)
		Smoking (ever)	2.71 (1.13-6.51)
		Smaller LDL	2.60 (1.21-5.58)
		White blood cell count	1.30 (1.05-1.59)
UK	Neil 2004[12] n=410	Smoking (ever)	2.53 (1.67-3.83)
Spain	Alonso 2008[13‡] n=811	Male	1.98 (1.09-3.56)
		Smoking (ever)	1.80 (1.03-3.16)
		Pre-treatment total cholesterol/HDL-C ratio	1.26 (1.01-1.58)
		Age	1.05 (1.02-1.07)
Australia	Chan 2015[14] n=390	Age (years)	1.07 (1.05-1.09)
		Male	2.69 (1.54-4.69)
		Smoking (ever vs. never)	2.24 (1.29-3.87)
		Hypertension (present vs. absent)	4.99 (2.80-8.89)
		Diabetes (present vs. absent)	2.74 (1.06-7.08)
		eGFR < 60 mL/min/1.73m^2	3.12 (1.18-8.27)
		LDL-cholesterol, pretreatment (mmol/L)	1.17 (1.05-1.30)
		LDL-cholesterol year score (mmol/L)	1.01 (1.00-1.01)
		Triglyceride, pretreatment (mmol/L)	1.34 (1.09-1.65)
		HDL-cholesterol, pretreatment (mmol/L)	0.32 (0.13-0.76)
		Lp(a) (g/L)	2.18 (1.31-3.62)

Cohort studies			Relative risk
Netherlands	Jansen 2004[15§] n=1956	Male	2.82 (2.37-3.36)
		Diabetes	2.19 (1.36-3.54)
		Smoking (ever)	1.67 (1.40-1.99)
		Hypertension	1.36 (1.06-1.75)
		Low HDL-C (<35 mg/dl for men, <43 mg/dl for women)	1.37 (1.15-1.63)
		High lipoprotein(a) (>30 mg/dl)	1.50 (1.20-1.79)
Canada	Allard 2014[4||] n=409	Male	2.4 (1.6-3.7)
		Diabetes	3.6 (2.0-6.5)
		Family history of premature CVD	1.8 (1.2-2.7)
		HDL-C at first clinic visit, per 1-mmol/l increment	0.4 (0.2-0.7)
		High lipoprotein(a) (>60 mg/dl)	1.8 (1.1-2.9)

* Adjusted for age at enrollment, diabetes, current smoking, hypertension, pre-treatment total cholesterol, and low HDL-C.
† Adjusted for age, gender, smoking, body mass index, waist to hip ratio, hypertension, diabetes, xanthoma, plasma insulin, HDL-C, triglycerides, lipoprotein(a), homocysteine, white cell count, C-reactive protein, carotid intima-medial thickness, angiotensin-converting enzyme I/D polymorphism.
‡ Adjusted for age, gender, smoking, hypertension, body-mass index, family history of premature cardiovascular disease, lipoprotein(a), apo E genotype, type of FH mutation, LDL-C, HDL-C, triglycerides.
§ Adjusted for gender, smoking, hypertension, diabetes, body-mass index, HDL-C, triglycerides, lipoprotein(a), homocysteine.
|| Adjusted for gender, body-mass index, smoking, family history of premature cardiovascular disease, diabetes, hypertension, LDL-C, HDL-C, triglycerides, lipoprotein(a).
Abbreviations: CHD, coronary heart disease; FH, familial hypercholesterolemia; HDL, high-density lipoprotein, LDL, low-density lipoprotein; MI, myocardial infarction

Supplementary Table 6: Overview of studies with ≥200 subjects reporting factors associated with LDL-C<100 mg/dl goal attainment in adults with heterozygous familial hypercholesterolemia.

Country	Reference	Factor	OR (95% CI)
US	CASCADE-FH 2015* n=1084	Current age, per 10-year increment	1.23 (1.07-1.41)
		Family history of premature MI	1.88 (1.16-3.04)
		Untreated LDL-C, per 10-mg/dl increment	0.93 (0.90-0.96)
		High-intensity statin	4.66 (2.15-10.13)
		Low- or moderate intensity statin	2.29 (1.05-4.95)
		>1 lipid-lowering therapy	1.88 (1.25-2.83)
Netherlands	Pijlman 2010[8†] n=1249	Cardiovascular disease	1.54 (1.05-2.25)
		Hypertension	1.49 (1.05-2.11)
		LDL-C, per 1-mmol/l increment	0.66 (0.59-0.73)
		Total cholesterol, per 1-mmol/l increment	0.70 (0.65-0.76)
Spain	Mata 2011[10‡] n=1262	Statin + ezetimibe	2.22 (1.10-4.48)

* Adjusted for recent LDL-C, coronary heart disease, statin use, and use of >1 LDL-lowering therapy.

† Adjusted for age and gender.

‡ Adjusted for age, gender, cardiovascular disease, cardiovascular risk factors.

Abbreviations: LDL, low-density lipoprotein; MI, myocardial infarction

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